

Synthesis of Essential Drugs

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Author: R.S. Vardanyan and V.J. Hruby
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Preface

This book, as is often the case with many others, represents an attempt to express a long overdue need of compiling information which has accumulated over the course of more than 30 years of our work in the area of the synthesis of medical drugs and 7 years of work on the book itself. In our opinion, the result can fill obvious gaps that exist in literature of this kind.

This book turned out to be different than what was originally planned. It was intended to show the synthesis of medications in action. For a few drugs, it was aimed at showing the synthesis of a body of potentially active substances that came about as a result of collaboration between chemists, biologists, pharmacologists, toxicologists, and others of various specialties. New drugs sometimes resulted from the application of capabilities provided by a new reagent or by a newly accessible derived substance. It was intended to briefly touch on the history of formation for at least a few drugs. We would like to share certain curious incidents that occurred while working with them, and to share the extremely curious histories behind the creation of their names and likewise the interesting histories associated with the change in the area of medicinal usage after undergoing clinical trials. However, at this moment in time, we understand that we are crossing the borders of the possible size for one book, and this work cannot be completed by a reasonable deadline.

Therefore, with few alternative approaches, we decided on the proposed, realistic option of presenting the synthesis of various groups of drugs in basically the same manner in which they are traditionally presented in pharmacological curriculum. This was done with a very specific goal—to harmonize the chemical aspects with the pharmacological curriculum that is studied by future physicians and pharmacists.

Practically every chapter begins with a universally accepted definition of the drug, the present model of its activity, a brief description of every group, classification of the medications to be examined, and also with a description of specific syntheses, each of which relates to the usage of the given drug. Of the thousands of drugs in circulation on the pharmaceutical market, these are mainly medicinal drugs that are included under their generic names in the ‘Essential List of Drugs’ that is recommended by the World Health Organization (WHO).

For practically all of the 700+ drugs, which is more than twice the number of those on “The List”, references to the methods of synthesis (around 2350) are given along with the most widespread synonyms. However, in an attempt to avoid any misunderstanding, the names are given only as their basic generic names.

The largest chapter, Antibiotics, does not formally belong in the book under that name, but since the primary attention of this chapter is focused on the description of the synthetic portions of the derivation of semisynthetic antibiotics, we think that it should definitely be included in this book.

After the aforementioned reductions, the text was carefully streamlined into a specific form, using a very small vocabulary, namely the extremely limited set of phrases traditionally used

in describing syntheses of chemical compounds. It turned out to be practically impossible to present descriptions of the syntheses in more complexity than needed to describe the straightforward approach to their synthesis.

In any case, we earnestly hope that the 7 years spent in writing this book will provide the kind of information that will interest those who work or plan to begin work in this captivating area of biologically active compounds, the synthesis of medicinal drugs.

R.S. Vardanyan
V.J. Hruby

– 1 –

General Anesthetics

In surgical practice, the term general anesthesia (narcosis) presently refers to the condition of an organism with a reversible loss of consciousness at a controlled level of nervous system suppression. It includes the following components: analgesia (absence of pain), amnesia (absence of memory), suppression of reflexes such as bradycardia, laryngospasm, and loss of skeletal muscle tonicity.

In modern medical practice, general anesthesia is a complex procedure involving preanesthetic assessment, administration of general anesthetic drugs, cardiorespiratory monitoring, analgesia, airway management, and fluid management .

Accordingly, general anesthetics are drugs that provide relief of pain, weaken the reflex and muscle activity, and ultimately result in loss of consciousness. The ideal anesthetic must include the aforementioned characteristics, as well as to have a wide range of therapeutic index and to have no significant side effects. Drugs used in anesthesiology, block or suppress neurological impulses mediated by the central nervous system, and permit surgical, obstetric, and diagnostic procedures to be completed painlessly. General anesthetics are divided into two types—inhalation (halothane, enflurane, isoflurane, methoxyflurane, and nitrous oxide), and noninhalation, intravenous (barbiturates, ketamine, and etomidate).

1.1 INHALATION ANESTHETICS

The object of inhalation anesthetics is to obtain a concentration (partial pressure) of the drug in the brain sufficient to reach the desired level of anesthesia. In order to do this, anesthetic molecules must pass through the lungs into the brain through various biological phases. Therefore, inhalation anesthetics must be soluble in blood and interstitial tissue.

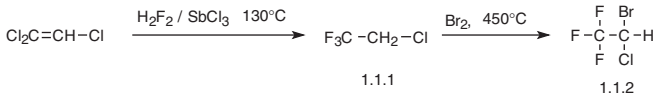
The wide variation in structure, ranging from complex steroids to the inert monatomic gas xenon, led to several theories of anesthetic action. The mechanism by which inhalation anesthetics manifest their effect is not exactly known. Since they do not belong to one chemical class of compounds, the correlations between structure and activity are also not known. Inhalation anesthetics are nonspecific and therefore there are not specific antagonists. Interaction of inhalation anesthetics with cellular structures can only be described as van der Waals interactions. There are a number of hypotheses that have been advanced to explain the action of inhalation anesthetics; however, none of them can adequately describe the entire spectrum of effects caused by inhalation anesthetics.

The action of general anesthetics can be explained as a blockage of ion channels, or as specific changes in mechanisms of the release of neurotransmitters. Three of the proposed mechanisms are mentioned below.

1. *Hydrate hypothesis:* Anesthetic molecules can form hydrates with structured water, which can stop brain function in corresponding areas. However, the correlation between the ability to form hydrates and the activity of inhalation anesthetics is not known.
2. *Ion channel hypothesis:* Anesthetics block ion channels by interacting with cellular membranes and reducing the flow of Na^+ ions and increasing the flow of K^+ ions into the cell, which leads to the development of anesthesia.
3. *Fluid membrane hypothesis:* Anesthetics stabilize, or rather immobilize the cell membrane, hampering membrane fluidity, which produces changes in the ion channel action.

Selection of a specific anesthetic or combination of anesthetics is made depending on the type of medical intervention. For a long time, ether, chloroform, tricholoroethylene, ethyl chloride or chloretane, and also cyclopropane were widely used as inhalation anesthetics. Today, the following anesthetics are used most regularly in medicine: halothane, enflurane, isoflurane, metoxyflurane, and nitrous oxide. Researchers are also actively exploring the use of xenon as an anesthetic.

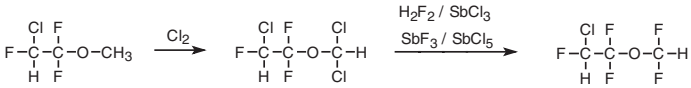
Halothane: Halothane, 2-bromo-2-chloro-1,1,1-trifluorethane (1.1.2), is made by the addition of hydrogen fluoride to tricholoroethylene and simultaneous substitution of chlorine atoms in the presence of antimony(III) chloride at 130 °C. The resulting 2-chloro-1,1,1-trifluorethane (1.1.1) undergoes further bromination at 450 °C to form halothane [1–3].



1.1.1 1.1.2

Halothane is a modern and widely used inhalation anesthetic. It begins to act very quickly, which is pleasing to patients, and it is very safe. The only drawback to using it is its hepatotoxicity. It is used in both short and long-lasting surgical operations. The most common synonym of halothane is fluothane.

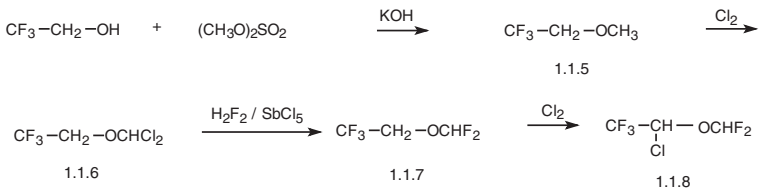
Enflurane: Enflurane, 2-chloro-1,1,2-trifluoroethyldifluoromethyl ether (1.1.4), is synthesized by chlorinating in light 2-chloro-1,1,2-trifluoroethylmethyl ether to give 2-chloro-1,1,2-trifluoroethyldichloromethyl ether (1.1.3), followed by substitution of chlorine atoms by fluorine on the dichloromethyl group using hydrogen fluoride in the presence of antimony(III) chloride, or by using antimony(III) fluoride with antimony(V) chloride [4,5].



1.1.3 1.1.4

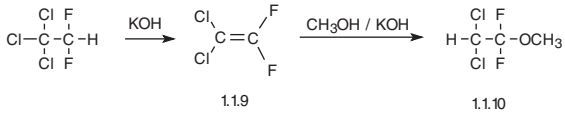
Enflurane has practically all the same characteristics as halothane and is used in the same situations. It is poorly absorbed. It is also prescribed under the name ethrane.

Isoflurane: Isoflurane, 2-chloro-2-(difluoromethoxy)-1,1,1-trifluorethane (1.1.8), is synthesized from 2,2,2-trifluoroethanol. 2,2,2-Trifluoroethanol is first methylated by dimethylsulfate. The resulting methyl ether (1.1.5) undergoes chlorination by molecular chlorine to give 2-(dichloromethoxy)-1,1,1-trifluoroethane (1.1.6). In the subsequent interaction (1.1.6) with hydrogen fluoride in the presence of antimony(V) chloride, chlorine atoms are ultimately replaced by fluorine atoms. The resulting ether (1.1.7) again undergoes chlorination by molecular chlorine to give isoflurane [6,7].



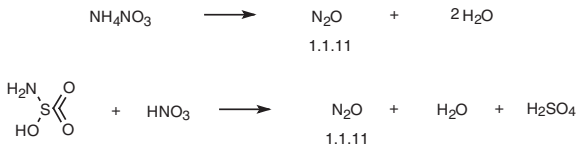
In terms of action, isoflurane is analogous to enflurane; however, it has a somewhat pungent odor which sometimes causes difficulties. Forane is a synonym of isoflurane.

Methoxyflurane: Methoxyflurane, 2,2-dichloro-1,1-difluoroethylmethyl ether (1.1.10), is synthesized from 1,1-difluoro-2,2,2-trichloroethane, which undergoes dehydrochlorination by potassium hydroxide to give 1,1-dichloro-2,2-difluoroethylene (1.1.9) to which methanol is added in the presence of potassium hydroxide [8].



Methoxyflurane is an extremely powerful inhalation anesthetic that is an excellent skeletal muscle relaxant. However, its use is somewhat limited by its relatively high solubility, which causes the patient to make a slow transition back into consciousness. Another disadvantage of methoxyflurane is that fluorine ions are the product of its biotransformation, which may lead to the development of renal failure. Therefore, it is recommended to use methoxyflurane for anesthesia during interventions of no more than 2 h. A very common synonym for methoxyflurane is penthrane.

Nitrous Oxide: Nitrous oxide (1.1.11) is synthesized either by the thermal decomposition of ammonium nitrate, or by the oxidation of sulfamic acid by nitric acid [9–11].



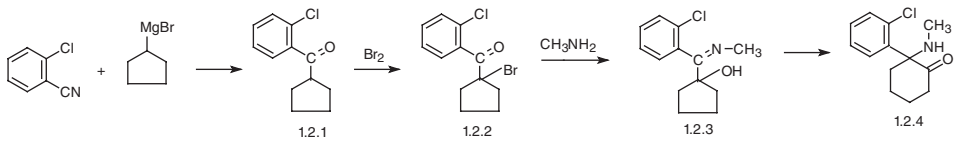
Nitrous oxide, which is also called laughing gas, is a weak anesthetic. It is usually used together with hypnotics, analgesics, and muscle relaxants. It is sometimes called an ideal anesthetic because of the absence of any kind of suppressive influence on respiration. However, according to the latest information, use of nitrous oxide for more than 2 h is counterproductive since it causes a severe reduction of methionine synthesis, which in turn can cause a severe decrease in the level of vitamin B_{12} with all its subsequent consequences.

1.2 NONINHALATION ANESTHETICS

In order to place a patient under narcosis in modern anesthesiology, multiple drugs are used both prior to using inhalation anesthetics and during the procedure. The compounds used (with a few special exceptions) are formally classified as noninhalation anesthetics and are representative of other pharmacological classes of compounds (analgesics, tranquilizers, neuroleptics, and others). It is worth mentioning that during noninhalation anesthesia, control and regulation during the procedure is significantly harder to accomplish that with inhalation anesthesia. However, the simplicity of intravenous anesthesia equipment and the various combinations (neuroleptanalgesia, ataragesia, tranquilizeresia) make the general anesthetic options extremely beneficial in clinical use.

For general anesthesia, ketamine and ethomidate are used as short-lasting, special drugs for noninhalation narcosis, as are a number of drugs that belong to completely different chemical classes, including: short-lasting barbiturates (thiopental, methohexital), opioid analgesics (morphine, fentanyl), and also a number of benzodiazepine tranquilizers (diazepam, lorazepam, and midazolam), which are drugs that refer in the given section, noninhalation anesthetics, despite the fact that formally they are not referred to them because they do not display all of the four characteristics that are unique to anesthetics by definition.

Ketamine: Ketamine, 2-(o-chlorophenyl)-2-(2-methylamino)cyclohexanone (1.2.4), is synthesized from 2-chlorobenzonitrile, which reacts with cyclopentylmagnesium bromide to give 1-(2-chlorobenzoyl)cyclopentane (1.2.1). The next step is bromination using bromine to the corresponding bromoketone (1.2.2), which upon interaction with an aqueous solution of methylamine forms the methylamino derivative (1.2.3). During this reaction a simultaneous hydrolysis of the tertiary bromine atom occurs. On further heating the reaction product in decaline, a ring expansion rearrangement occurs, causing formation of ketamine. Other possible mechanism of the transformation of the methylamino derivative (1.2.3) into the final product has also been suggested. One of them, in particular, suggested the formation of an epoxide intermediate; however, none of these proposed mechanisms can be regarded as completely proven [12,13].

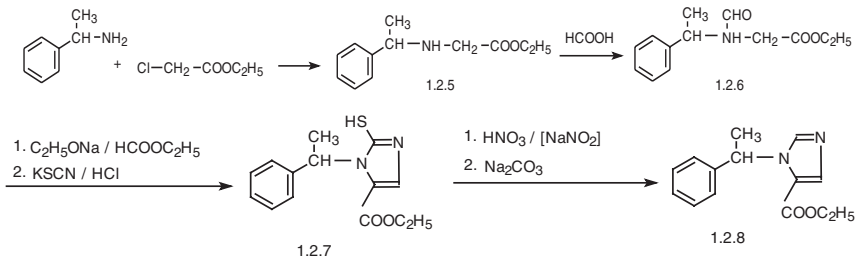


1.2.1 1.2.2 1.2.3 1.2.4

Ketamine is a specific drug for noninhalation narcosis that is used in brief surgical procedures. It causes a condition known as dissociative anesthesia, which ensures amnesia and analgesia, and preserves normal respiration and muscle tonicity in the patient. Ketamine is practically void of muscle relaxant capabilities.

Preanesthetic medications such as morphine, scopolamine, benzodiazepine, and butyrophenones lower dysphoric effects of ketamine. Synonyms for this drug are ketanest, ketalar, and others.

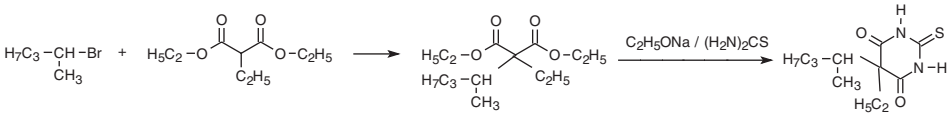
Etomidate: Etomidate, ethyl ester of 1-(α-methylbenzyl)imidazole-5-carboxylic acid (1.2.8), is prepared by the following procedure. It illustrates a special case of obtaining derivatives of imidazole by interaction of α-aminocarbonyl compounds with thiocyanates. The reaction of α-methylbenzylamine with ethyl chloroacetate gives *N*-ethoxycarbonylmethyl-*N*-1-phenylethylamine (1.2.5), which undergoes further formylation by formic acid. The resulting *N*-ethoxycarbonylmethyl-*N*-formyl-*N*-1-phenylethylamine (1.2.6) undergoes further C-formylation by ethylformate in the presence of sodium ethoxide. The product is further processed (without being isolated) by a solution of potassium thiocyanate in hydrochloric acid. As a result of the reaction of thiocyanate ions with the amino group which occurs as a result of acidic hydrolysis of the *N*-formamide protecting group and further interaction of the obtained intermediate with the newly inserted aldehyde group, a Marckwald reaction type heterocyclization takes place, resulting in formation of 5-ethoxycarbonyl-2-mercapto-1-(1-phenylethyl)imidazole (1.2.7). Finally, the thiol group is removed by oxidative dethionation upon interaction with a mixture of nitric and nitrous acids (nitric acid in the presence of sodium nitrite), which evidently occurs through formation of unstable sulfinic acid, which easily loses sulfur dioxide resulting the desired etomidate [14,15].



Etomidate is a derivative of imidazole that is structurally different than other anesthetics. It is a drug used for noninhalation narcosis, and the duration of its action depends on the administered dose. It does not display analgesic characteristics and it has an anticonvulsant activity. It can be classified as a sedative hypnotic drug because of the quick loss of consciousness upon intravenous administration. Due to its poor solubility in water at pH values higher than 3, it is used in clinical situations in a solution of propylene glycol, which causes pain during injection. Moreover, it causes post-operative nausea and vomiting, which somewhat limits its use. The speed by which it brings about loss and then restoration of consciousness is somewhat less than that of barbiturates. Synonyms of this drug are hypnomidate and others.

In surgical practice, two barbiturates are primarily used: thiopental and methohexital. However, it should be stated that barbiturates are hypnotics, and at therapeutic doses has a very weak analgesic and muscle relaxant effect, which general anesthetics must possess.

Thiopental: Thiopental, 5-ethyl-5-(1-methylbutyl)2-thiobarbituric acid (1.2.10), is synthesized by the alkylation of ethylmalonic ester with 2-bromopentane in the presence of sodium ethoxide. The product ethyl-(1-methylbutyl)malonic ester (1.2.9) undergoes heterocyclization with thiourea, using sodium ethoxide as a base [16,17].

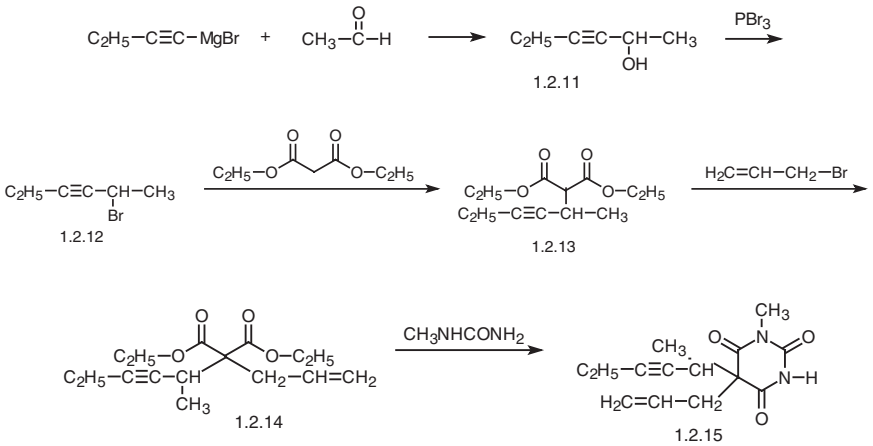


1.2.9 1.2.10

Thiopental is an extremely short-lasting barbiturate that makes anesthesia pleasant and smooth for the patient. When using the usual therapeutic doses, coming back into consciousness happens 15 min after administration. Thiopental has a straightforward dose-requiring oppressive effect on the myocardium, central nervous system, and to a lesser effect acts on the smooth muscle of blood vessels. It is used for narcosis in brief surgical operations.

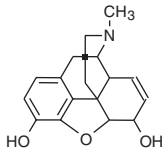
In general, barbiturates—thiopental in particular—change into soluble form on treatment with bases. Therefore, thiopental often appears in the market under the name sodium thiopental. In this case, the formation of a salt occurs due to the sulfur atom in an enethiolate form. The most common synonyms for thiopental are pentothal, trapanal, farmotal, intraval, and others.

Methohexital: Methohexital, (5-allyl-1-methyl-5-(1-methyl-2-pentinyl) barbituric acid) (1.2.15), is synthesized in the classic manner of making barbituric acid derivatives, in particular by the reaction of malonic ester derivatives with derivatives of urea. The resulting allyl-(1-methyl-2-pentynyl) malonic ester (1.2.14) is synthesized by subsequent alkylation of the malonic ester itself, beginning with 2-bromo-3-hexyne, which gives (1-methyl-2-pentynyl) malonic ester (1.2.13), and then by allylbromide. 2-Bromo-3-hexyne (1.2.12) is in turn synthesized from Normant's reagent, which is synthesized from 1-butyne and ethylmagnesium bromide and it is subsequent reaction with acetaldehyde followed by bromination of the resulting carbinol (1.2.11) using phosphorous tribromide. Interaction of obtained dialkyl malonic ester (1.2.14) prepared with N-methylurea, gives desired methohexital (1.2.15) [18].



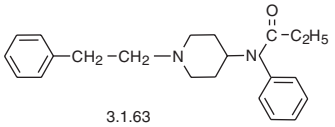
Methohexital is also an extremely short-lasting barbiturate, and it is used in same circumstances as is thiopental. It has a slightly shorter active time than thiopental; however, this difference is insignificant in clinical situations. Synonyms of methohexital are pentothal, intraval, farmotal, ravonal, and others.

As already mentioned, opioid analgesics, in particular morphine, fentanyl, alfentanil, and sufentanyl are widely used in the practice of anesthesiology as adjuncts.



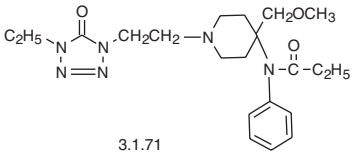
3.1.19

morphine



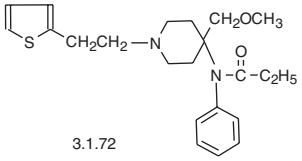
3.1.63

fentanyl



3.1.71

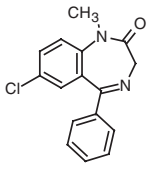
alfentanil



3.1.72

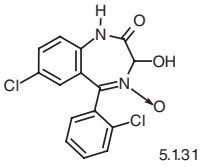
sufentanyl

The synthesis of these compounds will be described in Section 3.1, Opioid analgesics. Besides opioids, benzodiazepines (diazepam, lorazepam, and midazolam), which have anxiolytic, sedative, and anticonvulsant effects, that cause amnesia and muscle relaxation, are frequently used to relieve patients' anxiety during anesthesia.



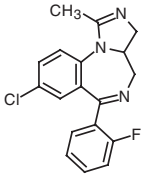
5.1.2

diazepam



5.1.31

lorazepam



midazolam

Synthesis of the first two is described in Section 5.1 of Chapter 5. Benzodiazepines are described in the same place where the synthesis of structural analogs of midazolam (alprazolam, etc.) are described.

Since general anesthetics are related to a variety of classes of chemical compounds, there is no general pattern that exists between their chemical structure and their activity. Particular patterns only exist for different groups of compounds (barbiturates, benzodiazepines, etc.).

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– 2 –

Local Anesthetics

Local anesthetics are medications used for the purpose of temporary and reversible elimination of painful feelings in specific areas of the body by blocking transmission of nerve fiber impulses. Local anesthesia is any technique to render part of the body insensitive to pain without affecting consciousness. In clinical situations, local anesthetics are used in many different ways and in various situations requiring local pain relief, beginning with simple procedures such as removing a small piece of the outer layer of damaged skin to complicated operations such as organ transplants. Local anesthetics are widely used in clinical use for pain relief in situations ranging from dental procedures to gynecological interventions. In therapeutic concentrations, local anesthetics reversibly block nerve transmission, cause local loss of feeling while relieving local pain and preventing muscle activity in the process.

These drugs, unlike general anesthetics, cause a loss of feeling in specific areas while keeping the patient conscious.

Local anesthetics are used for pain relief, soreness, itching, and irritation associated with disturbance of the integrity of the skin and mucous membranes (cuts, bites, wounds, rashes, allergic conditions, fungal infections, skin sores, and cracking).

They are used during opthalmological procedures such as tonometry, gonioscopy, removal of foreign bodies, and during minor surgical interventions. Local anesthetics are widely used in surgery, gynecology, and dentistry. In certain cases, local anesthetics (lidocaine, procainamide) can be used as antiarrhythmic drugs.

Local anesthetics can be classified according to the principal means of their clinical use, as well as how they fit into specific chemical classes of compounds.

From the medical point of view, local anesthetics can be differentiated by their method of clinical use in the following manner:

Topical anesthesia: Local use of drugs of this kind on the mucous membranes of the nose, mouth, larynx, tracheobrachial tree, eyes, urinary tract, and gastrointestinal tract causes superficial anesthesia.

Drugs such as benzocaine, cyclomethycaine, hexylcaine, cocaine, lidocaine, and tetracaine are primarily used for this purpose.

Infiltration anesthesia: The direct introduction of local anesthetic into the skin or deeper tissue for surgical intervention is called infiltration anesthesia.

Drugs such as lidocaine, mepivacaine, bupivacaine, ethidocaine, and procaine are primarily used for this purpose.

Block or regional anesthesia: The introduction of local anesthetic into an individual nerve or group of nerves during minor surgical interventions with the purpose of blocking the feeling and motor action is frequently called block or regional anesthesia. This method is often used during surgical intervention of the shoulder, arm, neck, or leg. Lidocaine, mepivacaine, and bupivacaine are most often used for this purpose.

Spinal anesthesia: Spinal anesthesia is the introduction of local anesthetics directly into the spinal fluid, which causes a sympathetic blockage, or loss of feeling as well as muscle relaxation resulting from the interaction of anesthetic with every spinal nerve tract. This method is used during major surgical interventions. As a rule, lidocaine, mepivacaine, and bupivacaine are used for this purpose.

Epidural anesthesia: This term is understood to be an introduction of local anesthetic into the spinal cord membrane of the intervertebral space. It is used during obstetrical and gynecological interventions that do not require a fast development of anesthesia. Drugs such as lidocaine, mepivacaine, bupivacaine, ethidocaine, and chloroprocaine are used for this purpose.

The alkaloid cocaine was first used in 1884 as a local anesthetic in a clinical opthalmological intervention. Today, due to the danger of drug addiction and high toxicity, its use is severely limited. However, by determining its structure, experimenting with its synthesis, attempting to deduct its structural activity profile, and simplifying the proposed pharmacophore areas of the molecule, one of the most powerful stimuli for the development of the chemistry of synthetic drugs was discovered. The most recent synthetic local anesthetic drug appeared in clinical practice in 1905. Later on there were thousands of compounds with analogous properties; however, only about 10–12 of those compounds were used in practice. In 1947, lidocaine was introduced, and bupivacaine, a long-lasting local anesthetic, followed in 1963.

As agents blocking conductivity in axons and dendrites, local anesthetics differ from the compounds that block neuron transmission in synapses.

A mechanism of local anesthetic action in which they serve as sodium channel blockers has been proposed. According to this mechanism, the molecular targets of local anesthetic action are the voltage-requiring sodium channels, which are present in all the neurons. The process of local anesthesia by respective drugs can be schematically represented in the following manner.

In a resting condition, there is a specific rest potential between the axoplasm and the inner parts of the cell. This rest potential is maintained by relative concentration of sodium and potassium ions along the membrane of the nerve. During nerve stimulation, the membrane is depolarized and sodium channels in that area are opened, allowing sodium ions to rush into the cell. At the peak of depolarization potassium channels are opened. The last ones leave the cell and the cell is repolarized.

This process lasts 1–2 msec, after which the nerve cell, having transmitted the necessary impulse, restores its ion gradient.

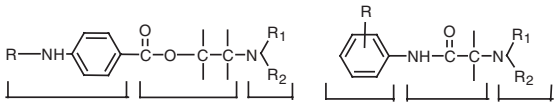
It is believed that after introduction of local anesthetic into the organism in the form of a water-soluble salt, equilibrium is established between the neutral and cationic forms of the used drug depending on the pKa of the drug and the pH of the interstitial fluid. It is also believed that only the uncharged (neutral) drug form can pass through—it passes through connective tissue surrounding the nerve fiber and through the phospholipid plasma membrane into the axoplasm. In the axoplasm, the base is once again ionized until it reaches an appropriate value determined by intracellular pH.

It is suspected that these drugs selectively bind with the intracellular surface of sodium channels and block the entrance of sodium ions into the cell. This leads to stoppage of the depolarization process, which is necessary for the diffusion of action potentials, elevation of the threshold of electric nerve stimulation, and thus the elimination of pain. Since the binding process of anesthetics to ion channels is reversible, the drug diffuses into the vascular system where it is metabolized, and nerve cell function is completely restored.

The mechanism of benzocaine action differs slightly from that mentioned above. It presumably acts by diffusing across the phospholipid membrane and then stretching it out. This deforms the sodium channels, which in turn, and in a unique manner, lowers sodium conduction.

An analogous mechanism of stretching (changing the fluidity) of the membrane was also suggested as an explanation for the action mechanism of general anesthetics.

From the chemical point of view, general anesthetics can be classified as esters of *n*-aminobenzoic acid and dialkylaminoalkanols, or as anilides of *N*,*N*-dialkyl substituted α-aminoacids.

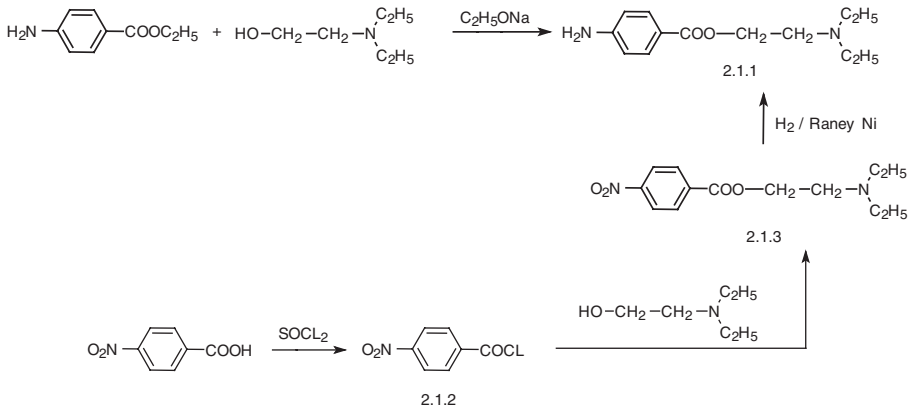


Upon formal examination, all of the commonly used anesthetics are made up of three parts: an aromatic ring (lipophilic region), an intermediate hydrocarbon chain, and an amine region (hydrophilic group). A substitution in the aromatic ring and in the amine region changes both the solubility and the extent of binding of anesthetics to the receptors, which in turn determines the strength and duration of the action of the drugs. It is an accepted belief that the ability to cause allergic reactions, stability, and in a number of cases, toxicity, is determined by the structure of the connecting chain, which also determines the site of biotransformation and inactivation of the drug: either by fermentative hydrolysis in the plasma (ester anesthetics), or decomposition in the liver (aminoamide anesthetics).

It is interesting that a number of antihistamine, anticholinergic, and adrenergenic drugs having analogous chemical structures, also exhibit local anesthetic properties. It is possible that by interacting with internal axoplasmic membranes, they reduce the ion flow; in particular, the flow of sodium ions inside nerve cells.

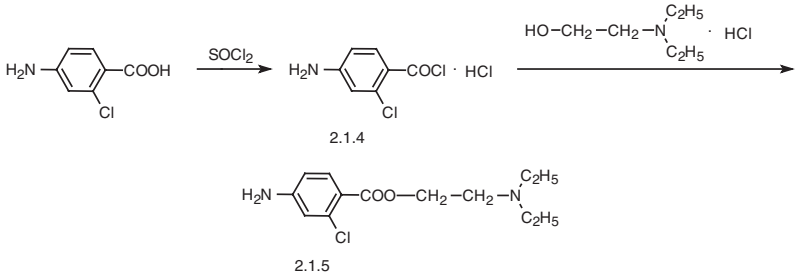
2.1 LOCAL ANESTHETICS OF THE AMINOETHER SERIES

Procaine: Procaine, the 2-diethylaminoethyl ester of 4-aminobenzoic acid (2.1.1), better known as novocaine, is synthesized in two ways. The first way consists of the direct reaction of the 4-aminobenzoic acid ethyl ester with 2-diethylaminoethanol in the presence of sodium ethoxide. The second way of synthesis is by reacting 4-nitrobenzoic acid with thionyl chloride, which gives the acid chloride (2.1.2), which is then esterified with *N*,*N*-diethylaminoethanol. Subsequent reduction of the nitro group by hydrogenation of the resulting ester (2.1.3) into an amino group takes place in the presence of Raney nickel [1–4].



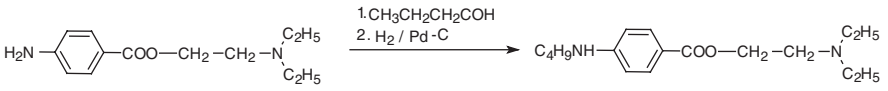
Procaine is a short-acting local anesthetic. It is used for reducing painful symptoms of various types, and it is widely used in infiltration, block, epidural, and spinal cord anesthesia, and for potentiating activity of basic drugs during general anesthesia. It may cause allergic reactions. The most common synonyms of procaine are novocaine, adrocaine, impletol, and melkaine.

Chloroprocaine: Chloroprocaine, the 2-diethylaminoethyl ester of 2-chloro-4-aminobenzoic acid (2.1.5), is the ortho-chlorinated (in relation to the carbonyl group of the benzene ring) analog of procaine. Synthesis of this drug is accomplished by directly reacting the hydrochloride of the 4-amino-2-chlorbenzoic acid chloride (2.1.4) with hydrochloride of diethylaminoethanol. The hydrochloride of 4-amino-2-chlorbenzoic acid chloride needed for synthesis is synthesized by reacting 2-chloro-4-aminobenzoic acid with thionyl chloride [5].



Chloroprocaine is used in situations requiring fast-acting pain relief. It is also used in infiltration anesthesia, blocking peripheral nerve transmission, and in spinal and epidural anesthesia. Nesacaine is a synonym for chloroprocaine.

Tetracaine: Tetracaine, the 2-diethylaminoethyl ester of 4-butylaminobenzoic acid (2.1.6), is also structurally analogous to procaine, in which the amino group of the benzene ring is replaced by a butylamine radical. The methods for its synthesis are the same as the above-mentioned methods for procaine or chloroprocaine, with the exception of using 4-butylaminobenzoic acid in place of 4-aminobenzoic acid. There is also a proposed method of synthesis that comes directly from procaine (2.1.1). It consists on its direct reaction with butyric aldehyde and simultaneous reduction by hydrogen using a palladium on carbon catalyst [6].



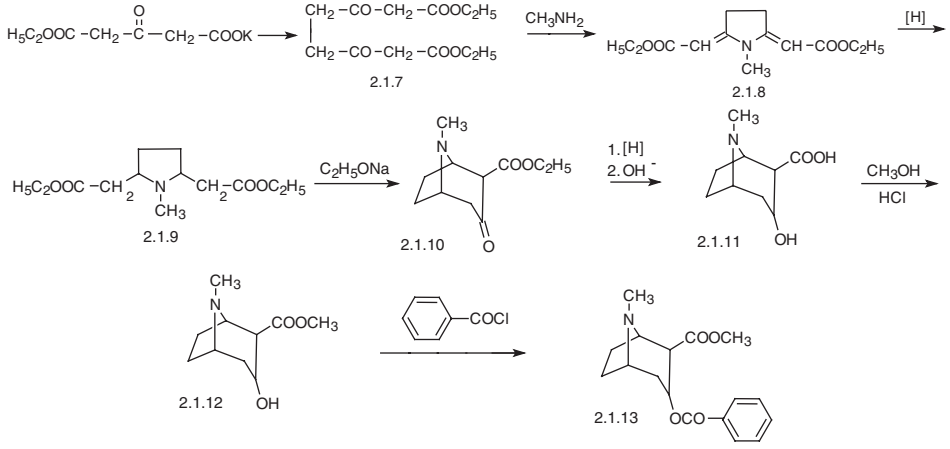
2.1.6

Tetracaine is a strong, long-lasting local anesthetic. It is primarily used in spinal cord anesthesia. The most well-known synonyms of tetracaine are pontocaine and butylcaine.

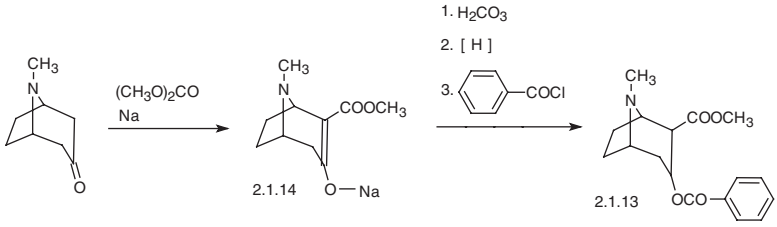
Cocaine: Cocaine, 3-β-benzoyloxy-2β-(2.1.13) can be considered the practical, and in a certain sense, the ideological ancestor of anesthetics of the aminoester series. The alkaloid cocaine was isolated in 1860 from leaves of the cocaine shrub (Erthroxylon coca), which contains various alkaloids that are ecogonic derivatives (2.1.11), of which cocaine makes up a significant portion. Its structure was established in 1898. The main part of obtaining cocaine is synthesized in a semisynthetic manner. By saponification of a number of alkaloids extracting from coca leaves, ecogonin is obtained (2.1.11), carboxylic group of which is methylated which gives the methyl ester of ecogonin (2.1.12). The hydroxyl group of the obtained product is further benzoylated, which gives cocaine (2.1.13). The process of these conversions corresponds with the final part of the first scheme of cocaine synthesis.

The first synthesis of cocaine was proposed in 1902. The two subsequent schemes could be considered the most rational of the proposed choices for cocaine synthesis. The first figure shows the cocaine synthesis which starts from the potassium salt of the acetonedicarbonic acid ethyl ester, which upon electrolysis gives the diethyl ester of succinyldiacetic acid (2.1.7), which upon further reaction with methylamine forms 1-methyl-2,5-dicarbethoxymethyldenepyrrolidin (2.1.8). Reduction of the two double bonds in this compound leads to the formation of 1-methyl-2,5-dicarboethoxymethylpyrrolidine (2.1.9). This undergoes intermolecular Dieckman cyclization using sodium ethoxide as a condensing agent, which gives the ethyl ester of tropin-2-carboxylic acid (2.1.10). Reduction of the keto group and final hydrolysis of the carboethoxy group gives tropin-2-carboxylic acid, or ecogonin (2.1.11). Methylation of the carboxyl group to an ester (2.1.12) and further esterification of the hydroxyl group by benzoyl chloride leads to a racemic mixture of 3-benzoyl-2-methoxycarbonyltropane (2.1.3), from which D,L-cocaine was isolated. The separation of optical isomers is accomplished through the transformation to D-bromocamphor-β-sulfonic

acid salts; however, upon hydrolysis both the bromocamphorsulfonic and the benzoyl groups detach, after which a repetitive benzoylation is performed [7].



According to the next scheme, synthesis of cocaine starts from tropanone, which undergoes methoxycarbonylation with dimethylcarbonate in the presence of sodium, forming the sodium salt (2.1.14), which after the cautious acidic hydrolysis and reduction of the carbonyl group of the resulting ketoester (by sodium amalgam or electrolytically) is esterified by benzoylchloride, giving the desired product [8].

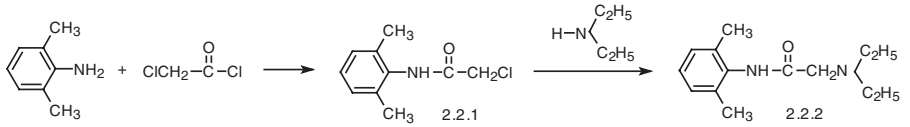


As in the previous example, the final product is a racemate from which the levorotary isomer is isolated. Other methods of synthesis were suggested later on [9,10].

Cocaine is only used in exceptional cases as a topical anesthetic in ophthalmology due to the fast onset of addiction and its powerful effect on the CNS.

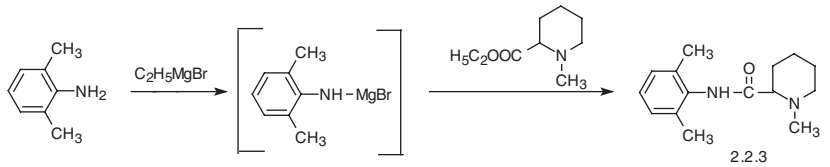
2.2 LOCAL ANESTHETICS OF THE AMINOAMIDE SERIES

Lidocaine: Lidocaine, 2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide (2.2.2), is synthesized from 2,6-dimethylaniline upon reaction with chloroacetic acid chloride, which gives α-chloro-2,6-dimethylacetanilide (2.1.1), and its subsequent reaction with diethylamine [11].



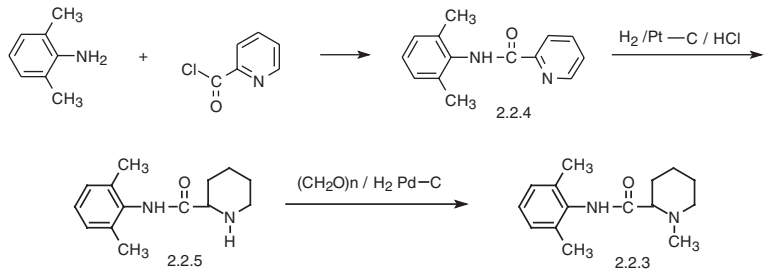
Lidocaine is the most widely used local anesthetic. Its excellent therapeutic activity is fast-acting and lasts sufficiently long to make it suitable for practically any clinical use. It stabilizes cell membranes, blocks sodium channels, facilitates the secretion of potassium ions out of the cell, and speeds up the repolarization process in the cell membrane. It is used for terminal infiltration, block, epidural, and spinal anesthesia during operational interventions in dentistry, otolaryngology, obstetrics, and gynecology. It is also used for premature ventricular extrasystole and tachycardia, especially in the acute phase of cardiac infarction. Synonyms for this drug are xylocaine, neflurane, and many others.

Mepivacaine: Mepivacaine is *N*-(2,6-dimethylphenyl)-1-methyl-2-piperindincarboxamide (2.2.3). Two primary methods of synthesis have been suggested. According to the first, mepivacaine is synthesized by reacting the ethyl ester of 1-methylpiperindine-2-carboxylic acid with 2,6-dimethylanilinomagnesium bromide, which is synthesized from 2,6-dimethylaniline and ethylmagnesium bromide [12–14].



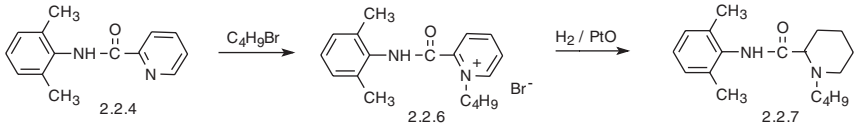
According to the figure below, reacting 2,6-dimethylaniline with the acid chloride of pyridine-carboxylic acid first gives the 2,6-xylidide of α-picolinic acid (2.2.4). Then the aromatic pyridine ring is reduced to piperidine by hydrogen in the presence of a platinum on carbon catalyst.

The resulting 2,6-xylidide α-pipecolinic acid (2.2.5) is methylated to mepivacaine using formaldehyde with simultaneous reduction by hydrogen in the presence of platinum on carbon catalyst [15].

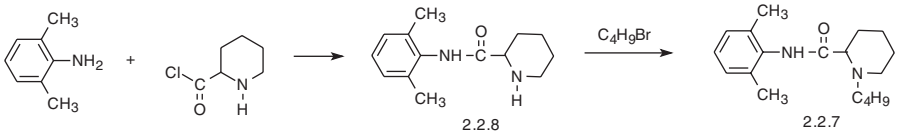


Mepivacaine is similar to lidocaine in terms of properties; however, it has longer lasting effects. Synonyms of mepivacaine are carbocaine and estradurin.

Bupivacaine: Bupivacaine, *N*-2,6-(dimethyl)1-butyl-2-piperidincarboxamide (2.2.7), is chemically similar to mepivacaine and only differs in the replacement of the *N*-methyl substituent on the piperidine ring with an *N*-butyl substituent. There are also two suggested methods of synthesis. The first comes from α-picolin-2,6-xylidide (2.2.4). The alkylation of the last with butyl bromide gives the corresponding pyridine salt (2.2.6). Finally, it is reduced by hydrogen using platinum oxide as a catalyst into a piperidine derivative—bupivacaine [13,16].

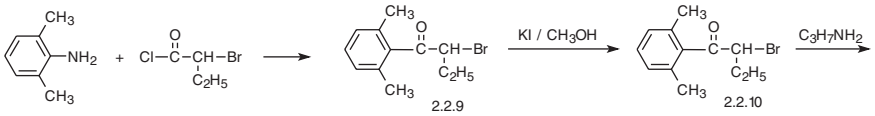


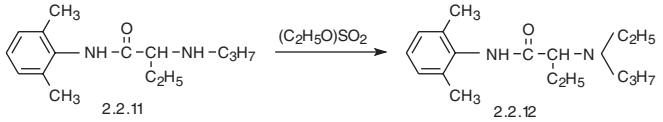
The other method results directly from the piperidine-2-carboxylic acid chloride, which is reacted with 2,6-dimethylaniline. The resulting amide (2.2.8) is further alkylated with butyl bromide to bupivacaine [17–19].



Like lidocaine and mepivacaine, bupivacaine is used in infiltration, spinal, and epidural anesthesia in blocking nerve transmission. Its most distinctive property is its long-lasting action. It is used for surgical intervention in urology and in lower thoracic surgery from 3 to 5 h in length, and in abdominal surgery lasting from 45 to 60 min. It is used to block the trifacial nerve, the sacral and brachial plexuses, in resetting dislocations, in epidural anesthesia, and during Cesarian sections. The most common synonym for bupivacaine is marcaine.

Ethidocaine: Ethidocaine, *N*-(2,6-dimethylphenyl)-2-(ethylpropylamino)butanamide (2.2.12), is also an anilide of α-dialkylaminoacid; however, the sequence of reactions for its formation differs somewhat from those examined above. In the first stage of synthesis, 2,6-dimethylaniline is reacted with α-bromobutyric acid chloride to give the bromoanilide (2.2.9). Next, in order to increase the yield of the final product a substitution of bromine atom for an iodine atom had been done. The resulting iodine derivative (2.2.10) easily reacts with propylamine, forming aminoamide (2.2.11), which undergoes further *N*-ethylation using diethylsulfate to give ethidocaine [20,21].

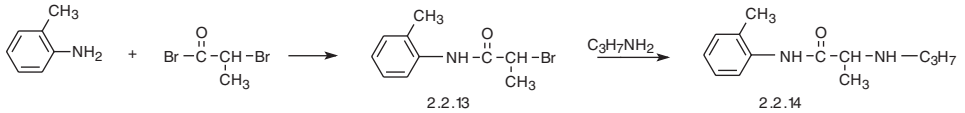




2.2.11 2.2.12

Ethidocaine is similar to mepivacaine in terms of its pharmacological properties; however, it possesses muscle relaxant properties to some extent. Synonyms for this drug are duranest and others.

Prilocaine: Prilocaine, 2-(propylamino)-o-propiontoluidine (2.2.14), is structurally related to the exact same group as ethidocaine, yet it differs structurally in that during synthesis, o-toluidine is used instead of 2,6-dimethylaniline, and instead of a butyric acid, a fragment of propionic acid, and a terminal propylethylamine group is replaced with a propylamine group. In order to synthesize prilocaine, o-toluidine is reacted with bromopropionyl bromide, and the resulting bromopropionyltoluidide (2.2.13) is then reacted with propylamine, which gives prilocaine [22,23].

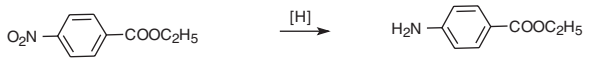


2.2.13 2.2.14

In terms of pharmacological parameters, prilocaine is comparable to lidocaine; however, because of a number of toxic manifestations, it is rarely used in medical practice. Citanest and xylonest are well-known synonyms for prilocaine.

2.3 TOPICAL ANESTHETICS

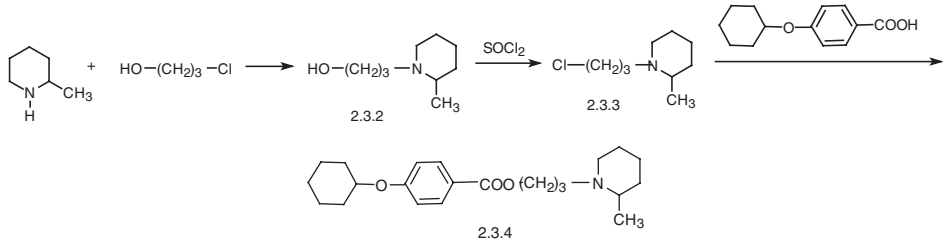
Benzocaine: Benzocaine is the ethyl ester of 4-aminobenzoic acid (2.3.1). The classic, optimal way of benzocaine synthesis is the reduction of the nitro group of the ethyl ester of 4-nitrobenzoic acid to benzocaine by hydrogen, which generates directly in the reaction medium by the reaction of iron filings with dilute acids [24–26].



2.3.1

Benzocaine is used in topical anesthesia on the skin and mucous membranes in the form of aerosols, or as creams for reduction of pain caused by itching, cuts, bites, etc. It begins to work 15–30 sec after application and lasts 12–15 min. It is also used under the names anestezin, dermoplast, and others.

Cyclomethycaine: Cyclomethycaine, the ethyl ester of 3-(2-methylpiperidino)propyl-*o*-cyclohexyloxybenzoic acid (2.3.4), is synthesized according to the figure below. Alkylation of 2-methylpiperidine with 3-chlorpropanol-1 gives 3-(2-methylpiperidino)propanol-1 (2.3.2), whose hydroxyl group is substituted by chlorine using thionyl chloride. The resulting 3-(2-methylpiperidino)propylchloride-1 (2.3.3) is further reacted with 4-cyclohexyloxybenzoic acid, which gives cyclomethycaine [27,28].



Cyclomethycaine is also used in topical anesthesia on the skin or mucous membranes for cuts, bites, and also for urological examinations. A common synonym of this drug is surfacaine.

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– 3 –

Analgesics

Analgesics are drugs that eliminate or alleviate the feeling of pain that accompanies many pathologic conditions. It is difficult to list all the situations in which it is necessary to use analgesics. Situations include, for example, muscle aches and headaches (for which aspirin-like analgesics are usually used), and where there is no possibility of becoming addicted. More intense pain originating during and after surgical intervention is relieved by utilizing opioid analgesics, such as morphine and meperidine. Unfortunately, even extremely short use of these analgesics can lead to habitual use, development of drug dependence, and tolerance. For chronic pain associated with chronic inflammatory reactions (rheumatoid arthritis, etc.), patients can use nonsteroidal, anti-inflammatory analgesics for years, though their pain modulatory effects vary greatly.

Pain is a very important protective phenomenon that accompanies many pathological conditions. However, in fulfilling its function of signaling, it can, upon excessive intensity, in turn aggravate the course of the primary disease, and in some cases such as severe trauma can facilitate the development of shock.

The problem of alleviating painful sensations is as old as mankind itself. It can probably be said with a fair degree of confidence that the isolation of morphine, the oldest of the known pain-relieving drugs, from opioid plants in the 19th century served as the initiation for the intensive development of the chemistry, pharmacology, and pharmacy.

Analgesics are divided into two groups: opioids (morphine-like substances), which predominantly influence the central nervous system (CNS) and nonopioids (nonsteroidal anti-inflammatory or fever-reducing drugs—NSAID), which act predominantly on the peripheral nervous system.

Opioid and nonopioid analgesics differ in many ways, making it useful to distinguish them by the following: opioids are the strongest analgesics; however, they do not possess anti-inflammatory capabilities. Opioids can cause dependence and tolerance, and therefore their use should be short term. In addition, nonopioid analgesics are rarely used in the form of injections.

Despite the fact that drugs of both groups relieve pain, their pharmacological actions are different, which is why they are examined separately.

3.1 OPIOID ANALGESICS

Opioids are subdivided into three large subgroups according to their action on opioid receptors: agonists, mixed agonists–antagonists, and antagonists. *Opioid agonists* have an affinity for opioid receptors, imitating the activity of endogenous opioid analgesics. *Mixed agonists–antagonists* can be semisynthetic derivatives of morphine or peptide analogs of endogenous opioids that display agonistic activity at some opioid receptors and antagonistic activity in others. *Opioid antagonists* bind to opioid receptors but do not activate them. These compounds are not used for analgesia. Their therapeutic value is in relieving side effects that result from either absolute of relative overdoses or intolerance of drugs by patients, and also in treating cases of opioid dependency.

Agonists include natural alkaloids of opium (morphine, codeine, and a large blend of natural alkaloids, pantopon, and omnopon), their analogs (hydrocodon and hydromorphone, oxycodone, and oxymorphone), derivatives of morphinane (levorphanol), and a number of synthetic compounds: derivatives of phenylpiperidine (meperidine, promedol), 4-anilidopiperidines (fentanyl, sufentanyl, alfentanil), and derivatives of diphenylheptane (methadone, propoxyphene).

The mixture of agonists–antagonists includes derivatives of morphinane (nalorphine, butorphanol), phenanthrene (nalbuphine), derivatives of benzomorphane (pentazocine, dezocine), and derivatives of opipravin (buprenorphine).

At last, naloxone and naltrexone are antagonists.

It is universally accepted that the action of opioids is mediated by specific receptors. It is presumed that several types of opioid receptors exist: μ, κ, δ, and σ. A few of these are in turn subdivided into subtypes. It has been found that opioid receptors are seven transmembrane G-protein-coupled receptors that are localized in the membranous part of the synaptosomal head; it has also been found that they are glycoproteins. They are prone to conformational changes in certain situations, which is essential for their selective binding with agonists or antagonists.

Opioids have various chemical structures, and their relative analgesic potential depends on several different factors, including their affinity to specific binding sites on receptors, activity on the receptors themselves, and distinctive pharmacokinetic properties.

Various types of opioid receptors have been postulated solely for explaining the different actions of opioids.

Receptors that cause reactions in the organism that are analogous to the reactions upon introduction of morphine (suppression of respiration, myosis, disorders of the gastrointestinal tract, euphoria) have been named μ-receptors. Receptors that cause effects analogous to those caused by ketazocine (analgesia, sedative effects, myosis) have been named κ-receptors. Analgesic receptors that also cause psychotomimetic reactions (hallucination dysphoria, stimulation of respiratory and cardiovascular system, mydriasis) are characteristic of those included in the class of the agonist–antagonists of the type of *N*-allylnormethazocine named σ-receptors. Receptors that react to the action of enkephalins and that cause analgesia and release of growth hormone have been named δ-receptors.

Despite the numerous studies that confirm the fact that influence on different receptors causes various effects, their exact nature and role require considerably more study.

The physiological role of the endogenous opioid system is not limited to pain and analgesia. It unambiguously plays a role in the regulation of the endocrine, behavioral,

thermoregulating, immunological, and gastrointestinal systems as well as taking part in the development of mechanisms of addiction and dependence on opioids. It is possible that endogenous opioids may be able to react with many other neurotransmitter systems.

The concept that opioids cause analgesia in response to reaction with certain receptors was suggested many years ago; however, until 1973 specific opioid-binding sites had not been identified, as receptors and their distribution had not been specified. The distribution frequency of opioid-binding sites varies significantly in different regions of the CNS; it is especially high in brain structures associated with physiological functions connected to opioid use, which indicates a correlation between the binding site and the effect. Opiate receptors are found outside the CNS, in particular in the vagus and the gastrointestinal tract.

Neurochemical data indicate that opioid receptors in the brain are associated with presynaptic structures, thus functioning by reducing neurotransmitter secretion.

It is believed that the reaction of agonists with opioid μ-receptors leads to an increase in the flow of potassium ions from the cell, simultaneously making it difficult for calcium ions to flow into the cell, which makes neurons less excitable. κ-Receptor agonists directly inhibit entrance of calcium ions into neurons by simply reducing their flow through voltage-gated calcium channels. These data are supported by facts indicating that heightened calcium ion concentrations weaken the effect of morphine, while reduced levels strengthen the effect. The action of morphine upon appreciation of pain differs from the action of local anesthetics. Local anesthetics reduce and weaken appreciation of pain by hampering transmission of signals from the source of pain. Opioids barely influence the axonal conduction; rather they block interneuronal transmission of pain impulses at different levels of CNS integration.

Endogenous oligopeptides that bind with parts of opioid receptors and act analogous to opioids were observed in the brain and other tissues. The first of these to be isolated and decoded were met- and leu-enkephalin. β-Endorphin, a peptide with quite a large molecular mass and with analogous action, was found produced in pituitary gland.

Another peptide called dynorphin was identified later on. Many other various functions including taking part in neurotransmission are ascribed to endogenous opioid peptides; however, their mechanism of opioid action as with nonpeptides is still unclear.

Opioids cause side effects that limits their use. They include respiratory depression, nausea, vomiting, constipation, a heightened level of blood pressure, urine retention, perspiration, and itching; of course, the most dangerous of these is respiratory depression. Opioids cause dependency and addiction.

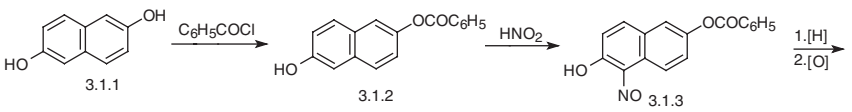
3.1.1 Agonists

The most widely used agonists in medical practice are the opium alkaloids morphine and codeine. However, semisynthetic derivatives (hydromorphone, oxymorphone, hydrycodon, oxycodone), whose use is even preferred in certain cases, and strong, purely synthetic compounds (methadone, meperidin, fentanyl, sufentanyl, and others) have found wide use.

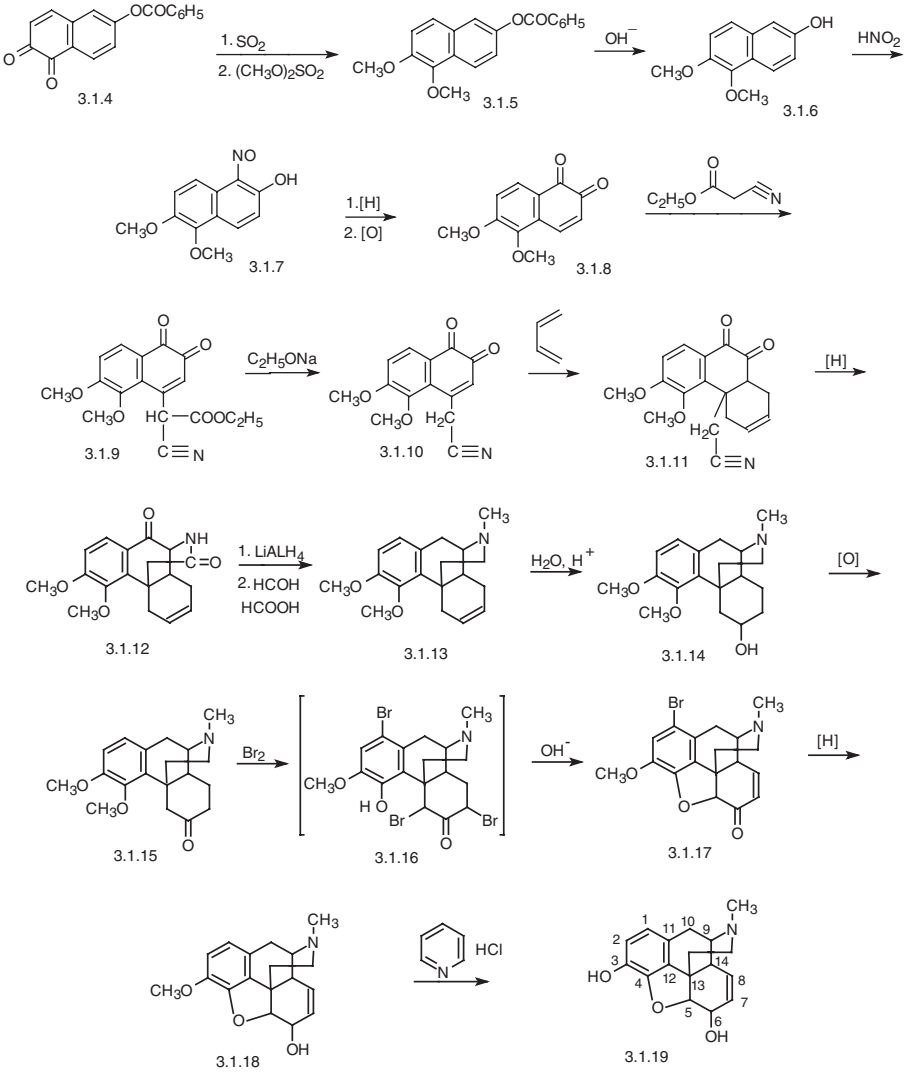
Opioid agonists act first and foremost on μ-receptors. It is essential to know that use of compounds of this class should be avoided in the event of cranial trauma, bronchial asthma and other hypoxic conditions, severe alcohol intoxication, convulsive conditions, and severe pain of organs in the abdominal cavity.

Morphine: Morphine, 4,5-epoxy-17-methymorphin-7-ene-3,6-diol (3.1.19), is the oldest and most well-known analgesic. It is made from opium—the dried, milky sap of unripe opium poppy bulbs, whose analgesic properties have been known for over 3000 years. This plant also contains a large number of other alkaloids that are subdivided into groups of phenanthrenes and benzylisoquinoline. However, ways of making synthetic morphine have also been proposed. One of the proposed, exquisite, multi-phase methods of morphine synthesis is described below.

In the proposed method, morphine is synthesized starting from 2,6-dioxynaphthelene (3.1.1), which upon reaction with benzoyl chloride transforms into monobenzoate (3.1.2), and upon further reaction with nitrous acid is converted into 1-nitroso compound (3.1.3). Next, hydrogenation of the nitroso group using a palladium catalyst and further soft oxidation of the product by iron trichloride gives 6-benzoyloxy-1,2-naphthoquinone (3.1.4). Using sulfur dioxide, it is reduced to 6-benzoyloxy-1,2,-naphthohydroquinone, which is methylated by dimethylsulfate to give 5,6-dimethoxy-2-benzoate (3.1.5). Further, alkaline hydrolysis transforms it into 5,6-dimethoxy-2-naphthol (3.1.6). Using the same successive stages of synthesis, namely nitrozation, reduction and oxidation (by the same reagents) gives 5,6-dimethoxy-1,2-napthoquinone (3.1.8). The last is condensed with ethyl cyanoacetate in Knoevenagel reaction conditions, but in the presence of potassium ferrocyanide, due to which oxidation of the condensation product is carried out. The resulting product (3.1.9) is hydrolyzed and further decarboxylated into 5,6-dimethoxy-4-cyanomethyl-1,2-naphthoquinone (3.1.10), on the basis of which formation of phenanthrene, and later the subsequent morphinan systems takes place. In order to do that, 5,6-dimethoxy-4-cyanomethyl-1,2-naphthoquinone (3.1.10) is reacted in 4+2 cycloaddition reaction with 1,3-butadiene, to give a moderate yield of 3,4-dimethoxy-9,10-dioxy-13-cyanomethyl-5,8,9,10,13,14-hexahydrophenanthrene (3.1.11). Hydrogenation of the resulting diketone (3.1.11) using a copper chromite catalyst gives ketolactam (3.1.12). Upon treating the resulting product with lithium aluminum hydride, the carbonyl groups, both ketone and amide, undergo an exhaustive reduction, and in addition the secondary nitrogen atom is methylated by a mixture of formaldehyde and formic acid to give racemic methyl ester β-Δ^6-dihydrodesoxycodeine (3.1.13). Treating the resulting product with L(+)-dibenzoyltartaric acid gives the (+) methyl ester of β-Δ^6-dihydrodesoxycodeine. This undergoes hydration in the presence of hot, dilute sulfuric acid, to give the methyl ester of β-dihydrothebainol (3.1.14). Upon vigorous treatment with potassium hydroxide in diethyleneglycol, partial demethylation to β-dihydrothebainol occurs the oxidation of which in potassium *tert*-butylate/benzophenone system gives β-dihydrothebainone (3.1.15). The β-dihydrothebainone (3.1.15) made in this manner undergoes further bromination by 3 mol of bromine in acetic acid into (−)-1-bromocodeinone (3.1.17), which is isolated in the form of 2,4-dinitrophenylhyrazone. It is apparent, that at this stage of the synthesis a double bond between both C_7–C_8 and an oxide bridge between C_4–C_5 simultaneously forms. Furthermore, an epimerization takes place at C_{14}, i.e. the isomorphinan system isomerizes into a morphinane system. The subsequent reduction of (−)-1-bromocodeinone (3.1.17) by lithium aluminum hydride gives codeine (3.1.18), which is demethylated into the desired morphine (3.1.19) by pyridine hydrochloride [1,2].



3.1.1 3.1.2 3.1.3



In the diagram, the structure morphine (3.1.19) is presented in a form that makes it easy to follow the sequence of transformations taking place. The more accepted image of morphine, which makes it easier to follow the changes that lead to the formation of its practically valuable derivatives is shown below.

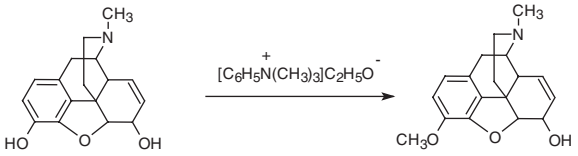


Morphine is presently the standard analgesic by which all the others are compared, and whose alternative methods of synthesis are still being developed [3–6]. Nevertheless, synthesis of morphine is not economically practical, since it is much cheaper to obtain from natural resources.

Morphine is the primary representative and primary prototype of the group of strong opioid analgesics. The most important use of morphine is its ability to eliminate pain. It is used in surgery and as a preanesthetic medication for surgical interventions before the general anesthesia procedure begins. It is widely used in myocardial infarction not only to relieve pain, but also for calming the patient and even for reducing the need of oxygen. It is used in pulmonary edema and in a few forms of diarrhea. Morphine is prescribed in all cases when NSAID action is not sufficient and requires the use of strong opioid analgesics.

Relatively simple modifications of morphine molecules lead to the formation of a number of compounds that differ in their analgesic activity.

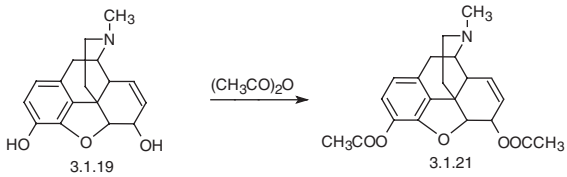
Codeine: Codeine, 4,5-epoxy-17-methylmorphin-7-ene-3-methoxy-6-ol (3.1.20), is an elemental part of opium poppy alkaloids. Codeine differs from morphine in that hydroxyl group on C_3 of the aromatic ring is methylated. The content of codeine in opium does not satisfy medicinal requirements and therefore codeine is made in a semisynthetic manner from morphine by selective methylation of the aromatic hydroxyl group on C_3. The usual methylating agents result in the methylation of both hydroxyl groups. Selective methylation of the hydroxyl group at C_3 of the aromatic ring can be accomplished using diazomethane, nitrosomethylurethane, or nitrosomethylurea. However, use of these reagents presents certain difficulties in completing the reaction in large industrial scale. It was suggested that trimethylphenylammonium chloride or dimethylaniline methyltoluenesulfonate in the presence of sodium alkoxides could be used as methylating agents. Codeine is basically synthesized by methylation of the 3-hydroxy group of the morphine ring by trimethylphenylammonium ethoxide [7,8].



3.1.19 3.1.20

Codeine is similar to morphine in terms of properties, but its pain-relieving ability is significantly less and it causes addiction to some degree. This drug is very effective in oral use and is used for average to moderate pain. It is often used as an antitussive drug. Synonyms for codeine are codyl, acutus, and others.

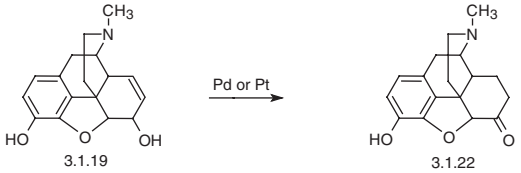
Heroin: Heroin, 3-diacetyl-4,5-epoxy-17-methylmorphin-7-ene (3.1.21), is synthesized by the simultaneous acetylation of the two hydroxyl groups of morphine with acetic anhydride or acetyl chloride [9,10].



3.1.19 3.1.21

Owing to its high solubility in lipids (compared to morphine), heroin quickly passes through the blood–brain barrier; however, it acts like morphine, into which it is transformed in the brain. Narcotic effects, respiratory depression, toxicity, narrow range of therapeutic action, and high danger of addiction make it less advantageous than morphine. Heroin use is prohibited in medicine, since it does not have any therapeutic value which cannot be found in other drugs.

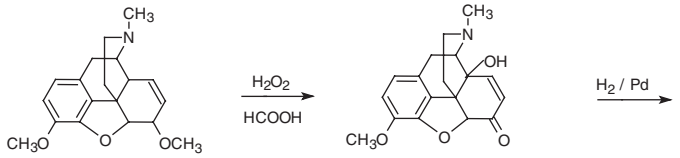
Hydromorphone: Hydromorphone, 4,5-epoxy-3-hydroxy-*N*-methyl-6-oxomorphinane (3.1.22), is a compound related to morphine that differs in the absence of a double bond between C_7–C_8 and the presence of a keto group instead of a hydroxyl group on C_6. The drug is synthesized by the isomerization of morphine in the presence of a palladium or platinum catalyst [11,12]. The other way is by oxidation of dihydroporphine [13,14].



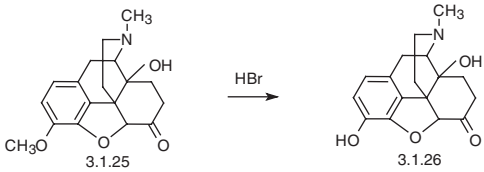
3.1.19 3.1.22

Hydromorphone is more soluble than morphine and approximately eight times more active upon parenteral administration. High solubility permits a lower volume of injected fluid, which is important if multiple injections are needed. It begins to work faster than morphine, but lasts for a shorter amount of time. It has a high sedative effect and a lessened capability of causing euphoria. Hydromorphone is used the same way as morphine. Side effects are analogous. Synonyms for this drug are dilaudid and others.

Oxymorphone: Oxymorphone, 4,5-epoxy-3,14-dihydroxy-*N*-methyl-6-oxyomorphinane (3.1.26), is chemically similar to hydromorphone. It differs from hydromorphone in that it contains a hydroxyl group on C_{13}. The drug is synthesized from thebaine (3.1.23), which during oxidation with hydrogen peroxide in formic acid changes into 14-hydroxycodeinone (3.1.24). The double bond is then hydrogenated, transforming the compound into oxycodone (3.1.25). It is demethylated by hydrogen bromide into oxymorphone [15,16].



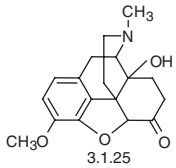
3.1.23 3.1.24



Oxymorphone is approximately 10 times more active than morphine. Euphoric effects as well as vomiting are expressed significantly stronger than in morphine. Oxymorphone also displays poor antitussive activity.

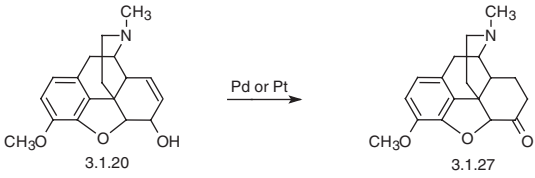
Side effects are analogous to those of morphine. It is intended for relieving moderate to severe pain in surgical and gynecological interventions and for post-operational pain.

Oxycodone: The synthesis of oxycodone, 4,5-epoxy-3-methoxy-14-hydroxy-*N*-methyl-6-oxomorphinane (3.1.25), from 14-hydroxycodeinone (3.1.24) was described above. It can also be synthesized in other ways; for example, by the oxidation of codeine using sodium dichromate in acetic acid [17], and is also a structural analog of morphine and codeine.



Unlike hydrocodone, it is used as an analgesic in combination with other drugs, such as aspirin or acetaminophen. Oxycodone is similar to morphine in terms of durational efficacy and is intended for oral use. Synonyms for this drug are roxicodone, proladone, perketan, eutagen, oxycon, and many others.

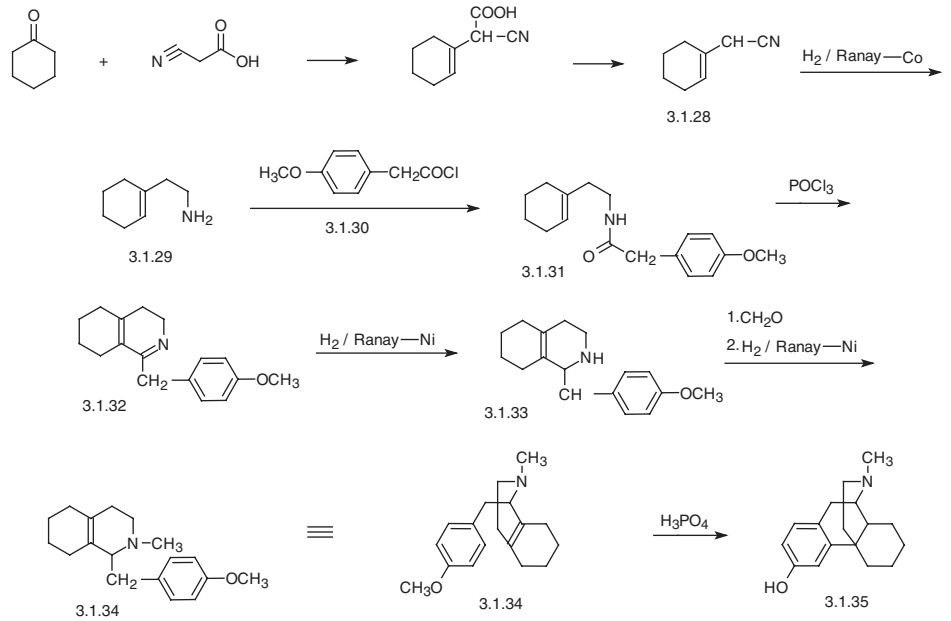
Hydrocodone: Hydrocodone, 4,5-epoxy-3-methoxy-*N*-methyl-6-oxomorphinane (3.1.27), is a compound that is chemically related to morphine and codeine. Hydrocodone is synthesized by the isomerization of codeine (3.1.20) using a palladium or platinum catalyst [18]. This drug has also been suggested to be synthesized by the hydration of codeinone [19] and by oxidation of dihydrocodeine [20].



Hydrocodone exhibits expressed analgesic and antitussive properties, which make up its primary clinical use. It may cause dependence and addiction. Synonyms for this medication are dicodid, detussin, vicodin, and others.

Levorphanol: Levorphanol, (–)-3-hydroxy-*N*-methylmorphinane (3.1.35), is a derivative of morphine. Levorphanol is synthesized starting from cyclohexanone by its condensation with

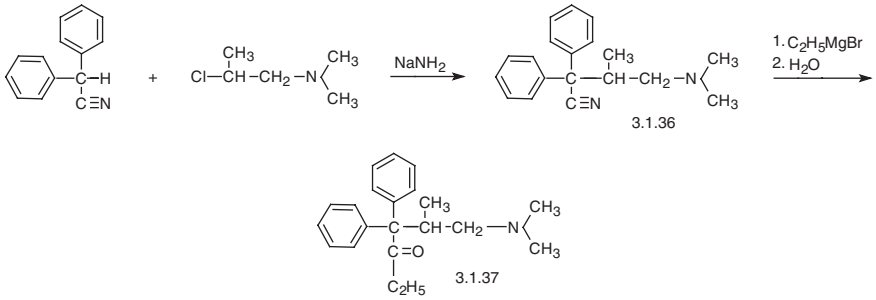
cyanoacetic acid (Knovenagel reaction), during which simultaneous decarboxylation occurs, forming 1-cyclohexenylacetonitrile (3.1.28). Reduction of the nitrile group by hydrogen in the presence of Raney cobalt gives 2-(1-cyclohexenyl)ethylamine (3.1.29). The resulting amine is further acylated by 4-methoxyphenylacetyl chloride (3.1.30), which forms the amide 2-(1-cyclohexenyl)ethyl-4-methoxyphenylacetamide (3.1.31). Cyclization of the last using phosphorous oxychloride leads to the formation of 1-(4-methoxybenzyl)-3,4,5,6,7,8-hexahydroquinolin (3.1.32). The imine bond in the obtained compound is hydrogenated in the presence of Raney nickel, forming 1-(4-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroquinolin (3.1.33), which is methylated by formaldehyde in the presence of Raney nickel into 1-(4-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroquinolin (3.1.34). In the final stage of synthesis, 1-(4-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroquinolin undergoes cyclization and simultaneous demethylation into 3-hydroxy-*N*-methylmorpinane—levorphanol (3.1.35), from which the optical antipodes are further separated using (+)-tartaric acid [21,22].



The dextrorotatory isomer is not an analgesic; however, it has antitussive properties. The levorotatory isomer, levomethorphane, exhibits activity similar to that of morphine; however, a number of side effects including nausea, vomiting, and the potential of causing constipation are less prevalent. It is 4–8 times more effective than morphine when injected. It also lasts longer than morphine. This drug is recommended for relieving moderate to high pain in biliary and renal colic, myocardial infarction, in serious trauma, and for relieving cancer pain and post-operative pain.

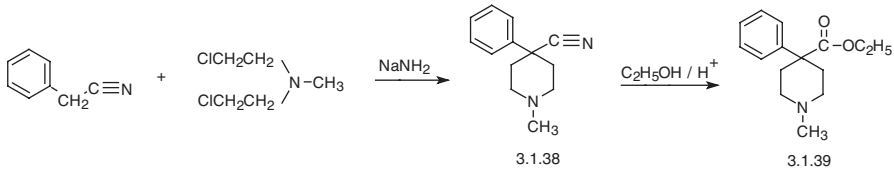
Methadone: Methadone, 6-dimethylamino-4,4-dephenyl-3-heptanone (3.1.37), is synthesized by alkylation of diphenylacetonitrile using 1-dimethylamino-2-propylchloride in the

presence of sodium amide. The resulting 4-dimethylamino-2,2-dephenylvaleronitrile (3.1.36) is reacted with the ethylmagnesiumbromide and then hydrolyzed [23–26]. This resulting racemate is separated using (+)-tartaric acid, thus isolating (−)-methadone [26–29].



Methadone is a synthetic opioid that acts on the μ-receptors and is both qualitatively and quantitatively analogous to morphine. The principal difference lies in its higher efficacy when taken orally, and its long-lasting effect. Other than its use as a strong analgesic, it is used in treating drug addiction, since it replaces other agonists on the receptor. Synonyms for this drug are fizepton, methenone, dolofin, and others.

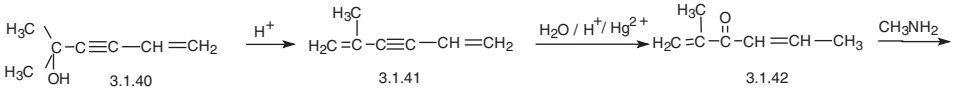
Meperidine: Meperidine, the ethyl ester of 1-methyl-4-phenylpiperidine-4-carboxylic acid (3.1.39), is a synthetic opioid analgesic. Its synthesis is accomplished by the alkylation of benzyl cyanide using *N*,*N*-*bis*-(2-chlorethyl)-*N*-methylamine in the presence of sodium amide, which forms 1-methyl-4-phenyl-4-cyanopiperidine (3.1.38), and its subsequent acidic ethanolysis into meperidine [30–32].

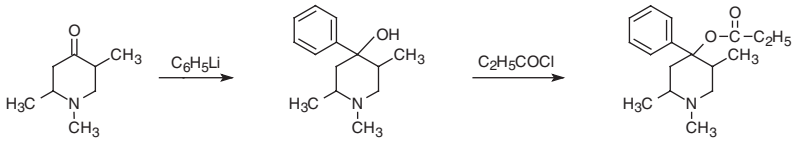


Meperidine is related to analgesics of the phenylpiperidine series. These compounds are also agonists, although they significantly differ from morphine in terms of structure. This drug also exhibits anticholinergic activity. Like morphine, it causes histamine release and spasm of the smooth muscles. It is practically inactive upon oral administration. Most of the pharmacological properties and administration indications are similar to those of morphine; however, this drug lacks antitussive properties. During parenteral administration, activity is basically one-eighth that of morphine. Meperidine is widely used in premedical and stabilizing anesthesia. It is preferred for use in obstetrical practice due to the quick onset of analgesia and its short-lasting action. The most frequently used synonyms are pethidine, dolantin, and demerol.

Promedol: Promedol, 1,2,5-trimethyl-4-phenyl-4-propionyloxypiperidine (3.1.45), is also related to analgesics belonging to the phenylpiperidine series, and in its own way represents

a “reversed” meperidine; it differs from meperidine in that the carbonyl group is joined to the fourth position of the piperidine ring through oxygen instead of through a carbon atom. Synthesis of this compound pretty much differs from the synthesis of meperidine and is based on using of 1,2,5-trimethylpeperidin-4-one. This product comes from dimethylvinylethynylcarbinol (3.1.40), a condensation product of vinylacetylene with acetone in the Favorskii reaction, which undergoes dehydration into vinylisopropenylacetylene (3.1.41). The triple bond in vinylisopropenylacetylene is hydrated in dilute sulfuric acid in methanol and in the presence of mercury (II) sulfate (Kucherov reaction). This results in vinylisopropenylketone (3.1.42), primarily in the form of methoxy derivatives, which are products of addition of methanol to activated double bonds, and the reaction of heterocyclization with methylamine to form 1,2,5-trimethylpiperidin-4-one (3.1.43). This undergoes a reaction with phenyllithium to form 1,2,5-trimethyl-4-phenylpiperidin-4-ol (3.1.44). Esterfication of this compound with propionyl chloride gives promedol [33].

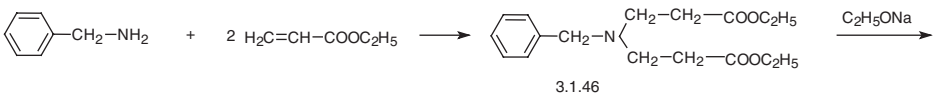




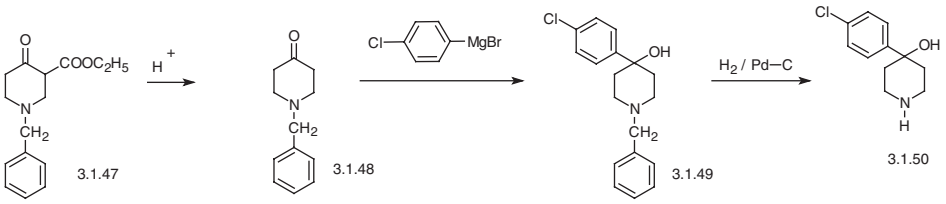
Promedol is quickly absorbed and displays strong analgesic action during both parenteral and oral administration. It gives less respiratory suppression than morphine. It also displays antispasmodic effects on smooth muscle. It is used as a pain-relieving agent during surgical intervention, trauma, and diseases that are accompanied by painful sensations. A synonym for this drug is trimeperidine.

Loperamide: Loperamide, 1-(4-chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-α,α-diphenyl-1-piperidinebutyramide (3.1.55), proposed here as an analgesic, is synthesized by the alkylation of 4-(4-chlorophenyl)-4-hydroxypiperidine (3.1.50) using *N*,*N*-dimethyl(3,3-diphenyltetrahydro-2-furylidene)ammonium bromide (3.1.54) in the presence of a base. The 4-(4-chlorophenyl)-4-hydroxypiperidine (3.1.50) is synthesized by reacting 1-benzylpiperidine-4-one (3.1.48) with 4-chlorophenylmagnesiumbromide, followed by debenzylation of the product (3.1.49) by hydrogenation using a palladium on carbon catalyst.

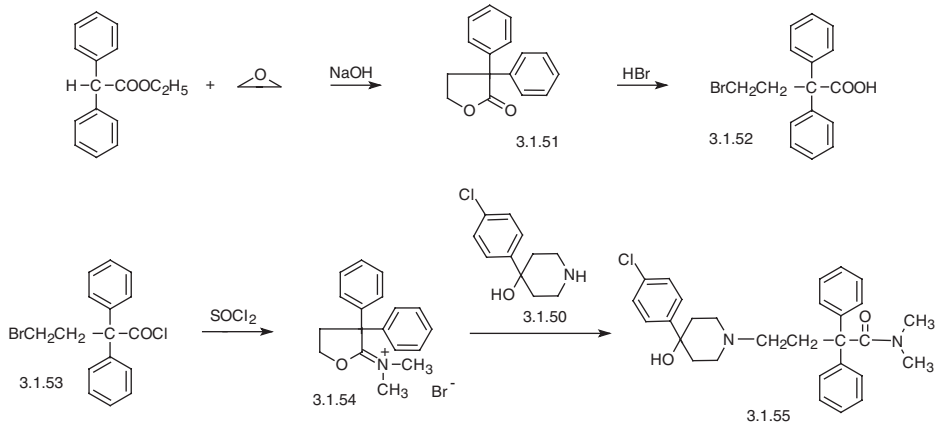
The starting 1-benzylpiperidin-4-one (3.1.48) is synthesized by Dieckmann intermolecular condensation of *N*-benzyl-*N*,*N*-*bis*-(β-carboethoxyethyl)amine (3.1.46), which is easily formed by reaction of benzylamine with ethyl acrylate to give 1-benzyl-3-carboethoxypiperidine-4-one (3.1.47) followed by acidic hydrolysis and thermal decarboxylation.



3.1.46



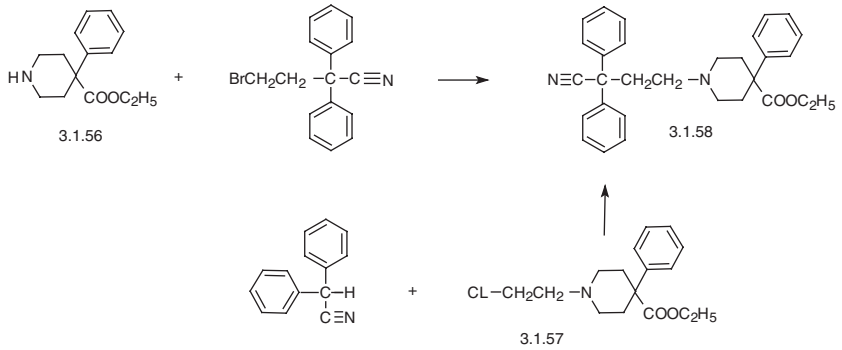
N,*N*-Dimethyl-(3,3-diphenyltetrahydro-2-furyliden)ammonium bromide (3.1.54) is synthesized from diphenylacetic acid ethyl ester, which is reacted with ethylene oxide in the presence of sodium hydroxide, giving 2,2-diphenylbutyrolactone (3.1.51). Reacting this with hydrogen bromide in acetic acid opens the lactone ring, forming 2,2-diphenyl-4-bromobutyric acid (3.1.52). This transforms into acid chloride (3.1.53) using thionyl chloride, which cyclizes upon further treatment with an aqueous solution of dimethylamine, thus forming the desired *N*,*N*-dimethyl-(3,3-diphenyltetrahydro-2-furyliden)ammonium bromide (3.1.54). Reacting this with 4-(4-chlorphenyl)-4-hydroxypiperidine (3.1.50) gives the desired loperamide (3.1.55) [34–36].



Loperamide is presently used more often as an antidiarrheal drug than as an analgesic, and it is also included in the list of over-the-counter drugs because of its insignificant action on the CNS. It reduces intestinal smooth muscle tone and motility as a result of binding to intestinal opiate receptors. It is used for symptomatic treatment of severe and chronic diarrhea of various origins. The most popular synonym for loperamide is imodium.

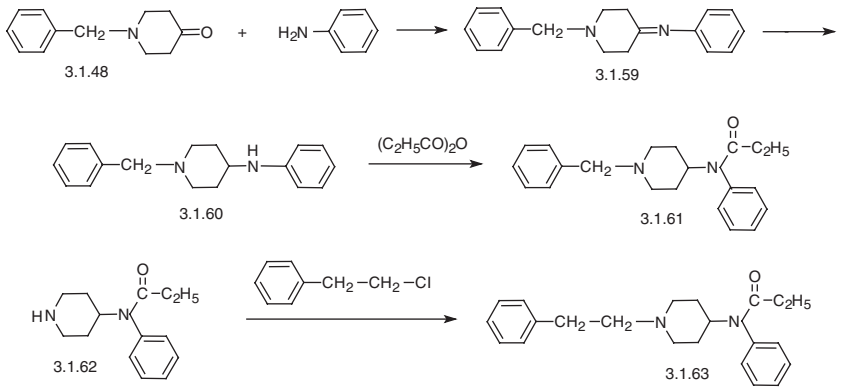
Diphenoxylate: Diphenoxylate, ethyl ester of 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid (3.1.58), is also a drug of 4-phenylpiperidine series. In practice there are two ways of making it. The first way is by the alkylation of the ethyl ester of 4-phenylpiperidine-4-carboxylic acid (3.1.56) with 2,2-diphenyl-4-bromobutyronitrile, which in turn is synthesized from 1-benzyl-4-phenyl-4-cyanopiperidine. The product undergoes ethanolysis in the presence of acid, followed by benzylation. The second way is a synthesis accomplished by alkylation of diphenylacetonitrile using ethyl ester of 1-(2-chloroethyl)-4-phenylpiperidine-4-carboxylic acid (3.1.57), which is synthesized by

reaction of ethyl ester of 4-phenylpiperidine-4-carboxylic acid with β-chloroethanol or ethylenoxide with the subsequent substitution of hydroxyl group, which results from the opening of the epoxide ring, by chlorine via action of thionyl chloride [37,38].



This drug is a structural analog of meperidine and loperamide; however, it practically duplicates all of the pharmacological properties of loperamide. Being analogous to loperamide, it is mainly used for treating diarrhea. Synonyms for this drug are fentanest, leprofen, and others.

Fentanyl: Fentanyl, 1-phenethyl-4-*N*-propinoylanilinopiperidine (3.1.63), is an extremely powerful intramuscular and intravenous analgesic. The synthesis of fentanyl is accomplished beginning with 1-benzylpiperidin-4-one (3.1.48), which is condensed with aniline to form the corresponding Schiff base (3.1.59). The double bond in this product is reduced by lithium aluminum hydride, and the resulting 1-benzyl-4-anilinopiperidine (3.1.60) is acylated using propionic acid anhydride. The resulting 1-benzyl-4-*N*-propinoylanilinopiperidine (3.1.61) undergoes debenzylation using hydrogen and a palladium on carbon catalyst, to give 4-*N*-propanoylanilinopiperidine (3.1.62), which is N-alkylated by 2-phenylethylchloride, to give fentanyl (3.1.63) [39,40].

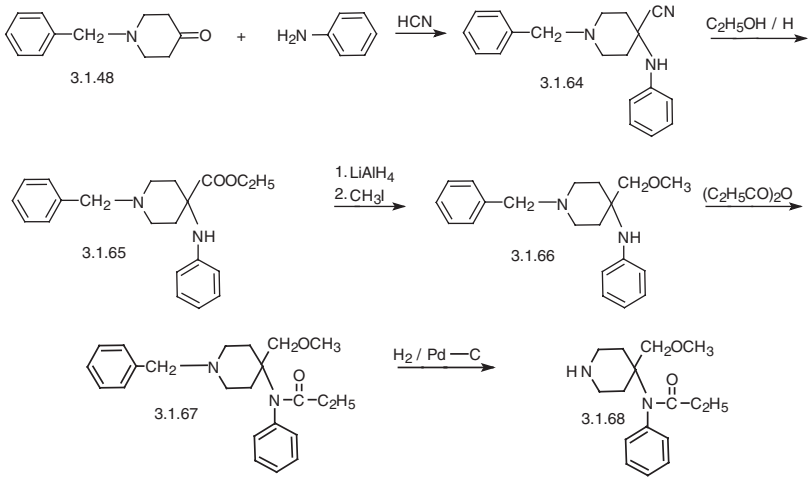


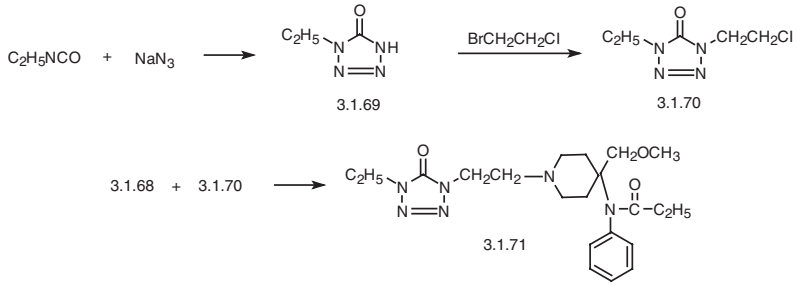
The analgesic action of fentanyl surpasses that of morphine by approximately 100-fold. It has a suppressive action on the respiratory center and slows heart rate. Fentanyl is used in

anesthesiology both independently and in combination with droperidol for neurolepthanalgesia, and in preanesthetic medication, in different forms of narcosis, and in post-operational anesthesia. Unlike morphine, it does not cause a release of histamines. It is used only in specialized hospital conditions. Synonyms for this drug are fentanest, leprofen, and others.

Alfentanil: Alfentanil, *N*-[1-(2-(4-ethyl-4,5-dihydro-5-oxy-1*H*-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidine]anilinopropionamide (3.1.71), is the next representative of drugs of the class of anilidopiperidines, which differ from fentanyl in that they have a second substituent on the fourth position of the piperidine ring, and also in the replacement of the phenyl group in the arylethyl substituent on the nitrogen atom of the piperidine ring for an aromatic heterocycle, tetrazolone. The synthesis of alfentanil consists in the alkylation of separately prepared *N*-(4-methoxymethyl)-4-piperidyl)-propionanilide (3.1.68) using 1-(4-ethyl-4,5-dihydro-5-oxo-1*H*-tetrazol-1-yl)ethyl-2-chloride (3.1.66).

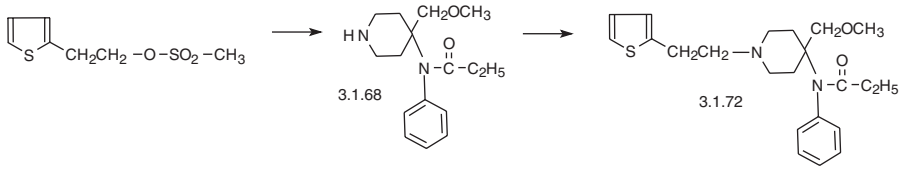
N-(4-Methoxymethyl)-4-piperidyl)-propionanilide (3.1.68) is synthesized from 1-benzylpiperidine-4-one (3.1.48) by means of condensation with aniline in the presence of hydrogen cyanide. The resulting 4-anilino-4-cyano-1-benzylpiperidine (3.1.64) undergoes ethanolysis, forming 4-anilino-4-carboethoxy-1-benzylpiperidine (3.1.65), which is reduced by lithium aluminum hydride into 4-anilino-4-hydroxymethyl-1-benzylpiperidine, which is methylated by methyl iodide to give 4-anilino-4-methoxymethyl-1-benzylpiperidine (3.1.66). The resulting product is acylated using propionic anhydride to give 1-benzyl-4-methoxymethyl-4-*N*-propionyl-anilinopiperidine (3.1.67), which undergoes debenzylation by hydrogen using a palladium on carbon catalyst to give 4-methoxymethyl-4-*N*-propionyl-anilinopiperidine (3.1.68). 1-(4-Ethyl-4,5-dihydro-5-oxy-1*H*-tetrazol-1-yl)ethyl-2-chloride (3.1.70) is synthesized starting with ethyl isocyanate and sodium azide. The product resulting from 2+3 cycloaddition to give 4-ethyl-4,5,dihydro-5-oxy-1*H*-tetrazol (3.1.69) undergoes further alkylation using 1-bromo-2-chloroethane, forming 1-(4-ethyl-4,5-dihydro-5-oxy-1*H*-tetrazol-1-yl)ethyl-2-chloride (3.1.70), which reacts with 4-methoxymethyl-4-*N*-propionyl-anilinopiperidine (3.1.68), to give alfentanil (3.1.71) [41–43].





The main difference between alfentanil and fentanyl lies in its short-lasting action. It is used in anesthesiological practice along with barbiturates during short surgical interventions. Synonyms for this drug are alfenta, rapifen, and others.

Sufentanyl: Sufentanyl, *N*-(4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-*N*-phenylpropanamide (3.1.72), is a drug that is analogous to alfentanil, but that differs by the substituent on the nitrogen atom of the piperidine ring. Its synthesis contains many of the same elements as the synthesis of alfentanil, and it only differs in the last stage, where alkylation of 4-methoxymethyl-4-*N*-propionilanilinopiperidine (3.1.68) is carried out with 2-hydroxyethylthiophofene methanesulfonate [44–46].



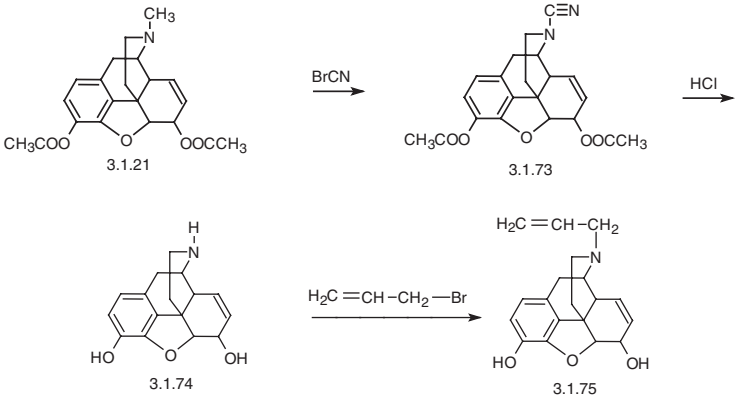
In terms of action, sufentanyl surpasses that of fentanyl by 5–10 times. It is used in anesthesiological practice during surgical interventions. Synonyms for this drug are sufenta and others.

3.1.2 Mixed agonists/antagonists

Drugs of this group display both agonistic and antagonistic activity. It is an accepted belief that agonist activity is exhibited as a result of the interaction with μ-receptors as well as its antagonistic activity on others, in particular the κ- and σ-receptors. The mechanism of their action is poorly understood. Despite the fact that their action can appear in the form of analgesic effects, certain respiratory depressions, and other forms characteristic of morphine-like drugs, also can block and even reverse the effects of agonists as well as cancel abstinence syndrome on patients with opioid dependence.

Interestingly, tolerance to the agonistic properties of these drugs may result, but not to the antagonistic properties. Dependence can also originate from their long-term use. This group of compounds is used for analgesia in cases of moderate to severe pain. They are less effective than morphine; however, they do not cause severe respiratory depression upon overdose.

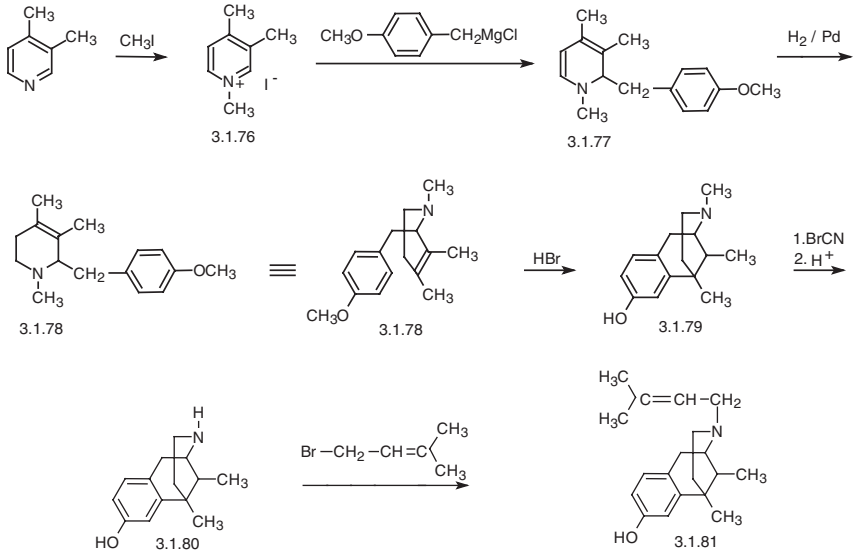
Nalorphine: Nalorphine, *N*-allylnormorphine (3.1.75), is synthesized from morphine by its complete acetylation, i.e. by transformation into heroin (3.1.21), in order to temporarily protect the hydroxyl groups, and then by undergoing demethylation. In order to do this, heroin (3.1.21) is processed with cyanogen bromide. The resulting *N*-cyano derivative (3.1.73) is hydrolyzed by a solution of hydrochloric acid into the N-demethylated morphine, normorphine (3.1.74), whose secondary amine group undergoes alkylation with allylbromide to give desired nalorphine [47,48].



Nalorphine has less of an analgesic effect than morphine; however, it does not have much value as an independent analgesic. It is used as an antagonist to narcotic analgesics. It eliminates suppression of the respiratory center, bradycardia, and vomiting caused by opiate receptor agonists.

Nalorphine was the first compound used for narcotic (heroin in particular) overdose treatment; however, it exhibits a number of side effects such as visual hallucinations, and therefore its use is prohibited in some countries. The most popular synonym for this drug is narkan.

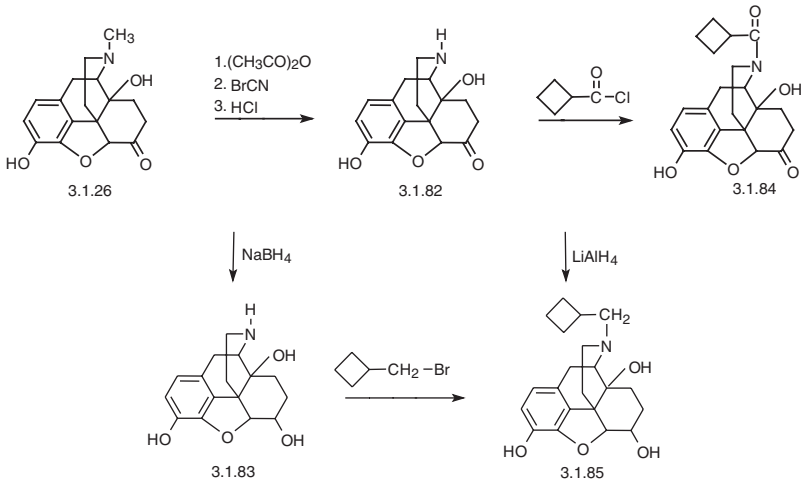
Pentazocine: Pentazocine, 1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol (3.1.81), is a derivative of benzomorphane. Pentazocine is synthesized starting from 3,4-dimethylpyridine. It undergoes a reaction with methyl iodide to give 1,3,4-trimethylpyridinium iodide (3.1.76), which is reacted with 4-methoxybenzyl magnesiumchloride, forming 2-methoxybenzyl-3,4-dimethyl-1,2-dihydropyridine (3.1.77). The double bond on C_5 of the resulting compound is hydrogenated using a palladium catalyst, giving 3-methoxybenzyl-3,4-dimethyl-1,2,3,4-tetrahydropyridine (3.1.78). The resulting product undergoes intramolecular alkylation and simultaneous demethylation of the ether bond by hydrobromic acid, which results in the formation of 2-hydroxy-2,5,9-trimethylbenzo-6-morphane (3.1.79), which undergoes N-demethylation by cyanogen bromide to form 2-hydroxy-5,9-dimethylbenzo-6-morphane-*N*-normetazocine (3.1.80). Alkylation of the resulting product by 1-bromo-3-methyl-2-butene gives pentazocine [49,50].



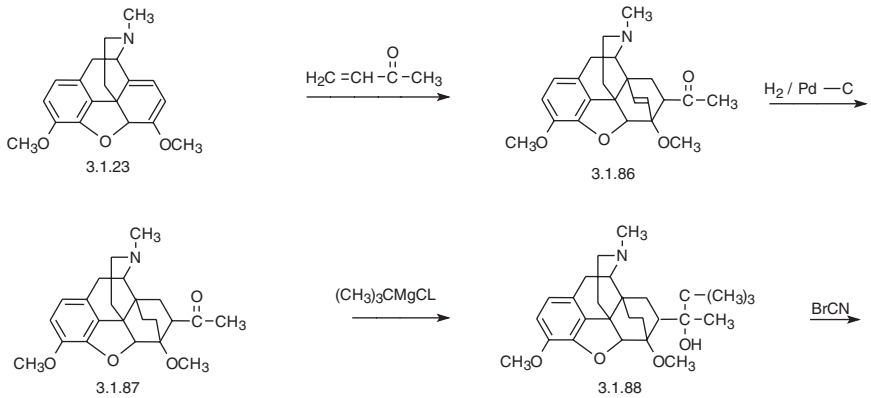
Pentazocine is a weak antagonist of morphine. It is substantially weaker than nalorphine or levallorphine, but it has a strongly expressed analgesic effect. Pentazocine is the first agonist–antagonist acting analgesic to appear on the pharmaceutical market. In terms of analgesic activity it is inferior to morphine; however, it suppresses the respiratory center to a much lesser extent. As an agonist, it acts primarily on κ-receptors. When taken orally, its activity is comparable to that of codeine. Cases of tolerance have been recorded. Pentazocine is used for various degrees of pain and for preanesthesia medication prior to surgical intervention. The most common synonym for this drug is fortral.

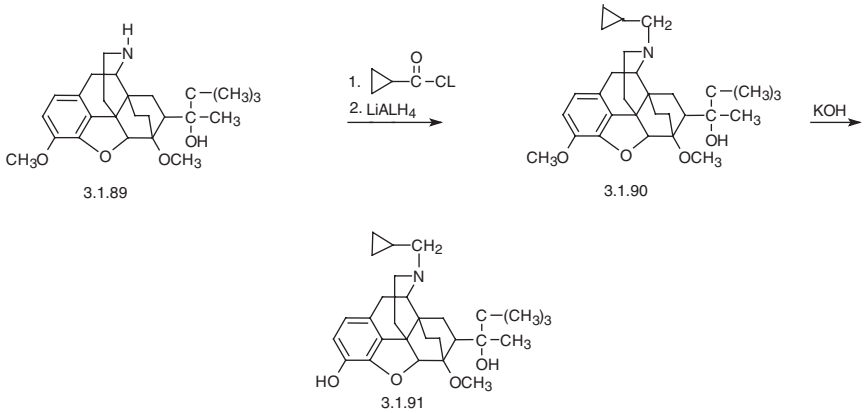
Nalbuphine: Nalbuphine, 17-(cyclobutylmethyl)-4,5-α-epoximorphinan-3,6α,14-triol (3.1.85), is synthesized from oxymorphone (3.1.26), which after protecting the hydroxyl group by acetylation undergoes a reaction with cyanogen bromide, giving an N-cyano derivative, and further hydrolysis of which using hydrochloric acid gives 14-hydroxydihydronormorphone (3.1.82). Transformation of the resulting product into the desired nalbuphine (3.1.85) is accomplished either by reduction of the carbonyl group of the resulting 14-hydroxydihydronormaphone by sodium borohydride into (3.1.83) and the subsequent alkylation of the product by cyclobutylmethylbromide, or by the acylation (3.1.82) with cyclobutancarboxylic acid chloride into (3.1.84) and the subsequent simultaneous reduction of two carbonyl groups in the resulting compound using lithium aluminum hydride, giving the desired product [51,52].

Nalbuphine is a strong analgesic with activity equal to that of morphine. It is structurally similar to oxymorphone and the opioid antagonist naloxone. It exhibits fewer side effects than nalorphine. Nalbuphine is prescribed as a drug for alleviating moderate to severe pain. It is used as a supplementary drug for balanced anesthesia, for pre- and post-operational analgesia, and in gynecological interventions. The most common synonym for nalbuphine is nubaine.



Buprenorphine: Buprenorphine, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphinan-7-methanol (3.1.91), is synthesized from one of the alkaloids of morphine, thebaine (3.1.23). Synthesis of buprenorphine begins on the basis of the reaction product of 4+2 cycloaddition of thebaine and methylvinylketone. The resulting product 7-acetyl-6,14-endoethanotetrahydrothebaine (3.1.86) is further hydrogenated using a palladium on carbon catalyst into 7-acetyl-6,14-endoethanotetrahydrothebaine (3.1.87). This is reacted with *tert*-butyl-magnesium chloride to form 6,14-endoethano-7-(2-hydroxy-3,3-dimethyl-2-butyl)-tetrahydrothebaine (3.1.88). The product is demethylated using cyanogen bromide, giving 6,14-endoethano-7-(2-hydroxy-3,3-dimethyl-2-butyl)-tetrahydronorthebaine (3.1.89). Acidifying this product with cyclopropancarboxylic acid chloride and further reduction of the introduced carbonyl group gives *N*-cyclopropylmethyl-6,14-endoethano-7-(2-hydroxy-3,3-dimethyl-2-butyl)-tetrahydronorthebaine (3.1.90). The final buprenorphine (3.1.91) is synthesized by selective demethylation of the methoxy group connected to the aromatic ring upon high-temperature reaction of (3.1.90) with potassium hydroxide [53,54].





3.1.89 3.1.90 3.1.91

Buprenorphine exhibits properties of a central-acting analgesic; it does not suppress the respiratory center or lead to addiction or drug dependence. It is generally devoid of dysphoric or psychotomimetic effects. Buprenorphine differs from the other examined agonist–antagonists in that it exhibits a partial agonistic effect on the μ-receptors. It blocks the effects of morphine for about 30 h. It exhibits a number of certain unique effects that are not typical of compounds of this series. It is used for moderately painful symptoms of various origins. The most common synonym is buprenex.

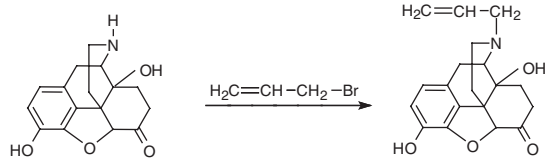
3.1.3 Opioid antagonists

Opioid antagonists are compounds that have expressed antagonistic activity, and that differ from the mixed agonist–antagonists in that they do not exhibit agonistic activity.

The efficacy and strength of opioid antagonists varies depending on the type of opioid receptors (μ-, δ-, κ-, σ-) with which they interact. The mechanism of their action is not fully clear. However, it has been suggested that they antagonize the action of endogenous opioid peptides.

These compounds are also antagonists in relation to agonist–antagonists. They antagonize the action of agonists, mixed agonists–antagonists, and they do not result in dependence or tolerance. They are used upon overdose of opioid analgesics or in the event of patient intolerance to them, and also in treating drug addiction.

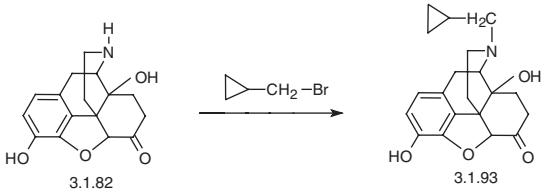
Naloxone: Naloxone, (−)-17-(allyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one (3.1.92), is synthesized by the alkylation of 14-hydroxydihydronormorphinane (3.1.82) by allylbromide [55–58].



3.1.82 3.1.92

It is worth mentioning that *N*-allylic substitution in a number of morphine derivatives, as a rule, leads to antagonistic properties. Naloxone is a few times stronger than nalorphine as an antagonist. It blocks opiate receptors. It eliminates central and peripheral action of opioids, including respiratory depression. Naloxone is used upon overdose of narcotic analgesics.Synonyms for this drug are narkan, talwin, and others.

Naltrexone: Naltrexone, (−)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one (3.1.93), is an *N*-cyclopropylmethyl derivative of oxymorphone (3.1.82). One of the methods of synthesis is analogous to the synthesis of naloxone, which consists of using cyclopropylmethylbromide instead of allylbromide [59].



3.1.82 3.1.93

This drug does not have agonistic properties. It is similar to naloxone in terms of pharmacological characteristics; however, it differs in two important ways—long-lasting action and that its metabolite 6-β-naltrexol is also a strong antagonist. Naltrexone is potentially hepatotoxic. Naltrexone is used for blocking pharmacological effects of opioids upon their overdose.Synonyms for this drug are nalorex, trexan, and others.

3.2 NONSTEROID ANTI-INFLAMMATORY DRUGS AND ANTI-FEVER ANALGESICS

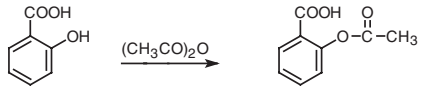
A huge quantity of drugs belonging to various classes of compounds exhibit analgesic, anti-fever, and anti-inflammatory action. In addition, they are devoid of many undesirable effects that accompany opioid analgesics (respiratory depression, addiction, etc.). They are called nonnarcotic analgesics, aspirin-like substances, anti-fever analgesics, etc., in order to differentiate nonsteroidal, anti-inflammatory, and anti-fever analgesics from opioids and glucocorticoids. The exact mechanism of action of these drugs is not conclusively known. It is supposed that it might be connected with its ability to inhibit synthesis of prostaglandins, which reduces their sensitizing influence on nerve endings, which in turn reduces the effect of neurotransmitter action—bradykinin in particular. However, analgesic and anti-inflammatory activity of these drugs is not always correlated with their ability to suppress prostaglandins. There are other assumptions about the mechanism of action of nonnarcotic analgesics. Experiments in animals show that the analgesic action of this series of drugs is peripheral; however, it is possible that the acetaminophen may have a central action by blocking painful impulses.

In general, nonopioid analgesics are characterized by three fundamental types of action: analgesic, anti-inflammatory, and fever-reducing action, which are used for alleviation of headaches, myalgia, arthralgia, and that do not have sedative or soporific effects. Euphoria, addiction, and drug dependence do not result from their use.

Nonsteroidal anti-inflammatory and fever-reducing analgesics are classified as salicylic acid derivatives (aspirin, diflusinal, etc.), pyrazolones (phenylbutazone, metamizol, etc., and others, in particular acetominophen), anthranylic acid derivatives (flufenamic acid, mephenamic acid, and meclophenamic acid, arylacetic acid derivatives (diclofenak, phenclofenak), arylpropionic acid derivatives (ibuprofen, ketoprofen, naproxene, fenprofen, etc.), indolyl/indeneacetic acid derivatives (indomethacin, sulindac, etc.), and oxicames (pyroxicam, isoxycam).

3.2.1 Salicylic acid derivatives

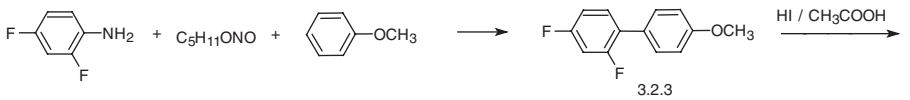
Aspirin: Aspirin, acetylsalicylic acid (3.2.2), is synthesized by the acetylation of salicylic acid (3.2.1) using acetic anhydride or acetyl chloride [60–63].



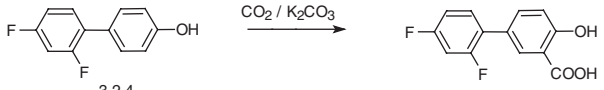
3.2.1 3.2.2

Aspirin exhibits analgesic, fever-reducing, and anti-inflammatory action, and it also reduces aggregation of thrombocytes. It is believed that the primary mechanism of action is the irreversible acetylation of cyclooxygenase, which results in the inability to synthesize prostaglandins, prostacyclins, and thromboxane. As a result, the pyrogenic effect of prostaglandins on the centers of thermoregulation and sensitive nerve endings is reduced, which leads to a lessening of sensitivity to painful neurotransmission. The antiaggregatory effect of aspirin is explained by the irreversible inability to synthesize thromboxane A_2 in the thrombocytes. Today, aspirin is used in larger quantities than any other drug. Aspirin is widely used for head and neuralgic pains, rheumatic conditions, painful symptoms of various etiologies, and eliminating painful feelings during menstruation. It is used in conditions such as fevers, prevention and treatment of thrombosis and embolism, and for prevention of ischemic abnormalities and cerebral blood circulation. Aspirin is probably the drug with the largest number of synonyms. They are acetosal, acetylsalicylic acid, cetosal, and a large number of others. Nonacetylated salicylates are also used in medical practice.

Diflunisal: Diflunisal, 2′,4′-difluoro-4-hydroxy-3-byphenylcarboxylic acid (3.2.5), is synthesized from a diazonium salt, which is synthesized from 2,4-difluoroaniline and isoamyl nitrite, and anisole in the presence of copper (I) salts by the classic scheme of making diaryls. The resulting 4-(2,4-difluorophenyl)anisole (3.2.3) is demethylated by hydrogen iodide into 4-(2,4-difluorophenyl)-phenol (3.2.4). This product is reacted with carbon dioxide in the presence of a base according to the Kolbe–Schmitt phenol carboxylation method, giving diflunisal (3.2.5) [64–67].



3.2.3



3.2.4 3.2.5

As a prostaglandin synthetase inhibitor, diflunisal exhibits analgesic, fever-reducing, and anti-inflammatory action. It is used for long- and short-lasting symptomatic relief of low to moderate pain in osteoarthritis and rheumatoid arthritis.Synonyms for this drug are dolobid, adomal, noladol, and others.

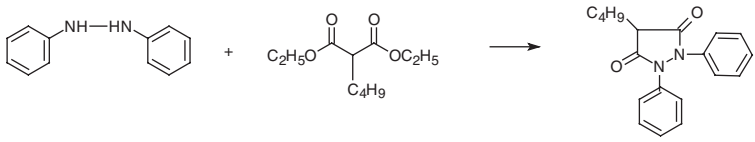
In medical practice, other salicylic acid derivatives are used in the form of salts. Magnesium salicylate and sodium salicylate are less effective than respective doses of aspirin; however, they are easier on patients that are sensitive to aspirin. Choline magnesium trisalicylate represents a mixture of choline salicylate and magnesium salicylate, which has the same effect as aspirin; however, it is easier on patients in which gastrointestinal effects are observed upon taking aspirin.

3.2.2 Pyrazolonees

In medicine, pyrazolonee derivatives play a significant role as analgesics, anti-inflammatory, and fever-reducing agents. Among these are antipyrin, butadion, amidopyrin, phenylpyrazon, sulfinpyrazone, sodium methamizol sodium (analgin), and a few others. In terms of analgesic and anti-inflammatory action, they are similar to salicylic acid derivatives. Although the mechanism of their action is not completely known, it is supposed that pyrazolone derivatives, like aspirin, inhibit biosynthesis of prostaglandins and reduce permeability of capillaries, thus preventing the development of inflammatory reactions. A serious limitation to the wide use of pyrazolonee in medicine is the cases of onset of agranulocytosis upon use of methamizol sodium.

Nevertheless, the most widely used derivative in medicine is methamizol sodium (although it is prohibited in some countries) as well as combined drugs on its base; in particular, baralgin, which represents a combined drug based on methamizol sodium with the spasmolytic 4′-(ethoxypiperidine)carbomethoxybenzophenone and the ganglionic blocker 2,2-diphenyl-4-piperidylacetamide.

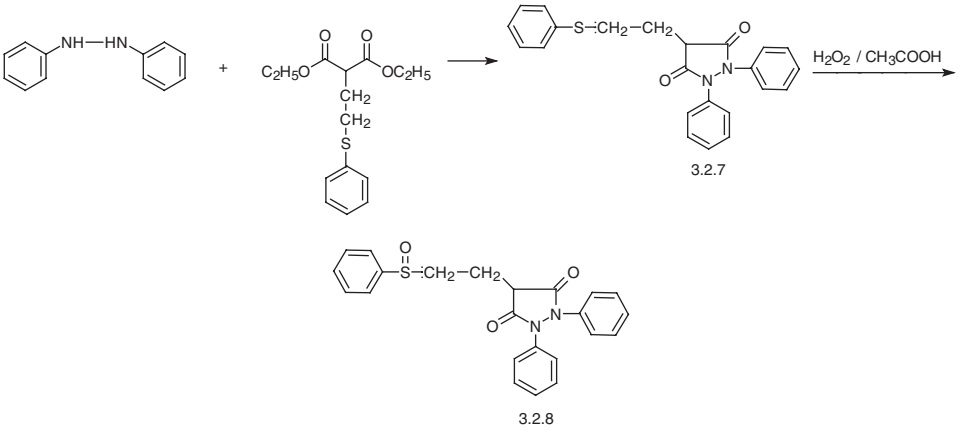
Phenylbutazone: Phenylbutazone, 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione (3.2.6), is synthesized in a single stage by reacting hydrazobenzol with butylmalonic ester [68,69].



3.2.6

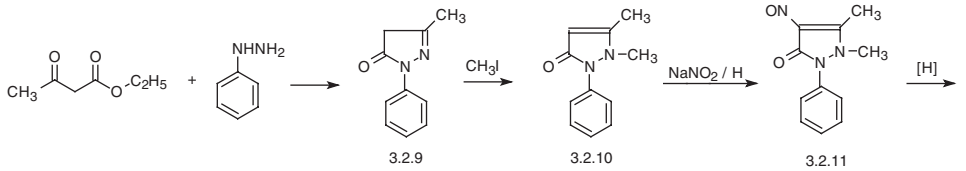
Phenylbutazone is used for relieving low to moderate pain in headaches, rheumatoid arthritis, and osteoarthritis. Its synonyms are algoverin, azolid, butazolidin, and others.

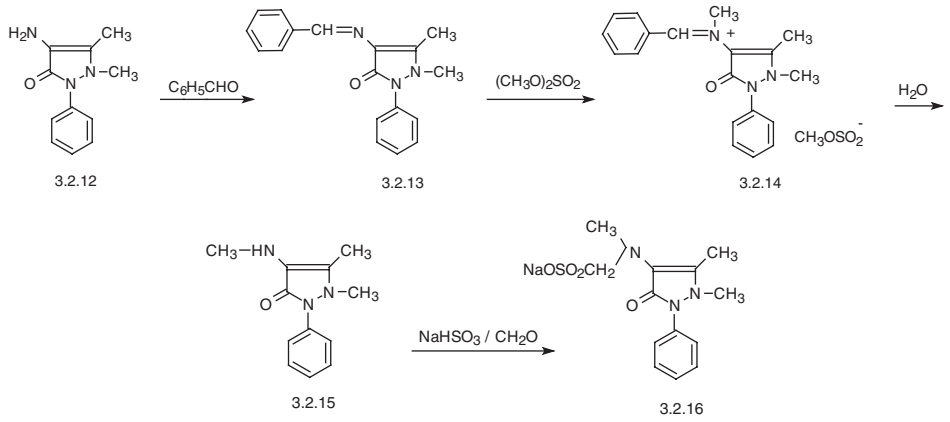
Sulfinpyrazone: Sulfinpyrazone, 1,2-diphenyl-4,2-(phenylsulfinil)ethyl-3,5-pyrazolidinedione (3.2.8), is an analog of phenylbutazone that is synthesized in the analogous manner of condensing hydrazobenzol with 2-(2-phenyltioethyl)malonic ester into pyrazolidinedione (3.2.7), and the subsequent oxidation of thiol ether by hydrogen peroxide in acetic acid into the sulfoxide, sulfinpyrazone (3.2.8) [70,71].



Sulfinpyrazone is used upon exactly the same indications as phenylbutazone. Synonyms for this drug are anturane and enturen.

Metamizole sodium: Methamizole sodium, 1-phenyl-2,3-dimethyl-4-methylaminopyrazolone-5-*N*-sodium methansulfonate (3.2.16), is synthesized in a multi-stage synthesis from acetoacetic ester and phenylhydrazine. Their reaction leads to the formation of 1-phenyl-3-methylpyrazolone-5 (3.2.9). Methylation of this product with methyl iodide gives 1-phenyl-2,3-dimethylpyrazolone-5 (3.2.10). This compound is used independently in medicine as a fever-reducing and anti-inflammatory analgesic under the name antipyrin. It undergoes nitrozation by sodium nitrite in an acidic medium, forming 1-phenyl-2,3-dimethyl-4-nitrozopyrazolone-5 (3.2.11). Reduction of the nitrous derivative (3.2.11) by different reducing agents leads to the formation of 1-phenyl-2,3-dimethyl-4-aminopyrazolone-5 (3.2.12). This product is reacted with benzaldehyde, forming an easily separable crystalline 1-phenyl-2,3-dimethyl-4-benzylidenaminopyrazolone-5 (3.2.13), which is methylated at the imine atom of nitrogen by dimethylsulfate, giving a quaternary salt (3.2.14). Hydrolysis of the resulting salt gives 1-phenyl-2,3-dimethyl-4-methylaminopyrazolone-5 (3.2.15). Treating the product with a water solution of a mixture of sodium bisulfite and formaldehyde leads to the formation of 1-phenyl-2,3-dimethyl-4-methylaminopyrazolone-5-*N*-sodium methanesulfonate (3.2.16), the desired sodium methamizole [72–75].

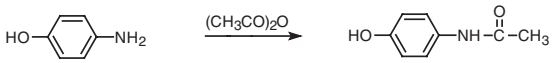




Methamizole sodium has expressed analgesic and fever-reducing properties and poorly expressed anti-inflammatory action, and is very convenient in cases where high concentrations of drug need to be quickly reached. Methamizole sodium is used for relieving pain of various origins (renal and biliary colic, neuralgia, myalgia, trauma, burns, headaches, and toothaches). Use of this drug may cause allergic reactions, and long-term use may cause granulocytopenia. Synonyms for this drug are dipyrone, analgin, and many others.

3.2.3 *p*-Aminophenol derivatives

Acetaminophen: Acetaminophen, *p*-acetaminophenol (3.2.80), is synthesized by reacting *p*-aminophenol with acetic anhydride [76,77].



3.2.17

Acetaminophen differs from the nonsteroidal anti-inflammatory agents described in that it is devoid of anti-inflammatory and antirheumatic properties. It was recently shown that acetaminophen, like aspirin, inhibits cyclooxygenase action in the brain and is even stronger than aspirin. On the other hand, the mechanism of analgesic action of acetaminophen is not fully clear, since it acts poorly on peripheral cyclooxygenase.

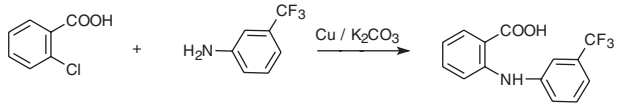
Acetaminophen is widely used as an analgesic and fever-reducing agent. Acetaminophen is designed for moderate analgesia. It is also effective like aspirin and is used in analgesia for headaches (from weak to moderate pain), myalgia, arthralgia, chronic pain, for oncological and post-operational pain, etc. Synonyms for this drug are paracetamol, tylenol, and many others.

3.2.4 Anthranylic acid derivatives

Anthranylic acid derivatives are direct structural analogs of salicylic acid derivatives. They possess analgesic, anti-inflammatory, and fever-reducing activity. They are similar to

pyrazolones in terms of analgesic and fever-reducing activity, yet they exceed the anti-inflammatory activity of salicylates. The mechanism of action of this series of nonsteroid, anti-inflammatory analgesics is not conclusively known.

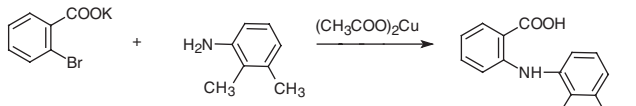
Flufenamic acid: Flufenamic acid, *N*-(α,α,α-trifluoro-*m*-tolyl)anthranylic acid (3.2.18), is synthesized by the reaction of 2-chlorobenzoic acid with 3-trifluoromethylaniline in the presence of potassium carbonate and copper filings [78,79].



3.2.18

Flufenamic acid is used for moderate pain and dysmenorrhea, but it should not be used for more than 1 week due to the possibility of nephrotoxicity, gastrointestinal toxicity, and anemia. It is frequently used in combination with the anticoagulant warfarin, the effect of which is strengthened when combined with flufenamic acid. Synonyms for this drug are arlef, flexocutan, romazal, and others.

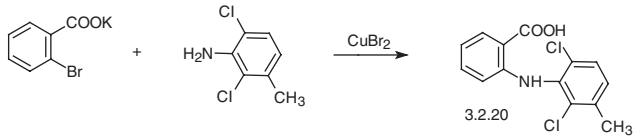
Mefenamic acid: Mefenamic acid, *N*-(2,3-xylyl)anthranylic acid (3.2.19), is synthesized in basically the same manner, by the reaction of the potassium salt of 2-bromobenzoic acid with 2,3-dimethylaniline in the presence of copper (II) acetate [80,81].



3.2.19

It is used for the same indications as flufenamic acid. Synonyms for this drug are parkemed, ponstan, ponstel, and others.

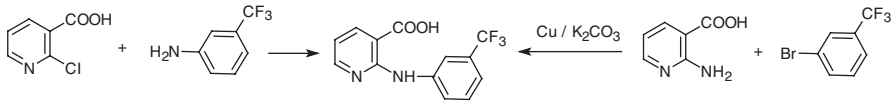
Meclofenamic acid: Meclofenamic acid, *N*-(2,6-dichloro-*m*-tolyl)anthranylic acid (3.2.20), is synthesized analogous to flufenamic acid, by the reaction of potassium salt of 2-bromobenzoic acid with 2,6-dichloro-3-methylaniline in the presence of copper (II) bromide in a mixture of *N*-ethylmorpholine and diglyme [82,83].



3.2.20

It is used for the same conditions as flufenamic acid. A synonym for this drug is movens.

Niflumic acid: Niflumic acid, 2-3-(trifluoromethyl)anilino nicotinic acid (3.2.21), is synthesized either by the reaction of 2-chloronicotinic acid with 3-trifluoromethylaniline [84–86], or 2-aminonicotinic acid with 1-bromo-3-trifluoromethylbenzene [87].



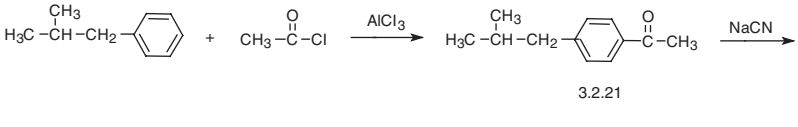
3.2.21

It is used for the exact same indications as the drugs described above. Synonyms for this drug are actol, flunir, nifluril, and others.

3.2.5 Propionic acid derivatives

This series of anti-inflammatory, analgesic, and fever-reducing compounds (ibuprofen, naproxene, ketoprofen, fenprofen) can be equally identified as both propionic acid derivatives as well as phenylpropionic acid derivatives. The mechanism of their action is not conclusively known; however, it has been suggested that it is also connected with the suppression of prostaglandin synthetase activity.

Ibuprofen: Ibuprofen, 2-(4-*iso*-butylphenyl)propionic acid (3.2.23), can be synthesized by various methods [88–98]. The simplest way to synthesize ibuprofen is by the acylation of *iso*-butylbenzol by acetyl chloride. The resulting *iso*-butylbenzophenone (3.2.21) is reacted with sodium cyanide, giving oxynitrile (3.2.22), which upon reaction with hydroiodic acid in the presence of phosphorus is converted into 2-(4-*iso*-butylphenyl)propionic acid (3.2.23), which subsequently undergoes phases of dehydration, reduction, and hydrolysis.

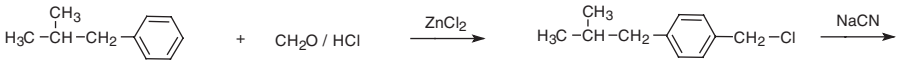


3.2.21

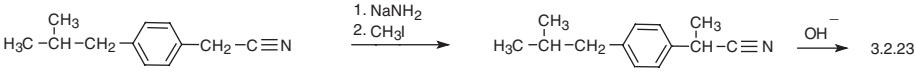


3.2.22 3.2.23

Another way to synthesize ibuprofen consists of the chloromethylation of *iso*-butylbenzene, giving 4-*iso*-butylbenzylchloride (3.2.24). This product is reacted with sodium cyanide, making 4-*iso*-butylbenzyl cyanide (3.2.25), which is alkylated in the presence of sodium amide by methyl iodide into 2-(4-*iso*-butylbenzyl)propionitrile (3.2.26). Hydrolysis of the resulting product in the presence of a base produces ibuprofen (3.2.23).



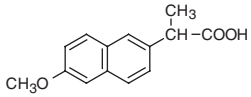
3.2.24



3.2.25 3.2.26 3.2.23

Ibuprofen is the first drug of the propionic acid derivatives that was permitted for clinical use. Ibuprofen exhibits analgesic, fever-reducing, and anti-inflammatory action comparable to, and even surpassing that of aspirin and acetaminophen. It is tolerated better than aspirin, and side effects are rarely observed. It is used in treating rheumatoid arthritis, in various forms of articular and nonarticular rheumatoid diseases, as well as for pain resulting from inflammatory peripheral nerve system involvement, exacerbation of gout, neuralgia, myalgia, ankylosing spondylitis, radiculitis, traumatic soft-tissue inflammation, and in the musculoskeletal system. It is used as an auxiliary drug in infections, inflammatory diseases of the ENT organs, adnexitis, dysmenorrhea, and for headaches and toothaches. It is not recommended for patients with stomach ulcers. The most common synonyms for ibuprofen are brufen, ibufen, motrin, rebugen, and others.

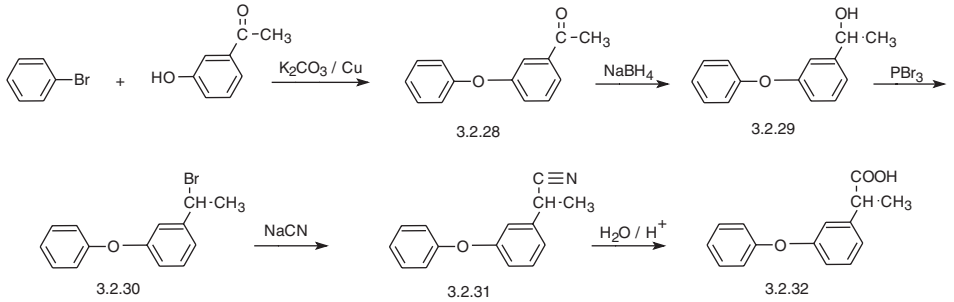
Naproxene: Naproxene, 2-(6-methoxy-2-naphthyl)-propionic acid (3.2.15) can be synthesized by the methods of synthesis described for ibuprofen as well as by the methods of fenoprofen (3.2.21) and ketoprofen (3.2.27) synthesis that will be described below from 2-acetyl or 2-chloromethyl-6-methoxynaphthaline [99–101].



3.2.27

Being analogous to other drugs of this series, naproxene exhibits analgesic, fever-reducing, and long-lasting anti-inflammatory action. It causes reduction and removal of painful symptoms including joint pain, stiffness, and swelling in the joints. It is used in the same indications as ibuprofen. Synonyms for naproxene are naprosyn, pronaxen, and apotex.

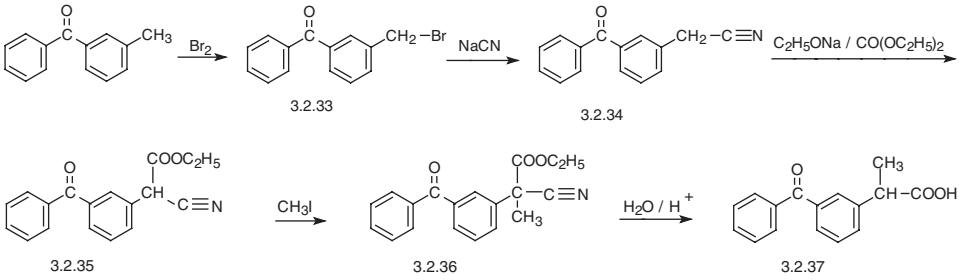
Fenoprofen: Fenoprofen, 2-(3-phenoxyphenyl)propionic acid (3.2.32), is synthesized from 3-hydroxyacetophenone, which is esterfied by bromobenzene in the presence of potassium carbonate and copper filings, forming 3-phenoxyacetophenone (3.2.28). The carbonyl group of the resulting product is reduced by sodium borohydride and the resulting alcohol (3.2.29) is brominated by phosphorous tribromide. The reaction of the resulting bromo derivative (3.2.20) with sodium cyanide gives 2-(3-phenoxyphenyl)propionitrile (3.2.31), which is hydrolyzed into the desired fenoprofen (3.2.32) [102,103].



3.2.28 3.2.29 3.2.30 3.2.31 3.2.32

Fenoprofen is chemically and pharmacologically similar to the series of compounds described above. It is used in treating symptoms of rheumatoid arthritis and osteoarthritis; however, fenoprofen exhibits a number of undesirable side effects. A synonym for fenoprofen is dista and others.

Ketoprofen: Ketoprofen, 2-(3-benzoyl)propionic acid (3.2.37), is synthesized from 3-methylbenzophenone, which undergoes bromination and forms 3-bromo-methylbenzophenone (3.2.33). The reduction of the resulting product by sodium cyanide gives 3-cyanomethylbenzophenone (3.2.34), which is reacted with the diethyl ester of carbonic acid in the presence of sodium ethoxide. The resulting cyanoacetic ester derivative (3.2.25) is alkylated by methyl iodide and the resulting product (3.2.36) undergoes acidic hydrolysis, forming ketoprofen (3.2.37) [104–106].



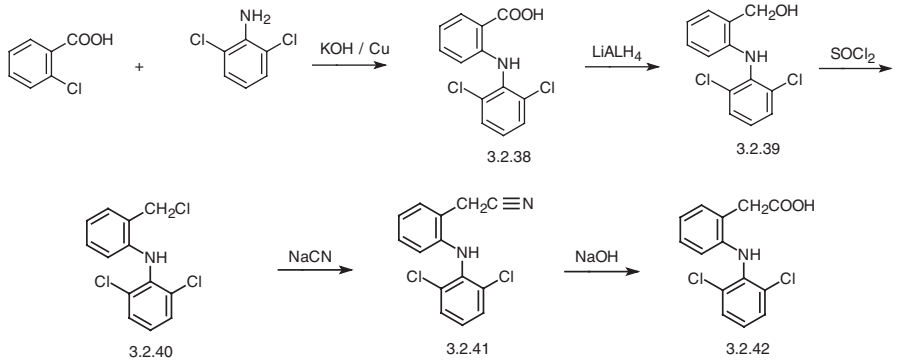
Ketoprofen is used for relieving weak to moderate pain in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout, back pain, neuralgia, and myalgia. It is also used for mild trauma; in particular, in sporting injuries such as sprains or ligament and muscle ruptures. It displays a number of undesirable side effects on hepatic and renal functions as well as on the gastrointestinal tract. The most common synonyms are alrheumat, fastum, ketalgin, reuprofen, and others.

3.2.6 Acetic acid derivatives

There are other drugs besides propionic acid derivatives—acetic acid derivatives in particular (diclofenac, feclofenac, alclofenac, among others)—that are very widely used as anti-inflammatory, analgesic, and fever-reducing compounds. It is supposed that their anti-inflammatory, analgesic, and fever-reducing action also is due to the suppression of prostaglandin synthetase activity.

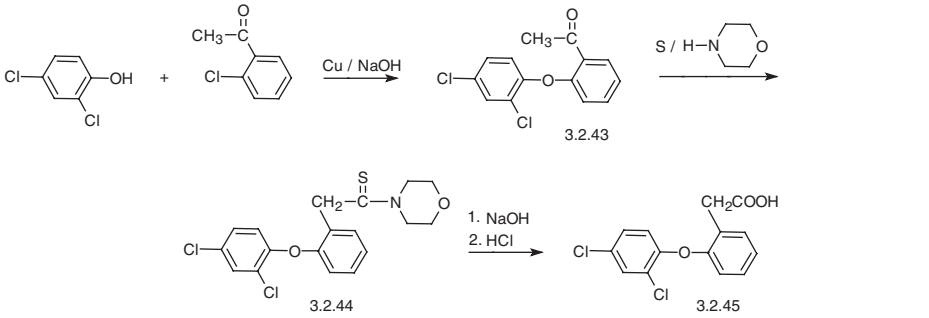
Diclofenac: Diclofenac, 2-[(2,6-dichlorophenyl)-amino]-phenylacetic acid (3.2.42), is synthesized from 2-chlorobenzoic acid and 2,6-dichloroaniline. The reaction of these in the presence of sodium hydroxide and copper gives *N*-(2,6-dichlorophenyl)anthranylic acid (3.2.38), the carboxylic group of which undergoes reduction by lithium aluminum hydride. The resulting 2-[(2,6-dicholorphenyl)-amino]-benzyl alcohol (3.2.39) undergoes further chlorination by thionyl chloride into 2-[(2,6-dichlorophenyl)-amino]-benzylchloride (3.2.40) and further, upon reaction with sodium cyanide converts into

2-[(2,6-dicholorophenyl)-amino]benzyl cyanide (3.2.41). Hydrolysis of the nitrile group leads to diclofenac (3.2.42) [107,108].



Diclofenac possesses all of the properties unique to the series of propionic acid drugs, yet in terms of anti-inflammatory and analgesic strength it exceeds that of aspirin, analgin, and ibuprofen. It is used in acute rheumatism, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, arthrosis, back pain, neuralgia, and myalgia. It rarely causes side effects. The most common synonym is voltaren.

Fenclofenac: Fenclofenac, *o*-[2,4-dichlorophenoxy)phenyl]acetic acid (3.2.45), is synthesized from 2,4-dichlorophenol and 2-chloroacetophenone, the reaction of which in the presence of sodium hydroxide and powdered copper forms the corresponding 2-acetyl-2′,4′-dichloro-diphenyl ester (3.2.43). The resulting product is reacted with sulfur and morpholine according to Willgerodt method, giving thioamide (3.2.44), which is further hydrolyzed to the desired fenclofenac [109,110].

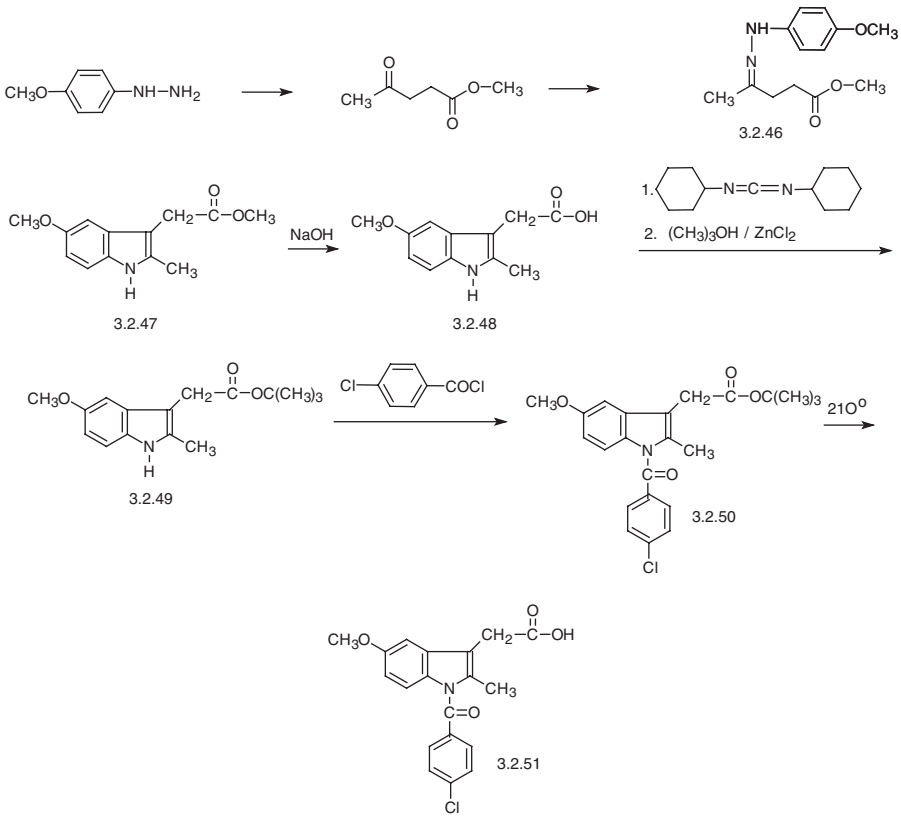


This drug is used for the same indications as diclofenac. A synonym for this drug is flenac.

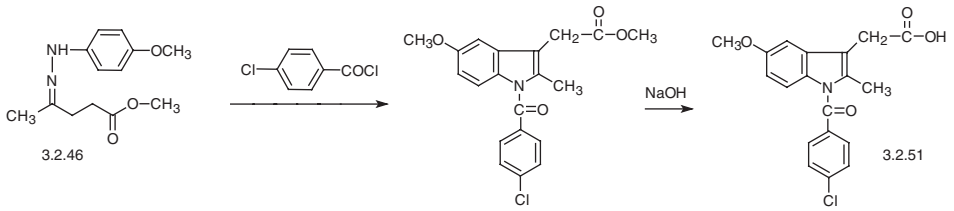
3.2.7 Indolyl/indeneacetic acids

Drugs of this series, indomethacin, tolmetin, sulindac, and others are very effective nonsteroidal anti-inflammatory drugs with strongly expressed analgesic action. They are strong inhibitors of prostaglandin biosynthesis.

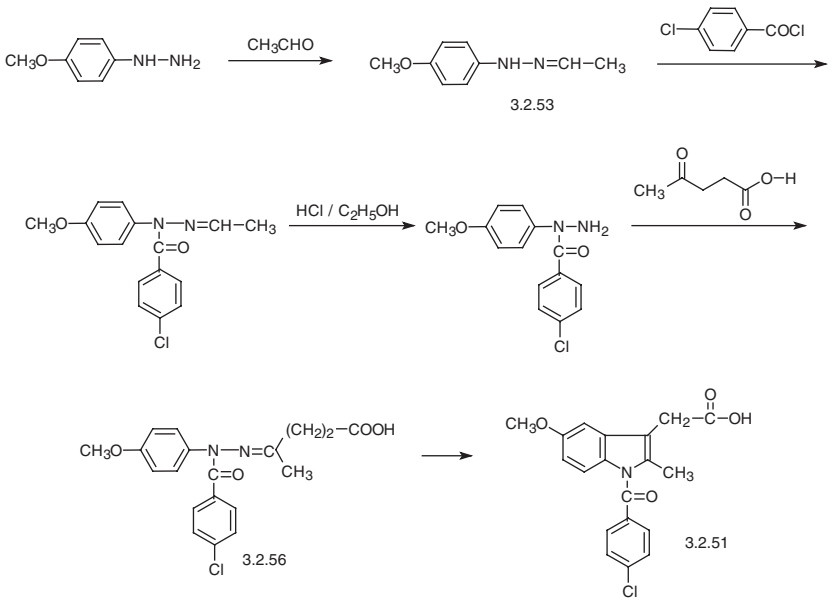
Indomethacin: Indomethacin, 1-(*n*-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetic acid (3.2.51), has been synthesized by various methods. All of the proposed methods of synthesis start with 4-methoxyphenylhydrazine. According to the first method, a reaction is done to make indole from phenylhydrazone (3.2.46) by Fischer's method, using levulinic acid methyl ester as a carbonyl component, hydrogen chloride as a catalyst, and ethanol as a solvent, to give the methyl ester of 5-methoxy-2-methyl-3-indolylacetic acid (3.2.47). This product is hydrolyzed by an alkali into 5-methoxy-2-methyl-3-indolylacetic acid (3.2.48), from which *tert*-butyl ester of 5-methoxy-2-methyl-3-indolylacetic acid (3.2.49) is formed by using *tert*-butyl alcohol and zinc chloride in the presence of dicyclohexylcarbodiimide. The resulting product undergoes acylation at the indole nitrogen atom by *p*-chorobenzoyl chloride in dimethylformamide, using sodium hydride as a base. The resulting *tert*-butyl ester of 1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid (3.2.50), further undergoes thermal decomposition to the desired acid, indomethacin (3.2.51) [111,112].



According to the other scheme, phenylhydrazone (3.2.46) undergoes cyclization in the presence of the same *p*-chlorobenzoic acid chloride, during which acylation of hydrazone and its cyclization into methyl ester of 5-methoxy-2-methyl-2-(*p*-chlorobenzoyl)-3-indolylacetic acid (3.2.52) simultaneously take place. The resulting product is further hydrolyzed by an alkali to give indomethacin (3.2.51) [113,114].



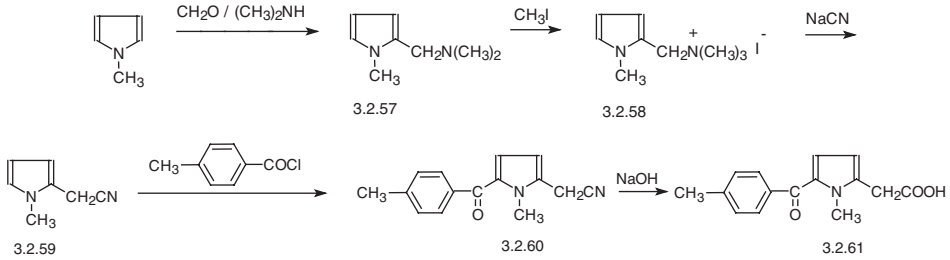
The same substance has been suggested to be synthesized directly from 4-methoxyphenyl-*n*-chlorobenzoylhydrazine and levulinic acid by cyclization of the respective hydrazone in the presence of hydrogen chloride. In order to do this, condensation of acetaldehyde with *n*-methoxyphenylhyrazine gives hydrazone (3.2.53), which is acylated by *p*-chlorobenzoyl chloride, forming hydrazone (3.2.54). The product is hydrolyzed into hydrazine (3.2.55). Interacting the product with levulinic acid gives hydrazone (3.2.56), which undergoes Fischer cyclization into indomethacin (3.2.51) [115].



Indomethacin is used in rheumatoid arthritis, nonspecific infectious polyarthritis, gouty arthritis, osteoarthritis, ankylosing spondylitis, arthrosis, back pain, neuralgia, myalgia, and other diseases accompanied by inflammation. Synonyms for indomethacin are, among others, metindol, indacide, and rumacide.

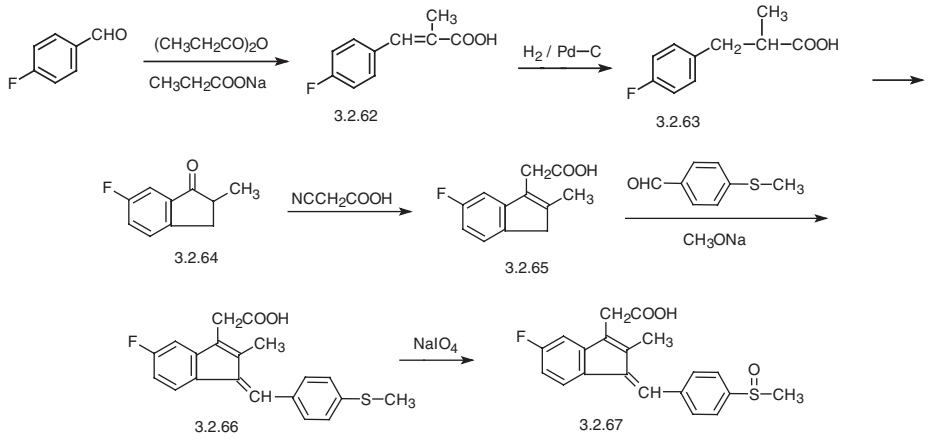
Tolmetin: Tolmetin, 1-methyl-5-*n*-tolylpyrrol-2-acetic acid (3.2.61) is synthesized from 1-methylindole, which is aminomethylated using formaldehyde and dimethylamine, forming 2-dimethylaminomethyl-1-methylindol (3.2.57). The product is methylated by methyl iodide, giving the corresponding quaternary salt (3.2.58). Reaction of the product with sodium cyanide gives 1-methylpyrrole-2-acetonitrile (3.2.59), which is acylated at the free

α-position of the pyrrole ring by 4-methylbenzoylchloride in the presence of aluminum chloride. The resulting 1-methyl-5-*n*-toluylpyrrol-2-acetonitrile (3.2.60) undergoes further alkaline hydrolysis, giving corresponding acid, tolmetin (3.2.61) [116–118].



Tolmetin, like all of the drugs described above, inhibits synthesis of prostaglandins and exhibits expressed analgesic, anti-inflammatory, and fever-reducing properties. It is used for relieving weak to moderate pain in rheumatoid arthritis and osteoarthritis. Synonyms for tolmetin are tolectin, tolmex, and others.

Sulindac: Sulindac, 5-fluoro-2-methyl-1-[*n*-(methylsulfinyl)benzyliden]inden-3-acetic acid (3.2.67) is synthesized in a multi-step synthesis from *n*-fluorobenzaldehyde, which upon condensation with propionic acid anhydride in the presence of sodium acetate gives 4-fluoro-α-methylcinnamic acid (3.2.62). Reduction of the double bond by hydrogene using a palladium on carbon catalyst gives 4-fluoro-α-methyldihydrocinnamic acid (3.2.63). In the presence of polyphosphoric acid, the resulting product undergoes cyclization to 5-fluoro-2-methyl-3-indanone (3.2.64). The resulting ketone undergoes a Knoevenagel reaction with cyanoacetic acid and is further decarboxylated into 5-fluoro-2-methyliden-3-acetic acid (3.2.65). Condensation of the product with *n*-mercaptobenzaldehyde in the presence of sodium methoxide gives 5-fluoro- 2-methyl-1-(4-methylthiobenzyliden)-3-indenacetic acid (3.2.66), and the sulfur atom is oxidized by sodium periodate into the desired sulfoxide (3.2.67), sulindac [119–122].

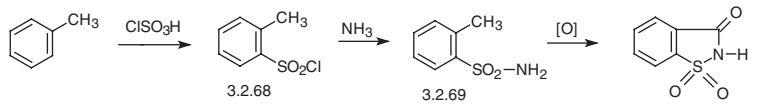


Sulindac is used for relieving weak to moderate pain in rheumatoid arthritis and osteoarthritis. Synonyms for sulindac are suprol, imbaral, and others.

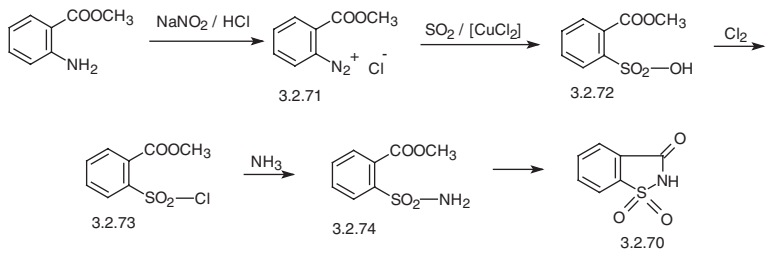
3.2.8 Oxicames

Oxicames are representatives of another series of anti-inflammatory, analgesic, and fever-reducing compounds whose mechanisms of action are most likely the suppression of prostaglandin synthesis. These drugs are capable of relieving painful symptoms of medium intensity.

Piroxicam: Piroxicam, 1,1-dioxid-4-hydroxy-2-methyl-*N*-2-pyradyl-2*H*-1,2-benzothiazine-3-carboxamide (3.2.78), is synthesized from saccharin (3.2.70). Two methods for saccharin synthesis are described. It usually comes from toluene, which is sulfonated by chlorosulfonic acid, forming isomeric 4- and 2-toluenesulfonyl chlorides. The isomeric products are separated by freezing (chilling). The liquid part, 2-toluenesulfonyl chloride (3.2.68) is separated from the crystallized 4-toluenesulfochloride and reacted with ammonia, giving 2-toluenesulfonylamide (3.2.69). Oxidation of the product with sodium permanganate or chromium (VI) oxide in sulfuric acid gives saccharin—*o*-sulfobenzoic acid imide (3.2.70) [123–126].

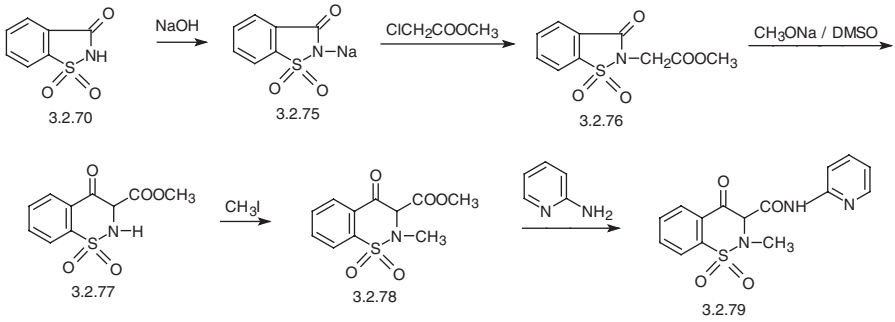


An alternative way for making saccharin is from methyl ester *o*-aminobenzoic (anthranylic acid). This undergoes diazotization using nitrous acid, and the resulting diazonium salt (3.2.71) is reacted with sulfur dioxide in the presence of copper dichloride, forming the methyl ester *o*-sulfobenzoic acid (3.2.72). Reaction of the resulting product with chlorine gives *o*-chlorosulfonylbenzoic acid methyl ester (3.2.73), which upon reaction with ammonium gives *o*-sulfonylamidobenzoic acid methyl ester (3.2.74). In the presence of hydrogen chloride, the resulting product undergoes cyclization into saccharin (3.2.70).



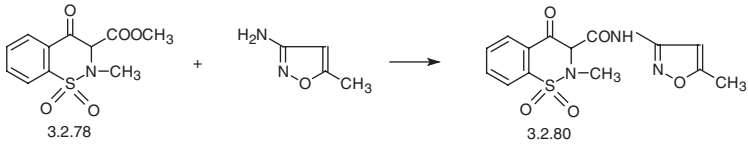
The reaction of saccharin with sodium hydroxide results in substitution of the imide hydrogen atom of saccharin with sodium, giving a sodium salt (3.2.75). The resulting product is reacted with methyl chloroacetate, giving the saccharin-substituted acetic acid methyl ester (3.2.76). Upon reaction with sodium methoxide in dimethylsulfoxide, the product undergoes

rearrangement into 1,1-dioxide 3-methoxycarbonyl-3,4-dihydro-2-*H*-1,2-benzothiazin-4-one (3.2.77). This product is methylated at the nitrogen atom using methyl iodide, giving (3.2.78). Finally, reaction of the resulting product with 2-aminopyridine gives piroxicam (3.2.79).



As was already mentioned, piroxicam also is a nonsteroidal, anti-inflammatory drug. It is used in inflammatory and degenerative diseases of the musculoskeletal system that are accompanied by painful symptoms. It is used for rheumatic heart disease, nonspecific infectious polyarthritis, gouty arthritis, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, arthrosis, back pain, neuralgia, myalgia, and other diseases associated with inflammation. Synonyms for piroxicam are feldene, dexicam, roxenan, and others.

Isoxicam: Isoxicam, 1,1-dioxide 4-hydroxy-2-methyl-*N*-(5-methyl-3-isoxazolyl)-2*H*-1,2-benzothiazine-3-carboxamide (3.2.80), is synthesized analogous to piroxicam, using amidation of 1,1-dioxide 3-methoxycarbonyl-3,4-dihydro-2-*H*-1,2-benzothiazine-4-one (3.2.78) in the last stage with 3-amino-5-methylisoxazole, instead of 2-aminopyridine [127–130].



It is used for the same indications as piroxicam. Synonyms for isoxicam are floxicam and maxicam.

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– 4 –

Soporific Agents (Hypnotics and Sedative Drugs)

Insomnia is a symptom, and its proper treatment depends on finding the cause of sleeplessness and treating the underlying etiology. The most common type of insomnia is transient insomnia due to acute situational factors. The typical factor is stress. Chronic insomnia is most commonly caused by psychiatric disorders. Numerous medical disorders can cause insomnia. Many drugs have been implicated as causing insomnia: alcohol, antihypertensives, antineoplastics, β-blockers, caffeine, corticosteroids, levodopa, nicotine, oral contraceptives, phenytoin, protriptyline, selective serotonin reuptake inhibitors (SSRIs), stimulants, theophylline, and thyroid hormones. The underlying cause or causes of insomnia should be treated whenever possible. The primary indication for use of hypnotic agents in patients with insomnia is transient sleep disruption caused by acute stress.

Soporific agents are drugs that facilitate the development and normalization of sleep. However, sleep induced by the majority of drugs is different than natural sleep. For approximately 100 years, bromides, followed by chloral hydrate, and subsequently barbiturates were the only drugs capable of relieving patient conditions of insomnia and neurological disorders. However, today there are many known compounds of various chemical classes that can be classified as hypnotics and sedative drugs, which are capable of causing various degrees of central nervous system (CNS) depression, relieving anxiety, and causing sleep. The efficacy of these drugs is directly proportional to the administered dosage, displaying various degrees of CNS depression from sedation and sleep to complete loss of consciousness.

Sedation is an intermediate degree of CNS depression, while hypnosis is a degree of CNS depression similar to natural sleep. From the chemical point of view, soporific, sedative, and hypnotic drugs are classified as barbiturates, benzodiazepine hypnotics, and so on. Except for a few rare exceptions, any one of these compounds can be used for acquiring a sedative effect or state of sleep. Presently, the less toxic benzodiazepines are edging out the class of barbiturates more and more because of the possibility of chronic dependence associated with the use of barbiturates. Drugs of both classes are primarily CNS depressants, and a few of their effects, if not all, are evidently linked to action on the GABA-receptor complex.

4.1 BARBITURATES

Barbiturate action on the CNS is expressed in very diverse ways, ranging from small changes in patient behavior to the onset of more obvious effects such as sedation, sleep, or general anesthesia, depending, as a rule, on the administered dosage. The pharmacological basis of such CNS depression is extremely complex in its own right. Drugs act on various parts of the CNS by interfering with transmission of impulses in synapses, and generally speaking, stopping transmission of impulses to the spinal cord. Despite the fact that the mechanism of barbiturate action is currently not completely known, it seems very possible that barbiturates strengthen the GABA-induced flow of chloride ions into the neuronal tissue, which results in the hyperpolarization of the cell membrane. It is possible that other effects of barbiturates on the CNS are connected with their ability to increase membrane permeability. It is assumed that barbiturate molecules penetrate the lipid bilayer membrane and increase the rigidity of its structural organization. It is hypothetically possible that they can act, as do a few other drugs of other classes such as general anesthetics, by changing the ability of the cell membrane to allow ion flow, influencing the secretion of neurotransmitters, and changing the conformation of enzymes. In other words, it is not improbable that they act according to receptor mechanisms, but by their own physical presence in the membrane. However, all of the stated hypotheses can be severely criticized.

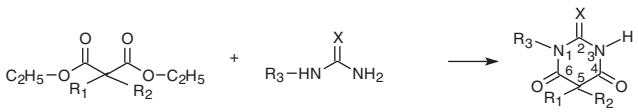
Clinically beneficial barbiturates are conventionally subdivided into four groups:

(a) Long-acting barbiturates (6–8 h): mephobarbital, metharbital, and phenobarbital.
(b) Intermediate-lasting barbiturates (4–6 h): amobarbital, butabital, and talbutal.
(c) Short-acting barbiturates (2–4 h): pentobarbital, secobarbital.
(d) Ultrashort-acting barbiturates (10–30 min): methohexital, thiopental.

Despite the fact that the present classifications are extremely convenient for practical medical personnel, it should be kept in mind that the duration of drug action—especially of the first three groups of compounds—depends on various factors besides the structure of the compounds, such as drug form, method of administration, pathology for which the drug is being used, general treatment time, etc.

Barbiturates are used for brief periods of time for treating insomnia, since regular use of barbiturates (on average around 3 weeks) can lead to tolerance. Barbiturates are also used for controlling severe convulsive conditions and for treating various forms of epilepsy. They are used for pre- and post-operational sedation as well as in daytime sedation, for relieving patient anxiety, nervousness, and tension. Barbiturates are also used for treating catatonic and maniacal reactions, and as agents used in psychoanalysis (narcoanalysis and narcotherapy). Ultrashort-acting barbiturates are used in anesthesia.

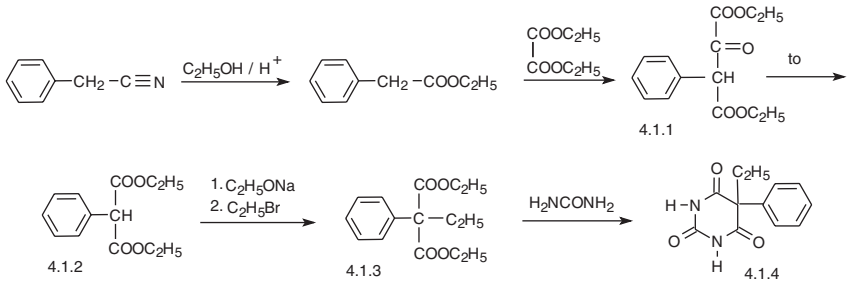
Barbiturates are derivatives of barbituric acid and are synthesized by condensation of malonic acid derivatives with urea derivatives.



They are weak acids that form salts. In the literature, specific rules dealing with the correlation and activity in this series of compounds are described. As a rule, in order to exhibit central depressive action, barbiturates should contain two substituents on C_5 of the hydrogenated pyrimidine ring. 5,5-Diethyl derivative of barbituric acid is a weak hypnotic, since barbiturates with one ethyl group and another substituent with a longer carbon chain exhibit a stronger hypnotic effect. Moreover, drugs with bifurcated alkyl substituents have stronger hypnotic activity than substituents with normal carbon chains. Barbiturates with phenyl groups on C_5 are weaker hypnotics than compounds with an aliphatic or alicyclic substituent; however, they have expressed antiepileptic and anticonvulsant action. N-methylation increases the lipid solubility of drugs and lessens the duration of drug action. It also can strengthen a drug's antiepileptic properties, while methylation on both nitrogen atoms leads to convulsions. Substitution of an oxygen atom for a sulfur atom in the second position (thiobarbiturate), causes marked elevation of the distribution coefficient in lipid–water mixtures in 5,5-disubstituted barbiturates. These compounds have more strength as hypnotics than their oxygenated analogs upon intravenous administration; however, their low solubility in water and localization in fat storage make them unfit for oral use as hypnotics. They are primarily used as intravenous anesthetics (ultrashort-acting barbiturates).

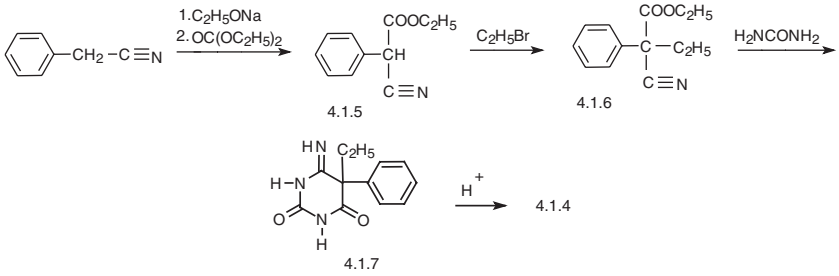
4.1.1 Long-acting barbiturates

Phenobarbital: Phenobarbital, 5-ethyl-5-phenylbarbituric acid or 5-ethyl-5-phenylhexahydropyrimidin-2,4,6-trione (4.1.4), has been synthesized in several different ways [1–4]. There is no major difference between them. The first method consists of ethanolysis of benzyl cyanide in the presence of acid, giving phenylacetic acid ethyl ether, the methylene group of which undergoes acylation using the diethyloxalate, giving diethyl ester of phenyloxobutandioic acid (4.1.1), which upon heating easily loses carbon oxide and turns into phenylmalonic ester (4.1.2). Alkylation of the obtained product using ethylbromide in the presence of sodium ethoxide leads to the formation of α-phenyl-α-ethylmalonic ester (4.1.3), the condensation of which with urea gives phenobarbital (4.1.4) [1].



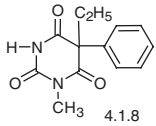
Another method of phenobarbital synthesis starts with condensation of benzyl cyanide with diethylcarbonate in the presence of sodium ethoxide to give α-phenylcyanoacetic ester (4.1.5). Alkylation of the ester (4.1.5) using ethylbromide gives α-phenyl-α-ethylcyanoacetic

ester (4.1.6), which is further converted into the 4-iminoderivative (4.1.7). Acidic hydrolysis of the resulting product gives phenobarbital (4.1.4) [2].



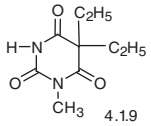
Phenobarbital exhibits relaxant, soporific, and anticonvulsant activities. It is widely used in treating epilepsy, chorea, and spastic paralysis, and is used as a component of a large number of combined drugs, valocordin and corvalol in particular. The most common synonyms are luminal, fenemal, hypnotal, and several others.

Mephobarbital: Mephobarbital, 5-ethyl-1-methyl-5-phenylbarbituric acid (4.1.8), is synthesized according to one of the diagrams used for the phenobarbital synthesis, except one uses methylurea instead [5].



Mephobarbital is used as a sedative agent for relieving anxiety and tension as well as for major and minor epileptic attacks. Synonyms for this drug are barbefenal, enfenemal, and methylphenobarbital.

Metharbital: Metharbital, 5,5-diethyl-1-methylbarbituric acid (4.1.9), is synthesized by condensation of diethylmalonic ester with methylurea [6,7].

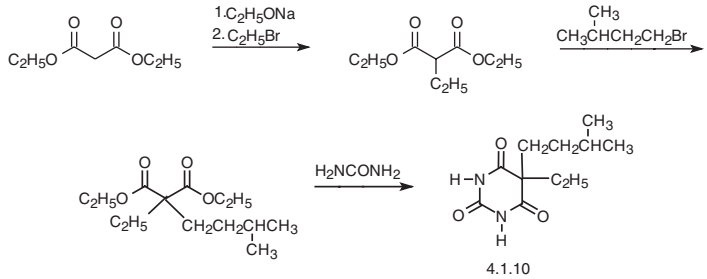


Metharbital, like phenobarbital and mephobarbital, exhibits anticonvulsant activity. It is used in major and minor epileptic attacks. Synonyms for this drug are endiemalum, gemonil, and methabarbital.

4.1.2 Intermediate-acting barbiturates

Amobarbital: Amobarbital, 5-ethyl-5-isoamylbarbituric acid (4.1.10), like all barbiturates, is synthesized by reacting malonic acid derivatives with urea derivatives. In

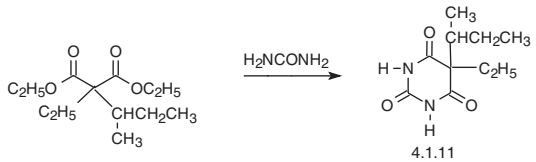
particular, in order to make amobarbital, α-ethyl-α-isoamylmalonic ester is reacted with urea (in the presence of sodium ethoxide), giving amobarbital (4.1.10) [8,9].



4.1.10

Amobarbital is used as a soporific drug in various forms of insomnia and as a sedative and anticonvulsant drug. The most frequently used synonyms are barbamil, amital, and hypnamil.

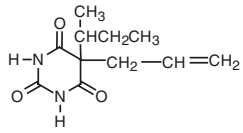
Butabarbital: Butabarbital, 5-ethyl-5-isobutylbarbituric acid (4.1.11), is also synthesized in an analogous manner by condensation of α-ethyl-α-isobutylmalonic ester with urea [9].



4.1.11

Butabarbital is also used as a soporific drug in various forms of insomnia and as a sedative. The most frequently used synonym is butizone.

Talbutal: Talbutal, 5-allyl-5-sec-butylbarbituric acid (4.1.12), is synthesized by reacting α-allyl-α-fluorobutylmalonic ester with urea [10].



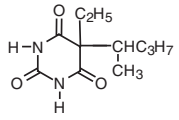
4.1.12

Talbutal differs from butabarbital in that a sec-butyl radical is used in talbutal, whereas in butabarbital, an isobutyl radical can be used as a substituent on C_5. Talbutal is used as a sedative, soporific drug for the same indications as butabital. Synonyms for this drug are profundol, lotusate, and others.

4.1.3 Short-action barbiturates

Pentobarbital: Pentobarbital, 5-ethyl-5-(2-amil)barbituric acid (4.1.13), is synthesized by methods analogous to that of amobarbital, the only difference being that the alkylation of

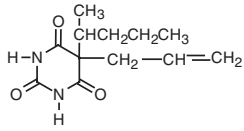
α-ethylmalonic ester is carried out with 2-bromopentane (not 1-bromo-3-methylbutane) to give pentobarbital (4.1.13) [11–13].



4.1.13

Pentobarbital is basically considered an isomer of amobarbital. They are similar in terms of action, and the difference lies in the fact that pentobarbital is shorter lasting and easier to tolerate. It is used as a relaxant as well as a soporific for short-term insomnia. The most frequently used synonym of this drug is nembutal.

Secobarbital: Secobarbital, 5-allyl-5-(1-methylbutyl)barbituric acid (4.1.14), is also synthesized by the same standard schema of reacting α-allyl-α-(1-methylbutyl)-malonic ester with urea [14].

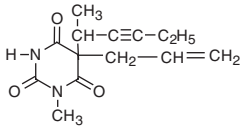


4.1.14

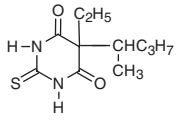
Secobarbital is used for the same indications as pentobarbital as a relaxant, and also as a soporific for short-term insomnia. The most frequently used synonyms are barbosec, hinased, and others.

4.1.4 Ultrashort-action barbiturates

The synthesis and properties of methohexital (1.2.15) and thiopental (1.2.10) are described in Chapter 1.



1.2.15



1.2.10

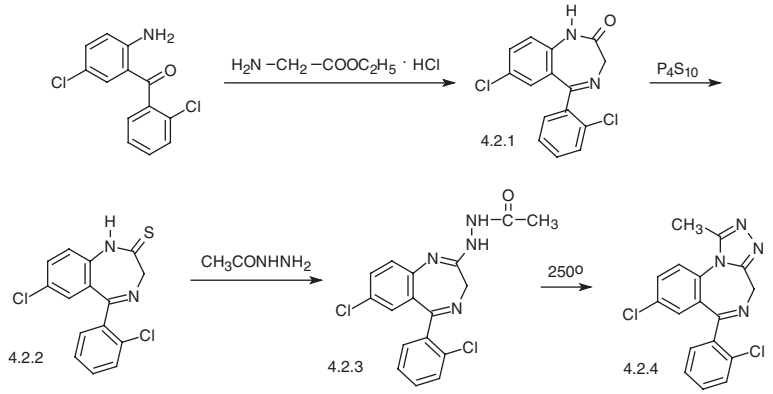
Of the barbiturates examined above, the most widely used in medicine are phenobarbital, amobarbital, butabarbital as well as methohexital and thiopental.

4.2 BENZODIAZEPINES

Benzodiazepine derivatives are a basic class of anxiolytics or tranquilizers—compounds for treating conditions of general anxiety, and their synthesis and properties as such will be considered separately. However, despite the fact that the principal clinical effect

of the benzodiazepines used in medicine is basically qualitatively identical, certain benzodiazepines are used for specific purposes other than relieving anxiety. In particular, representatives of this series of benzodiazepines such as flurazepam, temazepam, and triazolam are used as hypnotics, while clonazepam is used as an anticonvulsant drug. Moreover, the most pharmacologically effective drugs presently used for treating sleep disturbances are flurazepam, temazepam, and triazolam. However, in small doses the above hypnotics are sedative drugs. It is believed that their primary action consists of alleviation of psychological anxiety, the resulting calmness of which facilitates development of sleep. The mechanism of action of benzodiazepines is related to their interaction with specific benzodiazepine receptors, considering that as a result of binding, the affinity of inhibitory GABA neurotransmitters to their respective receptors is increased, which strengthens the inhibitory action of the GABA. The examined drugs flurezepam, temazepam, and triazolam evidently raise the inhibitory effect of GABA on the CNS.

Triazolam: Triazolam, 8-chloro-6-(2′-chlorophenyl)-1-methyl-4-*H*-s-triazolo[4,3-a]-[1,4]benzodiazepine (4.2.4), is synthesized according to a method that contains a key stage of benzodiazepine synthesis—the reaction of *o*-aminobenzophenones with α-amino acid derivatives. In the given example, the reaction of 2-amino-2′,5-dichlorobenzophenone with glycine ethyl ester gives 7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-*H*-1,4-benzodiazepin-2-one (4.2.1). By interacting this with phosphorus pentasulfide, the carbonyl group is transformed into a thiocarbonyl group, giving 7-chloro-5-(2-chlorophenyl)-2,3-dihydro-1-*H*-1,4-benzodiazepin-2-thione (4.2.2). The resulting cyclic thioamide on interaction with acetylhydrazine, gives the corresponding acetylhydrazone (4.2.3), which upon heating cyclizes into triazolam (4.2.4) [15–20].

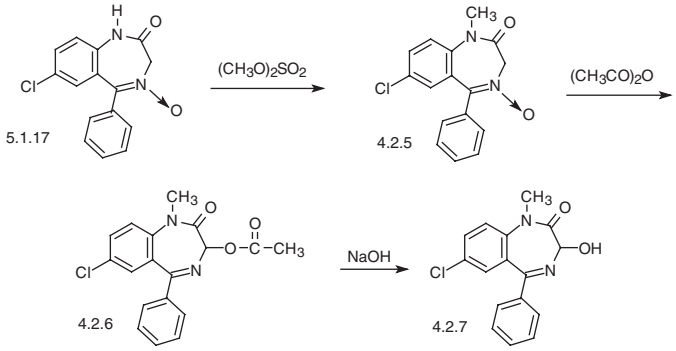


Triazolam is the most frequently prescribed drug for insomnia. However, addiction to triazolam can develop very quickly, as can a number of other side effects such as early-morning insomnia, daytime anxiety, and others. Synonyms for this drug are normison, remstan, restoril, and others.

Temazepam: Temazepam, 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (4.2.7), is synthesized from the intermediate product of oxazepam synthesis,

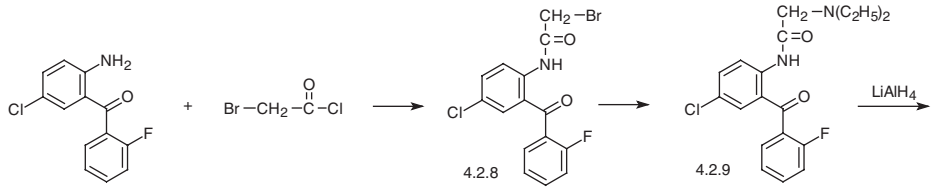
7-chloro-5-phenyl-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1,4-benzodia- zepin-2-on-4-oxide (5.1.17), by methylation of the nitrogen of the amide group in the first position of the benzodiazepine ring using dimethylsulfate, which gives 1-methyl-7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-on-4-oxide (4.2.5), which undergoes acetylation by acetic anhydride, to give 1-methyl-3-acetoxy-7-chloro-5-phenyl-1,3-dihydro-2*H*-1, 4-benzodiazepin-2-one (4.2.6) during which, a transformation like Polonovski reaction, obviously, takes place.

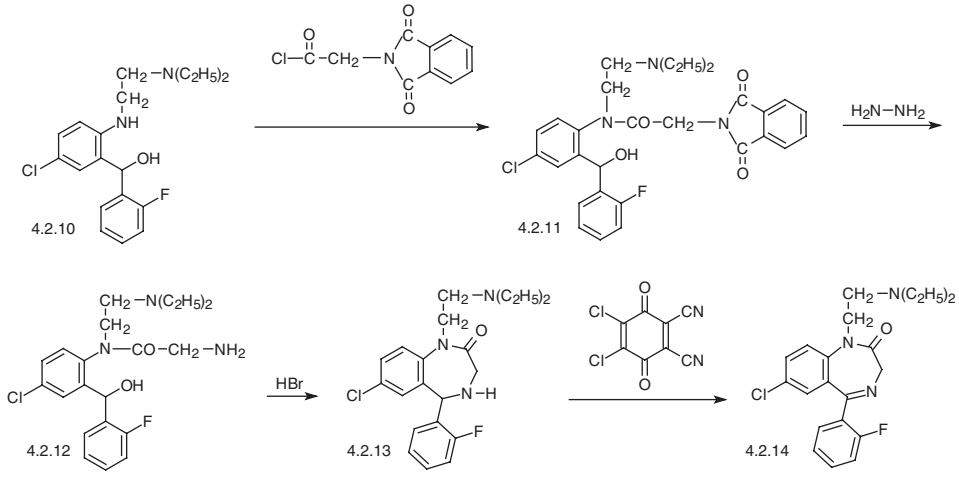
Alkaline hydrolysis of the resulting compound (4.2.6) removes the acetyl group, leading to the desired temazepam (4.2.7) [21–26].



Temazepam is a moderately effective hypnotic. Insomnia may again reappear upon completion of drug treatment. The most frequently used synonym for this drug is galcion.

Flurazepam: Flurazepam, 7-chloro-1[2-(diethylamino)ethyl]-5-(2′-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (4.2.14), has been synthesized in a multi-stage synthesis beginning with 2-amino-5-chloro-2′-fluorobenzophenone. Reacting this with bromoacetic acid chloride gives 2-(bromoacetyl)amino-5-chloro-2′-fluorobenzophenone (4.2.8), which on reaction with diethylamine gives 2-(diethylaminoacetyl)amino-5-chloro-2′-fluorobenzophenone (4.2.9). The reduction of both carbonyl groups by lithium-aluminum hydride gives 2-(2′-diethylamino)ethylamino-5-chloro-2′-fluorobenzhydrol (4.2.10). The amino group of this product is acylated by phthalimidoacetyl chloride, giving a phthalimido derivative (4.2.11). Removal of the protective phthalimide group by hydrazine hydrate gives 2-(2′-diethylamino)ethylaminoacetyl)amino-5-chloro-2′-fluorobenzhydrol (4.2.12). Treatment of this product with hydrobromic acid leads to intermolecular dehydration with ring closure to give a seven-member benzodiazepine cycle 7-chloro-1-[2-(diethylamino)ethyl]-5-(2′-fluorophenyl)-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (4.2.13). Finally, oxidation of the N_4–C_5 bond of the resulting 2,3-dichloro-5,6-dicyano-1,4-benzoxyanone gives the desired flurazepam (4.2.14) [27–30].



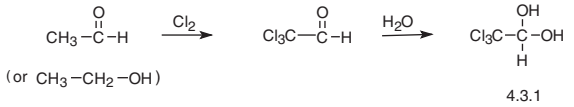


Flurazepam is the most well-studied hypnotic. It is used for difficulties in sleeping or falling asleep, and frequent or early waking. Side effects are rarely observed. The most common synonyms are dalmadorm, dalmane, valdrom, felison, and others.

4.3 OTHER HYPNOTICS AND SEDATIVE DRUGS

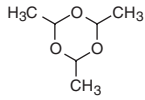
Before benzodiazepines emerged as a class of drugs, a number of empirically discovered compounds were used in medicine as hypnotics. Among these were chloral hydrate, paraldehyde, ethchlovinol, ethinamat, glutetimide, and methyprilone.

Chloral hydrate: Chloral hydrate, 2,2,2-trichloro-1,1-ethandiol (4.3.1), is synthesized either by chlorination of ethanol or chlorination of acetaldehyde and the subsequent addition of water molecules to the resulting trichloroacetic aldehyde [31].



The sedative–hypnotic action of chloral hydrate should be explained by the formation of trichloroethanol, which is synthesized as a result of its reduction in tissues. Despite the fact that the precise mechanism of action of chloral hydrate is not known, it evidently acts analogous to ethanol on the CNS by increasing membrane permeability, which leads to sedation or sleep. Chloral hydrate can be used for insomnia as an alternative to benzodiazepines. Synonyms for this drug are aquachloral, chloradorm, chloratol, noctec, and others.

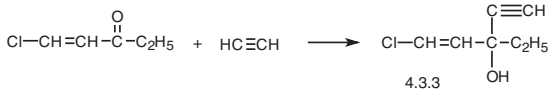
Paraldehyde: Paraldehyde, 2,4,6-trimethyl-1,3,5-trioxane (4.3.2), is a trimeric acetaldehyde which is synthesized by the acid-catalyzed polymerization of acetaldehyde and at moderate and high temperatures [32,33].



4.3.2

The exact mechanism of action of paraldehyde is not known; however, it is highly likely that it acts itself, and not as the products of its biotransformation. The indications for use are analogous to chloral hydrate. Synonyms for this drug are elaldehyde, paral, and paraaldehyde.

Ethchlorvynol: Ethchlorvynol, 1-chloro-3-ethyl-1-penten-4-in-3-ol (4.3.3), is synthesized by the condensation of acetylene with 1-chloro-1-penten-3-one in liquid ammonia [34,35].

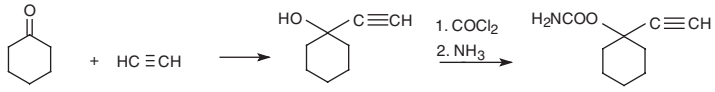


4.3.3

The sedative hypnotic ethchlorvynol has approximately the same activity and toxicity as phenobarbital; however, its hypnotic effect develops and dissipates quicker. It is used much less than benzodiazepines in treating insomnia for a number of reasons.

Synonyms for this drug are arvinol, nostal, placidyl, and others.

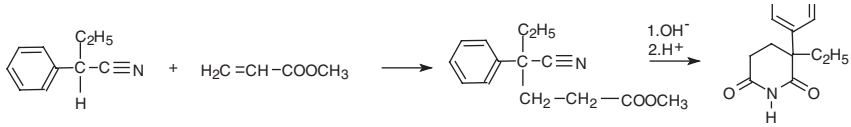
Ethinamate: Ethinamate, 1-ethynylcyclohexanone carbamate (4.3.4), is synthesized by the condensation of acetylene with cyclohexanone and the subsequent transformation of the resulting carbinol into carbamate by the subsequent reaction with phosgene, and later with ammonia [36,37].



4.3.4

Ethinamate is a hypnotic, which does not have, however, a considerable advantage over barbiturates and benzodiazepines, and is used much less in treating insomnia. Synonyms for this drug are valamide, ivalmad, valamin, and others.

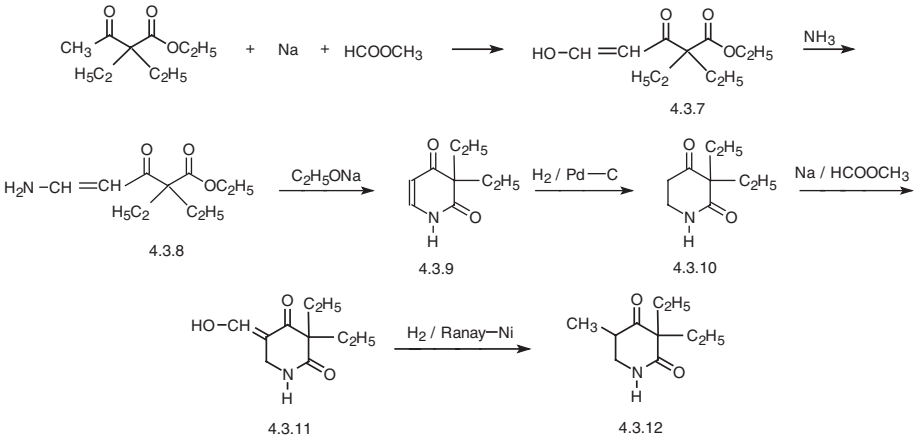
Glutethimide: Glutethimide, 2-ethyl-2-phenylgutarimide (4.3.6), is synthesized by addition of 2-phenylbutyronitrile to the methylacrylate (Michael reaction), and the subsequent alkaline hydrolysis of the nitrile group in the obtained compound (4.3.5) into an amide group, and the subsequent acidic cyclization of the product into the desired glutethimide (4.3.6) [38–42].



Glutethimide is a hypnotic and sedative agent intended to treat insomnia. The hypnotic effect is roughly analogous to that of pentobarbital. It is given to patients who cannot

tolerate barbiturates. However, it does not have any advantage over benzodiazepines, and therefore it is rarely used. Doriden is a synonym for this drug.

Methyprylon: Methyprylon, 3,3-diethyl-5-methyl-2,4-piperidinedion (4.3.12), is synthesized from sodium salt of diethylacetoacetic ester, which reacts with methylformate to give 4-oxymethylen-2,2-diethylacetoacetic ester (4.3.7). Reacting this with ammonia transforms it into 4-aminomethylen-2,2-diethylacetoacetic ester (4.3.8). Treatment of the resulting product with sodium ethoxide results in intermolecular cyclization into 3,3-diethyl-1,2,3,4-tetrahydropyridin-2,4-dione (4.3.9). Hydrogenation of the double bonds using a palladium catalyst gives 3,3-diethylpiperidin-2,4-dione (4.3.10), which once again undergoes formylation into 3,3-diethyl-5-hydroxymethylenpiperidine-2,4-dione (4.3.11) using methylformate in the presence of sodium. Reduction of the introduced hydroxymethyl group into a methyl group using hydrogen gives the desired methyprylon (4.3.12) [43,44].



As with all of the examined drugs in this chapter, methyprylon is intended for treating insomnia. The pharmacological effects of methyprylon are similar to those of barbiturates. However, barbiturates are beginning to give way, thanks to the introduction of benzodiazepines into medical practice. Synonyms for this drug are noctar, noludar, and others.

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– 5 –

Anxiolytics (Tranquilizers)

Many illnesses are accompanied by anxiety, a worried state during which a syndrome characterized by feelings of helplessness, despair, dark premonitions, and asthenia begins to develop. It can be accompanied by headaches, increased perspiration, nausea, tachycardia, dry mouth, etc. A state of anxiety can originate from neurological reasons, and can also be of a somatopsychic nature, which is associated with pathological development in diseases of the cardiovascular system, neoplasms, hypertonia, and diseases of the gastrointestinal tract. Drugs used for relieving anxiety, stress, worry, and fear that do not detract attention from or affect psychomotor activity of the patient are called anxiolytics or tranquilizers. Most of them have sedative and hypnotic action, and in high doses their effects are in many ways similar to barbiturate action. However, the primary advantage of this group over barbiturates lies in their significantly increased value in terms of the ratio of sedative/hypnotic effects. In other words, the ratio between doses that reduce stress and doses that cause sleep is significantly higher in anxiolytics than in barbiturates. The primary use of tranquilizers is alleviation of emotional symptoms associated with psychoneurotic or psychosomatic disturbances, such as excitement, anxiety, worry, muscle tension, and elevated motor activity. Used independently, they are not acceptable for rapid relief of severe psychotic conditions, and are used in such cases in combination with antipsychotic drugs. Anxiolytics that are presently used in medicine are divided into two groups. They are benzodiazepines: diazepam, chlordiazepoxide, chlorazepate, galazepam, lorazepam, midazolam, alprazolam, oxazepam, prazepam, and other anxiolytics, or nonbenzodiazepine structures which are represented by meprobamate, buspirone, chlormezanone, and hydroxyzine.

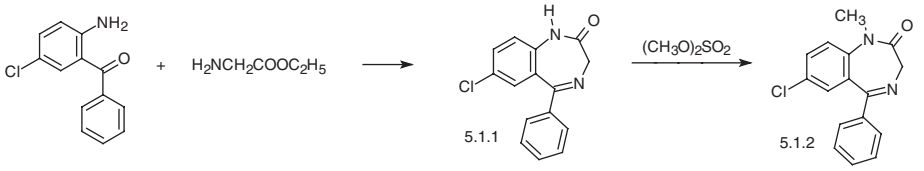
5.1 BENZODIAZEPINES

Before the introduction of the class of benzodiazepines, the primary drugs used for correcting psychoemotional disorders were sedative and hypnotic drugs, in particular phenobarbital and glutethimide. Benzodiazepines turned out to be extremely effective drugs for treating neurotic conditions. The first representative of this large group of compounds, chlordiazepoxide, was synthesized in the 1930s and introduced into medical practice at the end of the 1950s. More than 10 other benzodiazepine derivatives were subsequently introduced into medical practice. They all displayed very similar pharmacological activity and therapeutic efficacy, and differed only in quantitative indicators. The anxiolytic effect of benzodiazepines is specific and unique,

and it differs from sedative and hypnotic drugs of other classes. The primary effects of benzodiazepines on the central nervous system (CNS) are: relief of anxiety, and worry, sedative effect, relaxation of skeletal muscle, and soporific action. They depress the respiratory system to a lesser degree than hypnotics and sedative drugs, and they also cause addiction to a lesser degree. A few representatives of drugs of the benzodiazepine series have a slightly different spectrum of use. Flurazepam, triazolam, and temazepam are used as soporific agents, whereas carbamazepine is used as an anticonvulsant.

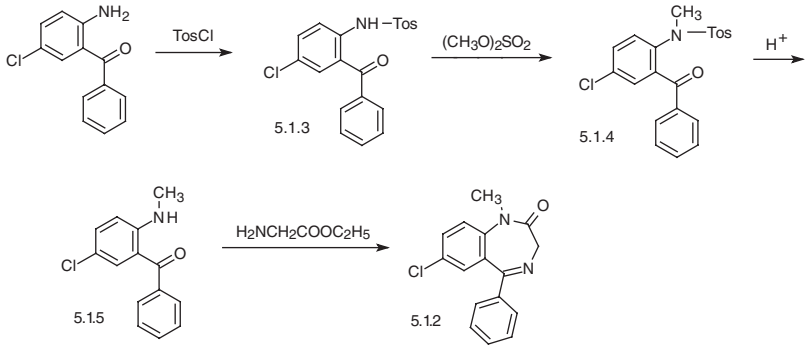
Benzodiazepines with expressed anxiolytic action and either the absence of or poorly expressed sedative–hypnotic effects are called "daytime tranquilizers" (medazepam). From the chemical point of view, benzodiazepines are formally divided into two main groups: simple 1,4-benzodiazepines (chlordiazepoxide, diazepam, lorazepam), and heterocyclic 1,4-benzodiazepines (alprazolam, medzolam, and others). A condition necessary for the expression of anxiolytic activity of benzodiazepines is the presence of an electronegative group on C_7 of the benzodiazepine system. The presence of a phenyl group on C_5 of the system also increases the pharmacological activity of these compounds. Experimental data permit the assumption that the mechanism of action of benzodiazepines lies in the stimulation of the benzodiazepin-GABA receptor complex. Therefore, benzodiazepines, as a class, potentiate activity of the inhibitory GABA-ergenic system of the brain. Although benzodiazepines do not react directly with the GABA receptors, it is possible that they bind with specific moieties on the chloride ionophore. The benzodiazepin-receptor interaction evidently causes allosteric changes in the GABA receptors, which in turn increases the inhibitory activity of GABA. This is expressed as an increase in the flow of chloride ions through GABA-activated ion channels. The primary use of benzodiazepines turns out to be symptomatic relief of feelings of anxiety, tension, and irritability associated with neurosis, neurosis-like conditions, depression, and psychosomatic disorders. Benzodiazepines are used in premedication before operational interventions in order to achieve ataraxia in the patient, as an adjuvant supplementary drug in treating epilepsy, tetanus, and other pathological conditions accompanied by skeletal muscle hypertonicity. As was previously mentioned, a few benzodiazepines are used as soporifics (flurazepam, triazolam, and temazepam) and even as anticonvulsant drugs (carbamazepine).

Diazepam: From a chemical point of view, diazepam, 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (5.1.2), is the most simple of all of the examined derivatives of 1,4-benzodiazepin-2-ones. Various ways for the synthesis of diazepam from 2-amino-5-chlorobenzophenone have been proposed. The first two ways consist of the direct cyclocondensation of 2-amino-5-chlorobenzophenone or 2-methylamino-5-chlorobenzophenone with the ethyl ester of glycine hydrochloride. The amide nitrogen atom of the obtained 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (5.1.1), is methylated by dimethylsulfate, which leads to the formation of diazepam (5.1.2).

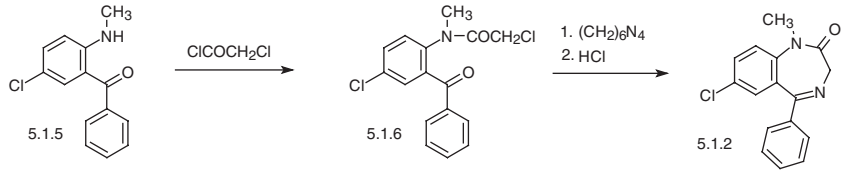


5.1.1 5.1.2

The second way differs from the first in that the methylation of nitrogen is accomplished before the cyclocondensation reaction. In order to do this, the initial 2-amino-5-chlorobenzophenone is first tosylated by *p*-toluenesulfonylchloride and the obtained tosylate (5.1.3) transformed into the N-sodium salt, which is then alkylated by dimethylsulfate. The resulting 2-*N*-tosyl-*N*-methyl-5-chlorobenzophenone (5.1.4) is hydrolyzed in an acidic medium, giving 2-methylamino-5-chlorobenzophenone (5.1.5), which undergoes cyclocondensation by reaction with ethyl ester of glycine hydrochloride, forming the desired diazepam (5.1.2) [1–5].

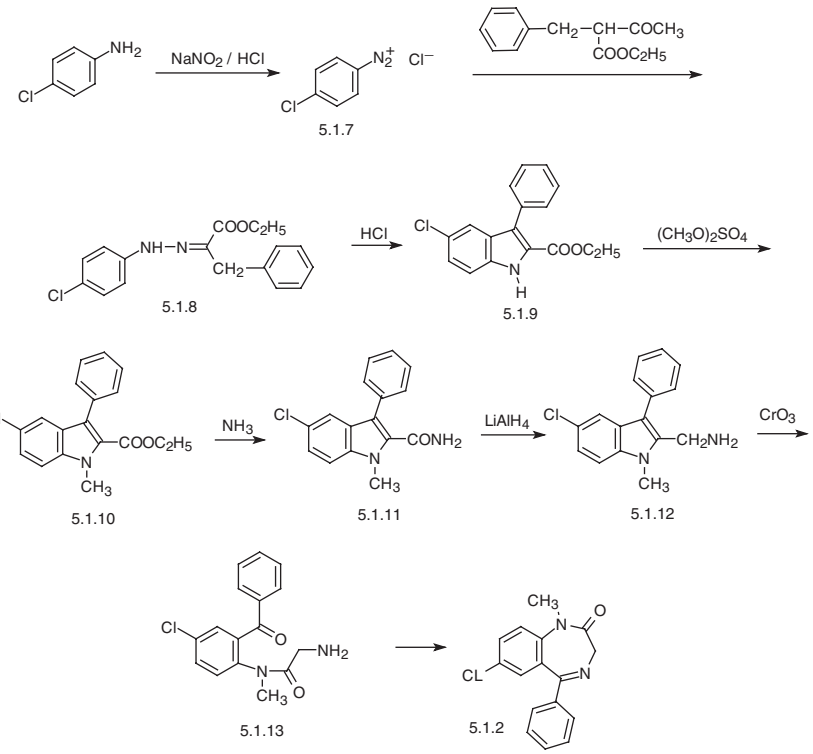


The third way for the synthesis emanates from 2-methylamino-5-chlorobenzophenone (5.1.5), which is acylated by chloracetic acid chloride, forming 2-chloracetylmethylamido-5-chlorbenzophenone (5.1.6). Reaction of this product with hexamethylenetetramine replaces the chlorine atom in the chloracetyl part of the molecule, giving a hexamethylenetetramino derivative of 2-aminoacetylmethylamido-5-chlorbenzophenone, which upon hydrolysis in an hydrochloric acid ethanol solution undergoes cyclocondensation and gives diazepam (5.1.2) [6,7].



One other way for diazepam synthesis has been suggested, which is derived from 1-methyl-3-phenyl-5-chloro-2-aminomethylindole (5.1.12), the oxidation of which by chromium(VI) oxide gives diazepam. The synthesis begins with 5-chloroaniline, which upon interaction with nitrous acid gives a diazonium salt (5.1.7). Azocoupling of this product with ethyl α-benzylacetoacetic ester in an alkaline solution gives the 4-chlorophenylhydrazone of the ethyl ester of phenylpyruvic acid (5.1.8), which in the presence of hydrochloric acid undergoes a Fischer indole synthesis reaction and transforms into the ethyl ester of 5-chloro-3-phenylindolyl-2-carboxylic acid (5.1.9). Alkylation of the resulting indole at the nitrogen atom using dimethylsulfate gives 1-methyl-5-chloro-3-phenylindolyl-2-carboxylic acid ethyl ester (5.1.10). The reaction of the resulting product with ammonia gives the respective amide (5.1.11), which is reduced by lithium aluminum

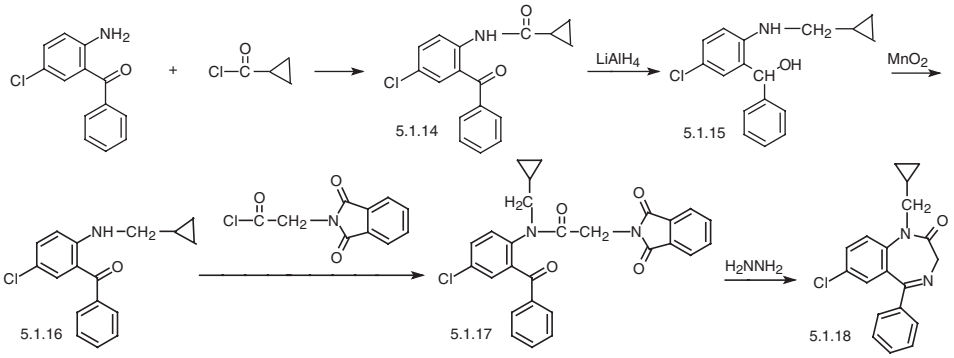
hydride to give 1-methyl-3-phenyl-5-chloro-2-aminomethylindole (5.1.12). Next, a valuable property of chromium(IV) oxide is used to open the indole ring into the respective aminobenzophenone derivative (5.1.13), which under the reaction conditions cyclizes into the diazepam [8].



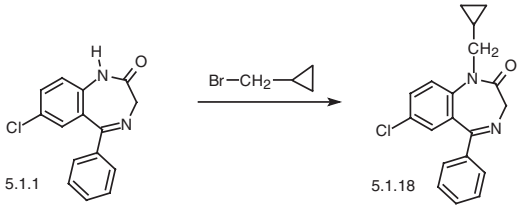
Diazepam exhibits anxiolytic, sedative, soporific, central myorelaxant, and anticonvulsant action. It suppresses feelings of fear, worry, and stress. It is used for nervous stress, excitement, anxiety, sleep disturbance, neurovegetative disorders, psychoneurosis, obsessive neurosis, hysterical or hypochondriac reactions, and phobias. The most frequently used synonyms are seduxen, relanium, valium, sibazon, apaurin, and many others.

Prazepam: Prazepam, 7-chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2*H*-1, 4-benzodiazepin-2-one (5.1.18), differs from diazepam in that it has a substituent on the nitrogen atom in the first position of the benzodiazepine system. This drug is made according to a scheme very similar to that of diazepam (5.1.2). It is derived from the same initial 2-amino-5-chlorobenzophenone, which undergoes acylation by cyclopropancarboxylic acid chloride. The resulting 2-cyclopropylcarbonylamino-5-chlorobenzophenone (5.1.14) is reduced by lithium aluminum hydride into 2-cyclopropylmethylamino-5-chlorobenzhydrol (5.1.15), and the resulting product is oxidized by manganese dioxide into 2-cyclopropylmethylamino-5-chlorobenzophenone (5.1.16). This is acylated by phthalimidoacetic acid chloride. The phthalimide protecting group in the resulting product (5.1.17) is

removed by treatment with hydrazine, during which an intermolecular reaction of imino formation occurs under the conditions of synthesis, leading to the formation of the desired prazepam (5.1.18) [9,10].

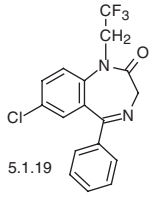


In the second, simpler scheme, synthesis begins with 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one (5.1.1), which is alkylated by cyclopropylmethylbromide in the presence of sodium amide into prazepam (5.1.11) [11,12].



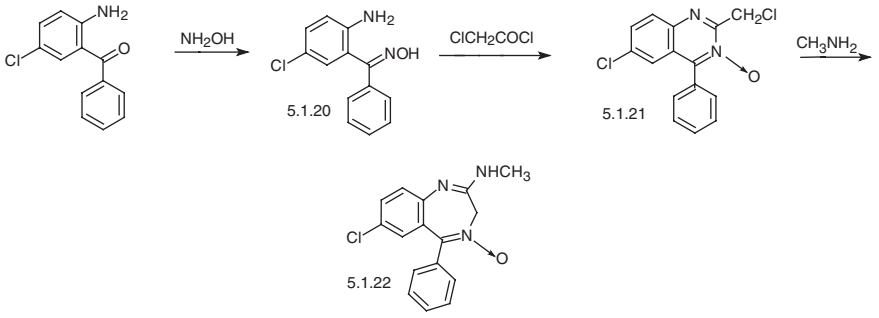
The pharmacological properties of this drug are basically the same as those of diazepam, the only difference being that it has longer-lasting action. It is used for the same indications as diazepam. The most common synonym for prazepam is centrax.

Halazepam: Halazepam, 7-chloro-1-(2′,2′,2′-trifluoro-1-ethyl)-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (5.1.19), also differs from diazepam in that it has a substituent on the nitrogen atom in the first position of the benzodiazepine system, which in this case is represented by the 2′,2′,2′-trifluoroethyl group. It can be made by any of the diagrams described above [13,14].



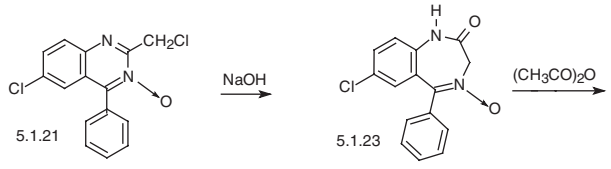
The pharmacological properties of halazepam are basically the same as those of diazepam, the only difference being that they are shorter lasting. They are primarily used for conditions of anxiety. The most common synonym is paxipam.

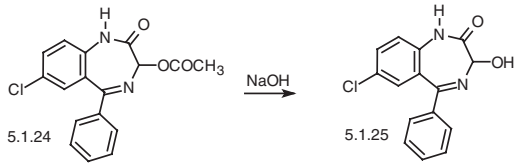
Chlordiazepoxide: Chlordiazepoxide, 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepin-4-oxide (5.1.22), is also synthesized from 2-amino-5-chlorobenzophenone. This is reacted in the usual manner with hydroxylamine, forming 2-amino-5-chlorobenzophenone oxide (5.1.20), which upon reaction with chloroacetic acid chloride in acetic acid easily cyclizes to 6-chloro-2-chloromethyl-4-phenylquinazolin-3-oxide (5.1.21). Reacting this with a primary amine, methylamine in particular, leads to an interesting rearrangement (with a ring expansion), and the reaction product turns out to be 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepin-4-oxide (5.1.22)—chlordiazepoxide. An analogous rearrangement with a ring expansion also proceeds upon reaction with alkaline or alcoxides; however, it should be noted that with dialkylamines, the reaction forms the expected substitution products, 2-dialkylaminomethyl derivatives of 6-chloro-4-phenylquinazolin-3-oxide. Chlordiazepoxide was the first representative of the benzodiazepine series of anxiolytics to be introduced into medical practice [15–17].



Chlordiazepoxide is used for treating neurotic conditions such as relieving feelings of fear, worry, and stress. It exhibits soporific action on the CNS, causes muscle relaxation, and possesses anticonvulsant activity. It is frequently used after operational interventions. The most frequently used synonyms are elenium and librium.

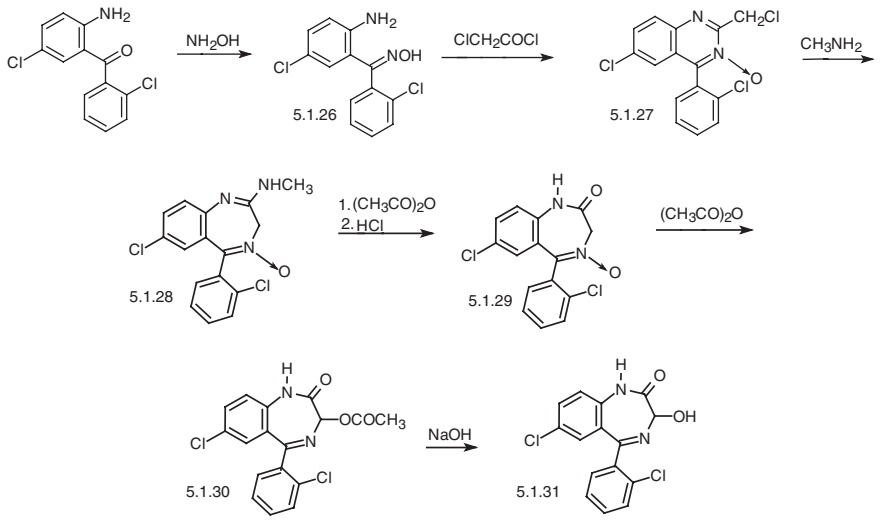
Oxazepam: Oxazepam, 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-benzodiazepin-2-one (5.1.25), is synthesized in a similar manner as described above, which was discovered during the synthesis of chlordiazepoxide, but instead of using a primary amine, a simple, inorganic base was used as a nucleophile. In order to do this, 6-chloro-2-chloromethyl-4-phenylquinazolin-3-oxide (5.1.21) undergoes treatment with sodium hydroxide, giving 7-chloro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-on-4-oxide (5.1.23). This undergoes an extremely curious acetoxylation reaction of the third position of the benzodiazepine ring, using acetic anhydride, and which reminiscents the Polonovski reaction, giving 7-chloro-1,3-dihydro-3-acetoxy-5-phenyl-2H-benzodiazepin-2-one (5.1.24). Subsequent hydrolysis of the product's acetyl group gives oxazepam (5.1.25) [18–24].





Oxazepam is similar to chlordiazepoxide in terms of pharmacological properties; however, it has a somewhat less harsh effect, is less toxic, and exhibits a less expressed myorelaxant effect. It is often tolerated better by patients than other tranquilizers. It is used in neurosis, conditions of anxiety, fear, stress, trouble falling asleep, and psychovegatative disorders. The most common synonyms are nozepam and tazepam.

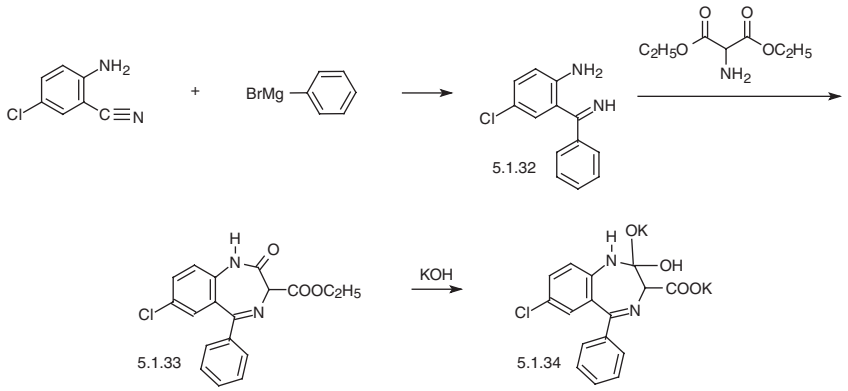
Lorazepam: Lorazepam, 7-chloro-4-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one (5.1.31), is synthesized according to a scheme containing some of the same elements for the synthesis of chlordiazepoxide and oxazepam, and comes from 2-amino-2′,5-dichlorobenzophenone. Reacting this with hydroxylamine gives (5.1.26), the reaction of which with chloracetyl chloride, and upon heterocyclization gives 6-chloro-2-chlormethyl-4-(2′-chlorophenyl)quinazolin-3-oxide (5.1.27). Reacting this with methylamine, as in the case of chlordiazepoxide, leads to rearrangement and a ring expansion, forming 7-chloro-2-methylamino-5-(2′-chlorphenyl)-3H-1,4-benzodiazepin-4-oxide (5.1.28). The resulting benzodiazepin-4-oxide undergoes acetylation by acetic anhydride at the secondary nitrogen atom, and is further hydrolyzed by hydrochloric acid into 7-chloro-5-(2′-chlorophenyl)-1,2-dihydro-3H-1,4-benzodiazepin-2-on-4-oxide (5.1.29). Reaction of this product with acetic anhydride leads to a Polonovski type rearrangement reaction, giving a 3-acetoxylated benzodiazepine, 7-chloro-1,3-dihydro-3-acetoxy-5-(2′-chlorphenyl)-2H-benzodiazepin-2-one (5.1.30), the hydrolysis of which forms the desired product lorazepam (5.1.31) [18,25–29].



Indications for its use are the same as those of other tranquilizers as well as in the capacity of a drug for cardioneurosis, preoperational medical anesthesia, and as an adjuvant drug

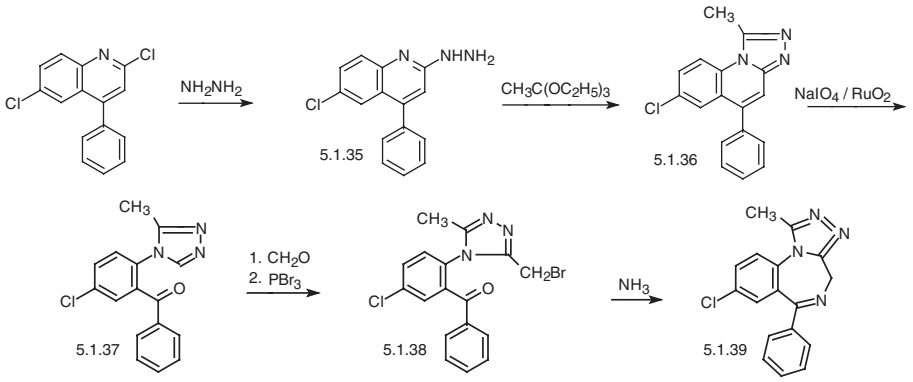
in endoscopic procedures. It differs somewhat in that it exhibits shorter-lasting action. The most common synonyms are ativan and tavor.

Chorazepate: Chorazepate, 7-chloro-2,3-dihydro-2,2-dihydroxy-5-phenyl-1H-1,4-benzodiazepin-3-carboxylic acid (5.1.34), which is used in the form of a dipotassium salt, is synthesized by yet another interesting synthetic scheme. 2-Amino-5-chlorobenzonitrile is used as the initial compound, which upon reaction with phenylmagnesiumbromide is transformed into 2-amino-5-chlorbenzophenone imine (5.1.32). Reacting this with aminomalonic ester gives a heterocyclization product, 7-chloro-1,3-dihydro-3-carbethoxy-5-phenyl-2H-benzodiazepin-2-one (5.1.33), which upon hydrolysis using an alcoholic solution of potassium hydroxide forms a dipotassium salt (5.1.34), chlorazepate [30–32].



Chlorazepate is among the long-acting tranquilizers used upon the same indications as other tranquilizers, and also as an adjuvant drug for epileptic attacks. The most common synonyms are tranxene, noctran, and others.

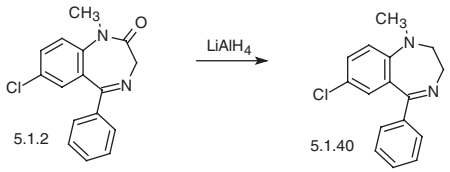
Alprazolam: Alprazolam, 8-chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (5.1.39), is a chemical analog of triazolam (4.2.4) that differs by the absence of a chlorine atom in the o-position of the 6-phenyl ring. The same scheme that was used to make triazolam can be used to make alprazolam, with the exception that it begins with 2-amino-5-chlorobenzophenone [33–35]. However, a non-standard way of making alprazolam has been suggested, which comes from 2,6-dichloro-4-phenylquinoline, the reaction of which with hydrazine gives 6-chloro-2-hydrazino-4-phenylquinoline (5.1.35). Boiling this with triethyl orthoacetate in xylene leads to the heterocyclization into a triazole derivative (5.1.36). The resulting product undergoes oxidative cleavage using sodium periodate and ruthenium dioxide in an acetone–water system to give 2-[4-(3′-methyl-1,2,4-triazolo)]-5-chlorobenzophenone (5.1.37). Oxymethylation of the last using formaldehyde and subsequent substitution of the resulting hydroxyl group by phosphorous tribromide, gives 2-[4-(3′-methyl-5′-bromomethyl-1,2,4-triazolo)]-5-chlorobenzophenone (5.1.38). Substitution of the bromine atom with an amino group using ammonia and the spontaneous, intermolecular heterocyclization following that reaction gives alprazolam (5.1.39) [36–38].



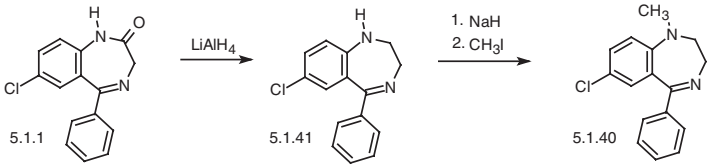
Alprazolam is short-lasting tranquilizer used in conditions of anxiety, panic disorders, and depressive syndrome. The most common synonym for this drug is xanax.

As already noted, there are drugs found among benzodiazepine derivatives that have expressed anxiolytic action and that lack or have poorly expressed sedative–hypnotic effects, which are called "daytime tranquilizers." Medazepam, a representative of the "daytime tranquilizers," is a drug that differs from diazepam only in the absence of a carbonyl group in the seven-membered azepine ring.

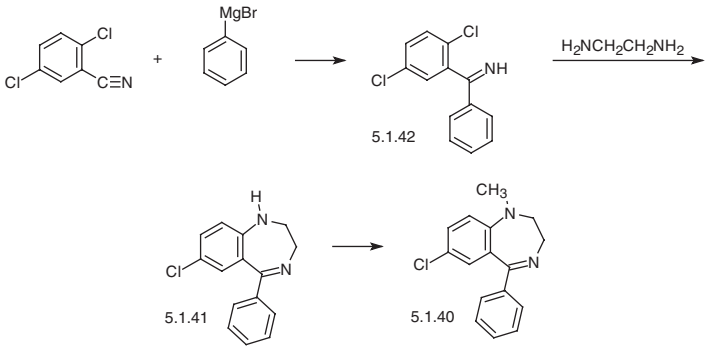
Medazepam: Medazepam, 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine (5.1.40), has been suggested to be synthesized in various ways. The first is the reduction of the carbonyl group in diazepam (5.1.2) by lithium aluminum hydride [39,40].



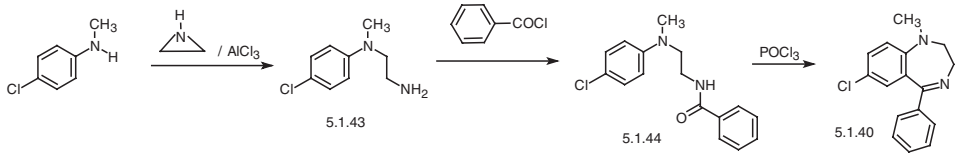
The second way of making medazepam consists of the initial reduction of the carbonyl group by lithium aluminum hydride into 7-chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one (5.1.1)—the first intermediate product in the synthesis of diazepam—which is synthesized by the cyclocondensation of 2-amino-5-chlorobenzophenone with glycine ethyl ester into 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (5.1.41), and the subsequent methylation of the secondary amine nitrogen atom of the resulting product by methyliodide, using sodium hydride as a base [41,42].



The third method of making medazepam consists of a new way of making 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (5.1.41), which consists in heterocyclization of 1-(2,5-dichlorophenyl)-1-phenylimine with ethylenediamine. The starting 1-(2,5-dichlorophenyl)-1-phenylimine (5.1.42) is synthesized by the reaction of 2,5-dichlorobenzonitrile with phenylmagnesiumbromide [43].



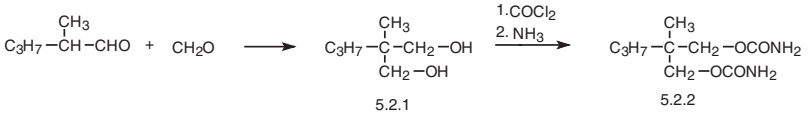
Finally, a method of making medazepam from 4-chloro-*N*-methylaniline is suggested. The last is reacted with ethyleneimine in the presence of aluminum chloride, giving *N*-(4-chlorophenyl)-*N*-methylethylenediamine (5.1.43). Acylation of the resulting product with benzoyl chloride gives the respective amide (5.1.44), which cyclizes into the desired medazepam (5.1.40) using phosphorous oxychloride [44,45].



Various modifications of the described methods have been suggested [46,47]. Medazepam is a daytime tranquilizer. It exhibits an anxiolytic, myorelaxant, and anticonvulsant action. This drug relieves the feeling of worry, restores emotional calmness, and has a stabilizing effect on the vegetative nervous system. Medazepam is used in neurosis, psychopathy accompanied by excitement, stress, elevated irritability, insomnia, and functional neurosis of the cardiovascular system. Synonyms for this drug are nobrium, tranquirax, azepamid, and others.

5.2 ANXIOLYTIC OF NONBENZODIAZEPINE STRUCTURES

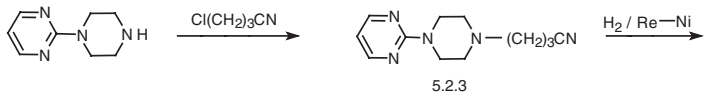
Meprobamate: Meprobamate, 2-methyl-2-propyl-1,3-propandiol dicarbamate (5.2.2) is synthesized by the reaction of 2-methylvaleraldehyde with two molecules of formaldehyde and the subsequent transformation of the resulting 2-methyl-2-propylpropan-1,3-diol (5.2.1) into the dicarbamate via successive reactions with phosgene and ammonia [48–50].



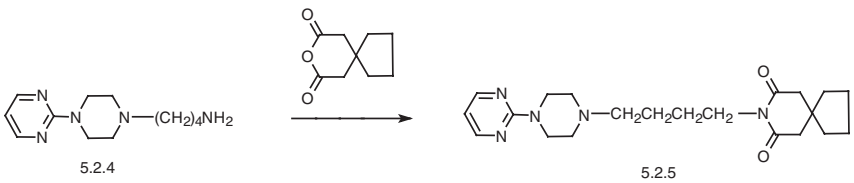
5.2.1 5.2.2

Meprobamate was proposed before the introduction of benzodiazepines into medical practice. The exact mechanism of action of this drug is not known; however, its effects on the CNS are more similar to the effects barbiturates than to benzodiazepines, but with shorter-lasting action. After the introduction of benzodiazepines into practice, the use of this drug became significantly less. Meprobamate is used primarily as a daytime anxiolytic in treating conditions of anxiety associated with everyday, usual, and common stress. Synonyms for this drug are cypron, equanil, stenzol, mepron, miltaun, and others.

Buspirone: Buspirone, 8-[4-[4-(2-pyrimidyl)-1-piperazinyl]butyl]-8-azaspiro [4,5] decan-7,9-dione (5.2.6), is synthesized by the reaction of 1-(2-pyrimidyl)-4-(4-aminobutyl)piperazine (5.2.4) with 8-oxaspiro[4,5]decan-7,9-dione (5.2.5). In turn, 1-(2-pyrimidyl)-4-(4-aminobutyl)piperazine (5.2.4) is synthesized by the reaction of 1-(2-pyrimidyl)piperazine with 4-chlorobutyronitrile, giving 4-(2-pyrimidyl)-1-(3-cyanopropyl)piperazine (5.2.3), which is hydrogenated with Raney nickel into buspirone (5.2.4) [51–55].



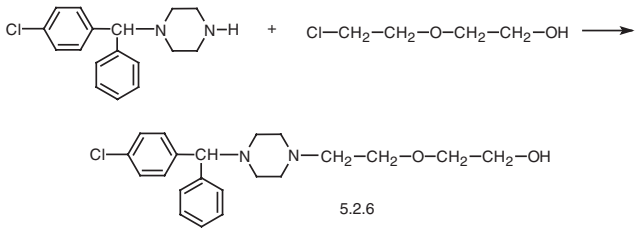
5.2.3



5.2.4 5.2.5

Buspirone is an extremely specific drug that could possibly represent a new chemical class of anxiolytics—azaspirones. As an anxiolytic, its activity is equal to that of benzodiazepines; however, it is devoid of anticonvulsant and muscle relaxant properties, which are characteristic of benzodiazepines. It does not cause dependence or addiction. The mechanism of its action is not conclusively known. It does not act on the GABA receptors, which occurs in benzodiazepine use; however, it has a high affinity for seratonin (5-HT) receptors and a moderate affinity for dopamine (D_2) receptors. Buspirone is effective as an anxiolytic. A few side effects of buspirone include dizziness, drowsiness, headaches, nervousness, fatigue, and weakness. This drug is intended for treatment of conditions of anxiety in which stress, muscle pain, rapid heart rate, dizziness, fear, etc. are observed; in other words, conditions of anxiety not associated with somewhat common, usual, and everyday stress. Synonyms for buspirone are anizal, axoren, buspar, buspimen, buspinol, narol, travin, and others.

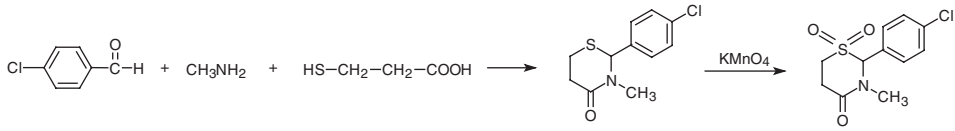
Hydroxyzine: Hydroxyzine, 2-[2-[4-(*p*-chloro-α-phenylbenzyl)-1-piperazinyl]-ethoxy] ethanol (5.2.6), is synthesized by the alkylation of 1-(4-chlorobenzohydril)piperazine with 2-(2-hydroxyotoxy)ethylchloride [56–61].



5.2.6

Hydroxyzine is intended for the symptomatic treatment of anxiety and stress associated with neurosis as well as with conditions of organic illness. This drug has muscle relaxant, antihistimine, analgesic, local anesthetic, and antiemetic action as well as a wide therapeutic effect. It is mainly used in premedication and following general anesthesia, during which it potentiates the action of meperidine and barbiturates. It is frequently used in pediatrics as a mild sedative drug. Synonyms for hydroxyzine are atarax, agirax, durrax, vistaril, and others.

Chlormezanone: Chlormezanone, 2-(p-chlorophenyl)-tetrahydro-3-methyl-4H-1,3-tiazin-4-on-1,1-dioxide (5.2.8), is synthesized by joint condensation of mercaptopropionic acid, methylamine, and 4-chlorobenzaldehyde, evidently through the intermediate stage of formation of 4-chlorobenzylidenemethylamine, giving the aminothioacetal 2-(p-chlorophenyl)-tetrahydro-3-methyl-4H-1,3-tiazin-4-one (5.2.7). Oxidation of the sulfur atom using potassium permanganate gives chlormezanone (5.2.8) [62,63].



5.2.7 5.2.8

Chlormezanone improves the emotional state of the patient, relieving moderate anxiety and stress. However, it has a number of side effects, and because it does not have any advantage over other anxiolytics, it is rarely used in practice. Synonyms of this drug are trancopal, alinam, flexipirin, and others.

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– 6 –

Antipsychotics (Neuroleptics)

Antipsychotics are drugs that have a specific sedative effect, and which improve the attitude and calm the behavior of psychotic patients. They do not cause dependence, and have been proposed for treating psychotic disorders (elimination of psychotic symptomatology—delirium, hallucinations) and schizophrenic patients. Drugs of this group are also frequently referred to as neuroleptics. The term major tranquilizer was used previously to distinguish them from minor tranquilizers/anxiolytics.

These drugs cause emotional calmness and are extremely effective for treating patients with severe and chronic symptoms. The introduction of such drugs into medical practice saved an innumerable number of patients from necessity to live within the closed walls of psychiatric clinics.

The initial indication for the use of antipsychotic agents is the symptomatology of the following disorders: schizophrenia and schizophrenic-like disorders, delirious (paranoid) conditions, brief psychotic disorders, affective disorders with psychotic symptomatology, and psychotic disorders developing as a result of underlying somatic disease. A clear distinction should be made between antipsychotics used for treating severe and chronic psychosis, and anxiolytics intended for treating anxiety and stress associated with psychoneurotic or psychosomatic disorders. Antipsychotic drugs have a significantly stronger effect on the central nervous system (CNS), but they are not CNS depressants, and as a rule they are more toxic. However, even in long-term use they do not cause dependence and addiction, which is a very serious problem that originates from long-term use of anxiolytics.

Medications for mental illnesses were first introduced in the early 1950s with the antipsychotic chlorpromazine. Other medications have followed.

From the pharmacological point of view antipsychotics are subdivided into two groups, the newer atypical and older typical. They work in different ways. The newer atypicals tend to have fewer side effects and are generally less sedating.

The first atypical antipsychotic is clozapine. Several other atypical antipsychotics have been developed since clozapine was introduced. The first was risperidone, followed by olanzapine, quetiapine, and ziprasidone.

From the chemical point of view antipsychotic drugs are subdivided into six chemical groups, as well as to the group of non-classifiable drugs. They are phenothiazines (chlorpromazine, promazine, triflupromazine, acetophenazine, fluphenazine, perphenazine, prochlorpherazine, trifluoperazine, mesoridazine, and thioridazine), thioxanthenes

(chlorprothixene, thiothixene), butyrophenones (haloperidol, trifluperidol, droperidol, fluanisone), dihydroindolones (molindone), dibenzoxazepines (loxapine) and dibenzdiazepines (clozapine), diphenylbutylpiperidines (pimozide, fluspirilene, and penfluridol), and also others which include sulpiride, lithium drugs, and a few others. It should be kept in mind that despite the presence of quantitative differences, which undoubtedly exist in one group of antipsychotic agents or another as well in different groups, there is no substantial qualitative difference between their pharmacological actions. In other words, in using therapeutically equivalent doses, their clinical efficacy is practically identical. The selection of specific antipsychotic drugs generally varies from case to case in an attempt to minimize side effects. For example, drugs with less sedative effects are given to patients working with equipment, or drugs with less hypotensive effects are given to elderly patients.

The specific etiology of psychotic disorders has not currently been sufficiently investigated. It is believed, however, that the initial cause of psychotic behavior may originate from an imbalance of dopaminergic functions in the CNS. Many researchers adhere to the opinion that a large increase of dopamine activity in specific regions of the CNS is the cause of abnormal behavior.

The mechanism of action of neuroleptics is not sufficiently clear. However, it is believed that they are antagonists of dopamine and dopaminomimetics, and that their effect is connected in some way with the blockage of dopamine D receptors, which results in changes of behavioral reactions. Moreover, it is possible that they also block action on the serotonin receptors and M-choline receptors. It also is possible that antipsychotic agents disrupt the process of the release and return neuronal uptake of a number of biogenic amines.

It also seems plausible that antipsychotic drugs competitively bind with dopamine receptors and block the action of dopamine on corresponding receptor sites, thus lowering psychotic activity. Central dopamine receptors are subdivided into D_1, D_2, and according to some sources, D_3 receptors. These receptors have a high affinity for dopamine, but they differ in sensitivity to neuroleptics of various chemical classes. For example, drugs of the phenothiazine series are nonselective competitive D_1 and D_2 antagonists. Unlike phenothiazines, antipsychotics of the butyrophenone series such as haloperidol display selective action only on D_2 receptors.

The pharmacological action of antipsychotic agents is very complicated. Besides the ability to change behavior, these drugs also have a number of other central and peripheral effects.

Antipsychotics or neuroleptics are used for intervention in patients with severe and chronic psychosis of an organic as well as induced nature. These drugs are used for controlling manic phases in manic-depressive psychosis such as relieving anxiety, fear, excitement associated with somatic diseases, controlling aggression, tics, and other unequal conditions.

6.1 PHENOTHIAZINE DERIVATIVES

Phenothiazine derivatives are nonselective, competitive D_1 and D_2 antagonists that block dopamine activity on corresponding receptor sites. In addition, their action is

expressed by blocking α-adrenoreceptors, serotonine, cholinergic, nicotinic, and muscarinic receptors.

Phenothiazines exhibit a complex pharmacological range of action on the CNS and the peripheral nervous system. In addition, they act on the endocrine system.

Every compound of this series differs to a certain degree from the other in their qualitative, yet primarily quantitative characteristics. They all act on the CNS by causing moderate sedative and antiemetic effects, affecting thermoregulatory processes, skeletal muscle, endocrine system, and by potentiating action of analgesics.

This group of drugs is subdivided into three subgroups depending on the type of substitution on the nitrogen atom of the phenothiazine ring. The subgroups are: phenothiazines with an aliphatic side chain (chlorpromazine, promazine, triflupromazine), piperazine derivatives (acetophenazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine), and piperidines (mesoridazine, thioridazine).

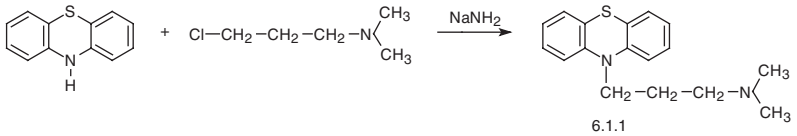
Drugs of the first subgroup (with an aliphatic side chain), along with expressed antipsychotic action, differ in their ability to cause lethargy, sluggishness, and intellectual lethargy. The sedative action of these drugs exceeds activity of other drugs of the phenothiazine series.

Piperazine derivatives inherent presence of stimulatory components.Phenothiazines with an aliphatic side chain and piperidine substituents have more of a sedative effect than piperazine derivatives.

The nature of the substituent in the second position of the phenothiazine ring has an extremely important influence on the activity of these compounds; an acceptor group is preferred.

Phenothiazines have a diverse use in medicine. They are primarily used as antipsychotics. Despite the fact that they do not cure the disease, they reduce psychotic symptoms to a point where the patient is provided with a better sense of reality. Phenothiazines are sometimes used for relieving severe anxiety, especially in panic attacks caused by dependence on amphetamines or lycergic acid diethylamide (LSD). Phenothiazines are used for alleviating behavioral problems in children that do not respond to treatment of other agents. Phenothiazines are sometimes used during the preoperational period because they relieve anxiety, control nausea, hiccups, diarrhea, and also cause muscle relaxation.

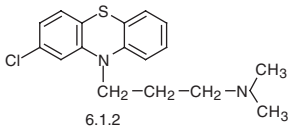
Promazine: Promazine, 10-(3-dimethylaminopropyl)phenothiazine (6.1.1), is prepared by the alkylation of phenothiazine with 3-dimethylaminopropylchloride in the presence of sodium amide [1–3].



6.1.1

In psychiatric practice, promazine is used in minor cases of psychomotor excitement in schizophrenics, in paranoid and manic-depressive conditions, for neurosis, alcoholic psychosis, and others. It is sometimes used in anesthesiological practice. The most common synonyms are propazine, trilafon, sparine, permitil, and others.

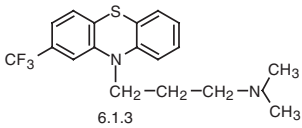
Chlorpromazine: Chlorpromazine, 2-chloro-10-(3-dimethylaminopropyl)phenothiazine (6.1.2), is synthesized in an analogous manner, except by alkylation of 2-chlorophenothiazine with 3-dimethylaminopropylchloride [4–6].



6.1.2

In psychiatric practice, chlorpromazine is used in various conditions of psychomotor excitement in patients with schizophrenia, chronic paranoid and also manic-depressive conditions, neurosis, alcohol psychosis and neurosis accompanied by excitement, fear, stress, and insomnia. In comparison with other neuroleptics, chlorpromazine is unique in that it has an expressed sedative effect. It is sometimes used in anesthesiological practice for potentiating narcosis. It also has moderate anticonvulsant action. The most common synonyms are aminazine, megaphen, largactil, thorazine, prompar, and others.

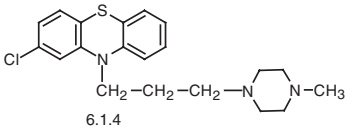
Triflupromazine: Triflupromazine, 2-trifluoromethyl-10-(3-dimethylaminopropyl) phenothiazine (6.1.3), also is synthesized by the alkylation of 2-trifluoromethylphenothiazine using 3-dimethylaminopropylchloride in the presence of sodium amide [7–12].



6.1.3

In psychiatric practice, triflupromazine is used for psychomotor excitement in patients with schizophrenia for paranoid and manic-depressive conditions, and for neurosis. The most common synonym is vesprin.

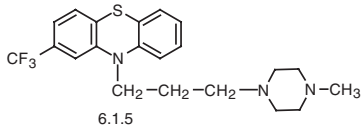
Prochlorpherazine: Prochlorpherazine, 2-chloro-10-[3-(4-methyl-1-piperazinyl) propyl]-phenothiazine (6.1.4), is synthesized by the alkylation of 2-chloromethylphenthizine using 4-methyl-1-piperazinyl)propyl-3-chloride in the presence of sodium amide, or alkylation of 2-chloro-10-[(3-chloropropyl)]phenothyazine using 1-methylpiperazine [13–16].



6.1.4

Like other piperazine derivatives of phenothiazine, prochlorpherazine reduces psychotic symptomatology and has a stimulatory effect. The most common synonym is meterazine.

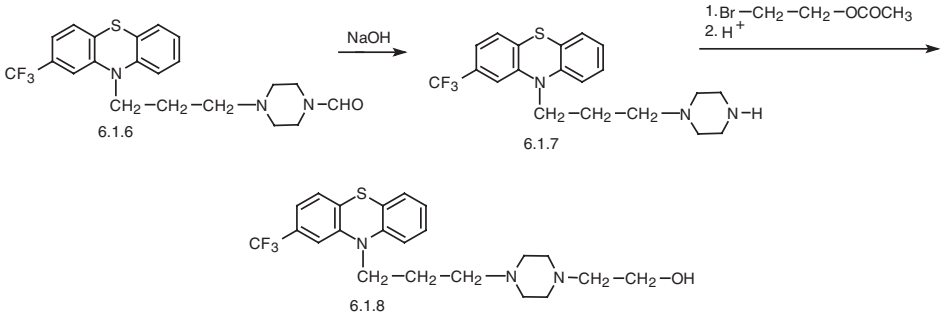
Trifluoperazine: Trifluoperazine, 2-trifluoromethyl-10-[3-(4-methyl-1-piperazinyl) propyl]-phenothazine (6.1.5), is synthesized in the manner described above of alkylation using 2-trifluoromethylphenothazin-4-methyl-1-piperazinylpropylchloride [11,17–20].



6.1.5

Trifluoperazine is one of the most active antipsychotic drugs. A moderate stimulatory effect accompanies the neuroleptic effect. Trifluoperazine is unique in that, patients instead of the usual stiffness and weakness characteristic of phenothazine derivatives, become more lively. This drug has a strong anticonvulsant activity. It is widely used in psychiatry for treating schizophrenia and other mental illnesses. The most common synonyms are mobadid, triftazin, stelazine, calmazin, and others.

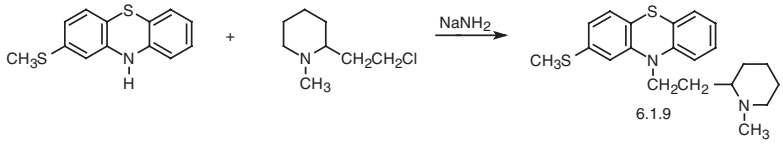
Fluphenazine: Fluphenazine, 4-[3-[2-(trifluoromethyl)phenothiazin-10-yl]propyl]-1-piperazineethanol (6.1.8), is synthesized by any of the methods described above [21–27]. Alkylation of 2-trifluoromethylphenothiazine using 4-formyl-1-piperazineylpropylchloride in the presence of sodium amide synthesizes 2-trifluoromethyl-10-[3-(4-formyl-1-piperazinyl)propyl]phenothizine (6.1.6). Further alkaline hydrolysis removes the *N*-formyl group, giving 2-trifluoromethyl-10-[3-(1-piperazinyl)propyl]phenothiazine (6.1.7). This is alkylated by 2-bromethanol-1 acetate, which upon further acidic hydrolysis removes the protecting acetyl group, yielding fluphenazine (6.1.8) [27,28].



6.1.6 6.1.7 6.1.8

Fluphenazine is an extremely strong antipsychotic drug. A stimulatory effect accompanies the neuroleptic effect. It is used in psychiatry for treating various forms of schizophrenia and other mental illnesses. The most common synonyms are fluorphenazine, moditen, dapotum, motival, permitil, and others.

Thioridazine: Thioridazine, 10-[2-(1-methyl-2-piperidyl)ethyl]-2-(methylthio)phenothiazine (6.1.9), is synthesized in an analogous manner by alkylating 2-methylthiophenothiazine with 2-(2-chloroethyl)-1-methylpiperidine [29,30].

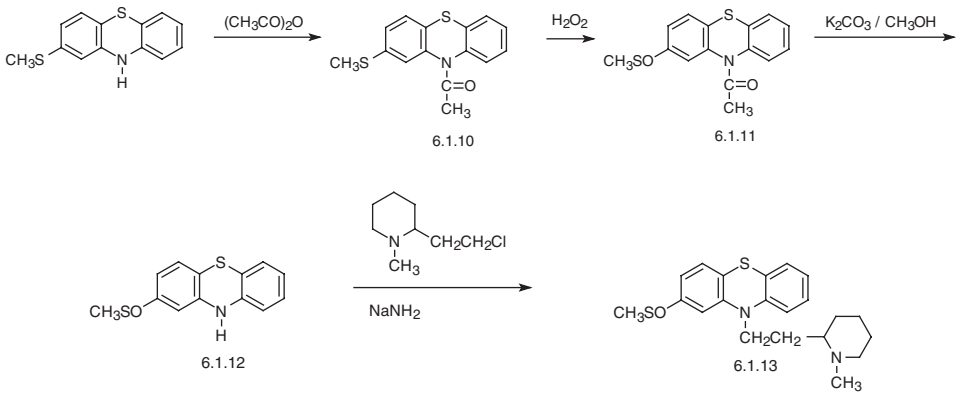


6.1.9

In terms of antipsychotic activity, thioridazine is inferior to aminazine. It is most effective in mental and emotional disorders accompanied by fear, stress, and excitement. It is prescribed for various forms of schizophrenia, psychosis, and neurosis. The most common synonyms are conapax and mellaril.

Mesoridazine: Mesoridazine, 10-[2-(1-methyl-2-piperidyl)ethyl]-2-(methylsufinyl)phenothiazine (6.1.13), is synthesized by an analogous scheme, however, it is also synthesized by alkylating the acidic form of 2-methylthiphenothiazine—methylsulfonylphenothiazine — using 2-(2-chlorethyl)-1-methylpiperidine.

In order to do this, 2-methylthiophenothiazine is initially acylated at the nitrogen atom using acetic anhydride, giving 10-acetyl-2-methylthiophenothiazine (6.1.10). The resulting acetyl derivative is further oxidized by hydrogen peroxide into 10-acetyl-2-methylsulfonylpenothiazine (6.1.11). Deacylation of this product in potassium carbonate methanol solution gives 2-methylsulfonylphenothiazine (6.1.12), which is alkylated by 2-(2-chlorethyl)-1-methylpiperidine in the presence of sodium amide, affording the desired mesoridazine (6.1.13) [31].



Mesoridazine acts analogous to other phenothiazine neuroleptics and is used for schizophrenia, behavioral problems, psychoneurotic displays, and in severe and chronic alcoholism. Synonyms of this drug are lidanil, serentil, and others.

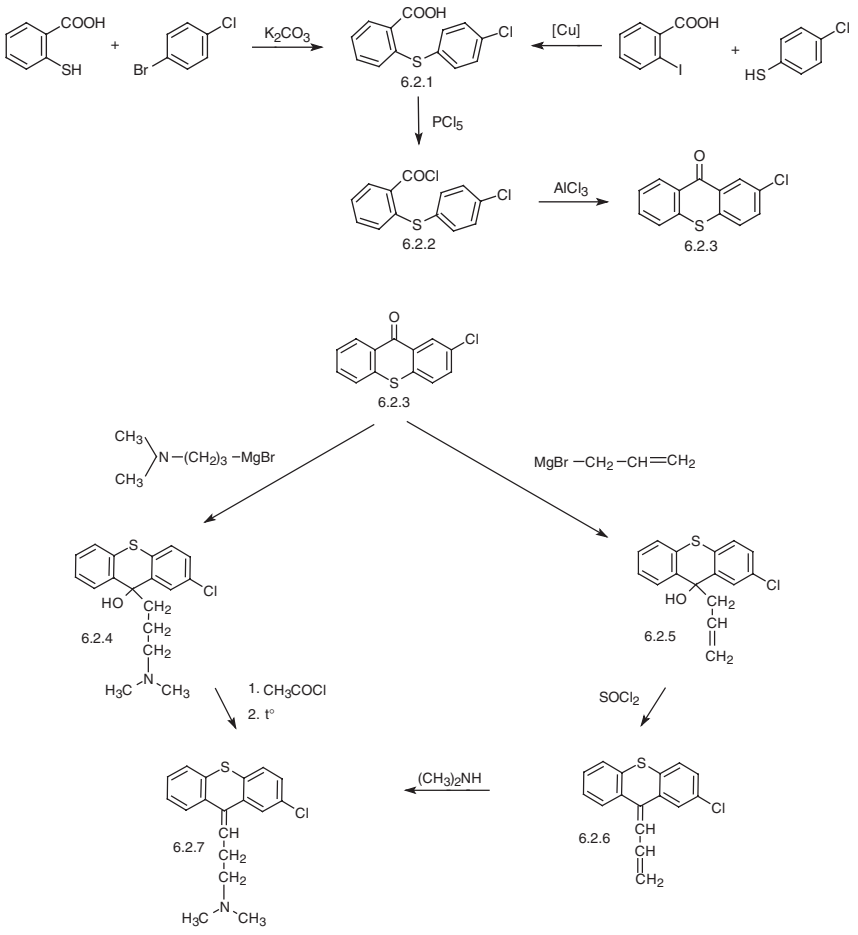
6.2 THIOXANTHENE DERIVATIVES

Thioxanthenes differ structurally from phenothiazine in that the nitrogen atom of the central ring of the tricyclic system is replaced by carbon, which is joined to a side chain with a double bond. Their pharmacological action is similar to the corresponding phenothiazine analogues. They have the exact mechanism of action and an analogous effect on the CNS. Drugs of this series differ from one another by quantitative indexes.

Chlorprothixene: Chlorprothixene, 2-chloro-9[(1-dimethylamino)-3-propyliden]thioxanthene (6.2.7), has been proposed to synthesize starting from 2-chlorothixantone (6.2.3). The initial 2-chlorothixantone (6.2.3) is prepared from 2-mercaptobenzoic acid, the reaction of

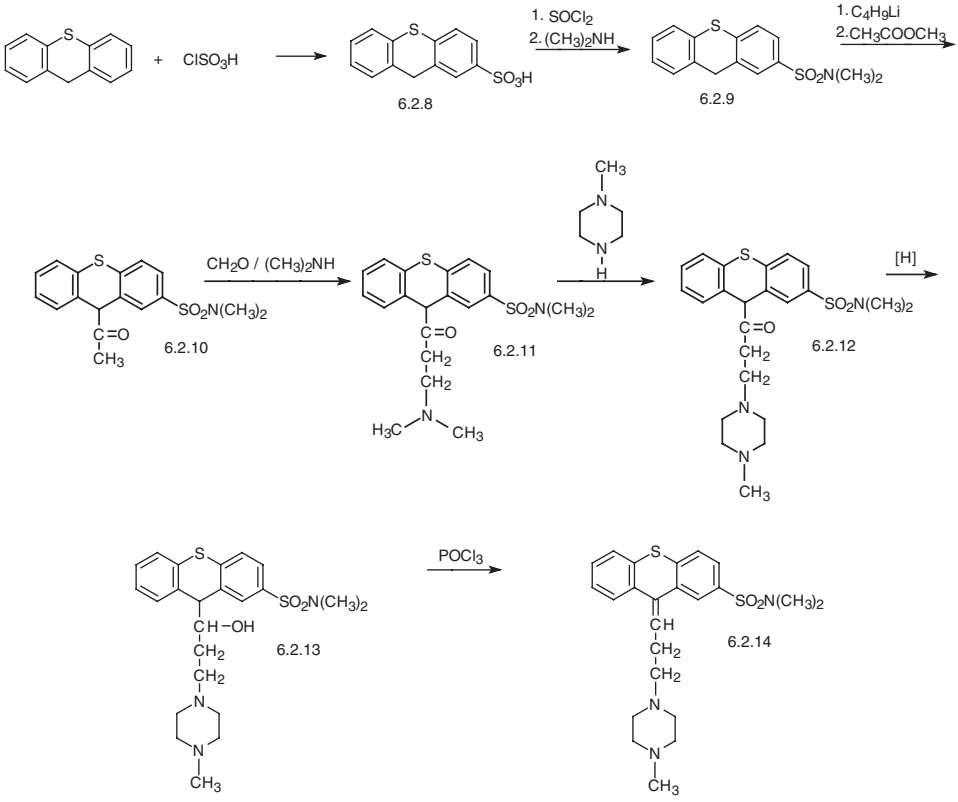
which with 1-bromo-4-chlorobenzene forms 2-(4-chlorophenylthio)benzoic acid (6.2.1), which upon reaction with phosphorous pentachloride transforms into acid chloride (6.2.2), and further undergoes intramolecular cyclization with the use of aluminum chloride to give 2-chlorthioxantone (6.2.3) [32]. An alternative way of making 2-chlorthioxantone (6.2.3) is by making 2-(4-chlorophenylthio)benzoic acid (6.2.1) by reacting 2-iodobenzoic acid with 4-chlorothiophenol [33]. The resulting 2-chlorthioxantone (6.2.3) is reacted as a carbonyl component with either 3-dimethylaminopropylmagnesiumbromide [33], or with allylmagnesiumbromide [34–36], giving the corresponding tertiary alcohol (6.2.4) or (6.2.5). Dehydration of the first is accomplished by acylation of the tertiary hydroxyl group using acetyl chloride and the subsequent pyrolysis of the formed acetate, which leads to the desired chlorprothixene (6.2.7).

Dehydration of the tertiary alcohol (6.2.5) is accomplished by chlorination of the tertiary alcohol group by thionyl chloride, forming the diene 2-chloro-9-(3-propen-1-iliden)thioxanthene (6.2.6), the addition to which of dimethylamine at high temperature forms the desired chlorprothixene (6.2.7).



Chlorprothixene has an antipsychotic and sedative action. It has expressed antiemetic activity. It is used in various psychoses, schizophrenia, reactive and neurotic depression with prevalent anxious symptomatology, and in conditions of excitement associated with fear and stress. It may be used in small doses as a sedative agent in neurosis. Synonyms of chlorprothixene are clothixene and tarasan.

Thiothixene: Thiothixene, *N*,*N*-dimethyl-9-[3-(4-methyl-1-1piperazinyl)propyliden]-thioxanten-2-sulfonamide (6.2.14), is synthesized from 9*H*-thioxantene, which is reacted with chlorosulfonic acid to give 9*H*-thioxanten-2-sulfonic acid (6.2.8). This is transformed into 2-dimethylaminosulfonyl-9*H*-thioxantene (6.2.9) by reaction of 6.2.8 with thionyl chloride and dimethylamine. The reaction of 2-dimethylaminosulfonyl-9*H*-thioxantene (6.2.9) with butyllithium and then with methylacetate forms 9-acetyl-2-dimethylaminosulfonyl-9*H*-thioxantene (6.2.10). Aminomethylation of the resulting product with dimethylamine and formaldehyde gives 9-(2-dimethylamineopropionyl)-2-dimethylaminosulfonyl-9*H*-thioxantene (6.2.11). Reacting this with 1-*N*-methylpiperazine results in a substitution of the dimethylamine group in the acylic part of the molecule with a *N*-methylpiperazine group, giving the product (6.2.12). The carbonyl group of the product is reduced to a secondary hydroxyl group using sodium borohydride followed by the dehydration of the product (6.2.13) with the help of phosphorous oxychloride to give the desired thiothoxene (6.2.14) [37–40].

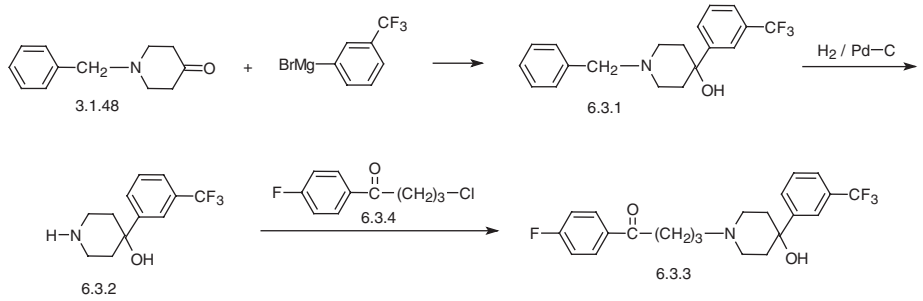


Thiothixene displays a specific chemical and pharmacological similarity to piperazine derivatives of the phenothiazine series, and is used for treating psychotic disorders. The indications for using thiothixene are the same as for chlorprothixene. Synonyms of this drug are orbinamon, navane, and others.

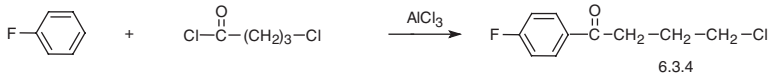
6.3 BUTYROPHENONE DERIVATIVES

A number of different compounds of the piperidine and piperazine series with *p*-fluorobutyrophenone group substitutions at the nitrogen atom display significant neuroleptic activity (haloperidol, trifluperidol, droperidol, methorin). There is a considerable interest in butyrophenone derivatives as antipsychotic agents as well as in anesthesiology. They exhibit pharmacological effects and a mechanism of action very similar to that of phenothiazines and thioxanthenes in that they block dopaminergic receptors. However, they are more selective with respect to D_2 receptors.

Trifluperidol: Trifluperidol, 4-[4-(α,α,α-trifluoro-*m*-tolyl)-4-hydroxypiperidino]-4′-fluorobutirophenone (6.3.3), is synthesized by reacting 1-benzyl-4-piperidone (3.1.48) with a Grignard reagent prepared from 1-trifluoromethyl-3-bromobenzene and magnesium that forms 1-benzyl-4-hydroxy-4-(3-trifluoromethylphenyl)piperidine (6.3.1), the reduction of which with hydrogen in the presence of a palladium on carbon catalyst removes the benzyl protecting group giving 4-hydroxy-4-(3-trifluoromethylphenyl)piperidine (6.3.2). Alkylation of the nitrogen atom of the last by *ω*–chloro-4-fluorobutyrophenone gives trifluperidol (6.3.3) [41–42].



The 4′-chloro-4-fluorobutirophenone (6.3.4) needed for this is synthesized by the acylation of fluorobenzene using 4-chlorobutyric acid chloride.

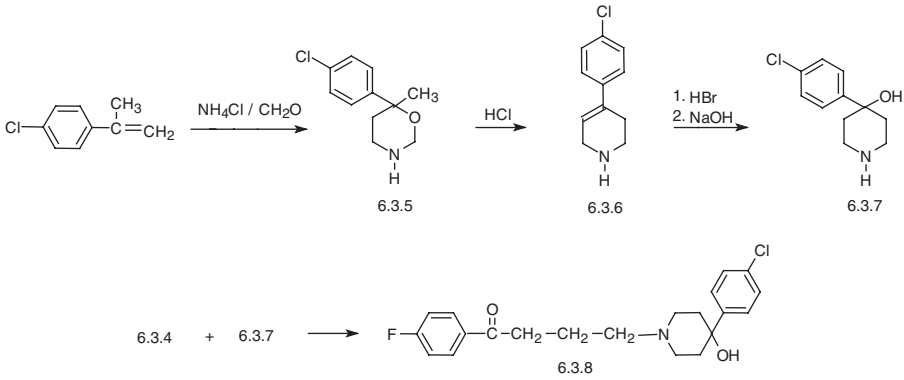


Trifluperidol is a powerful antipsychotic drug. It enhances the action of soporifics, narcotics, and analgesics. It also possesses anticonvulsant and antiemetic action.

It is used in psychoses accompanied by motor and mental excitement, in prolonged attacks of recurrent schizophrenia, in cases accompanied by severe depression and delirium, and in

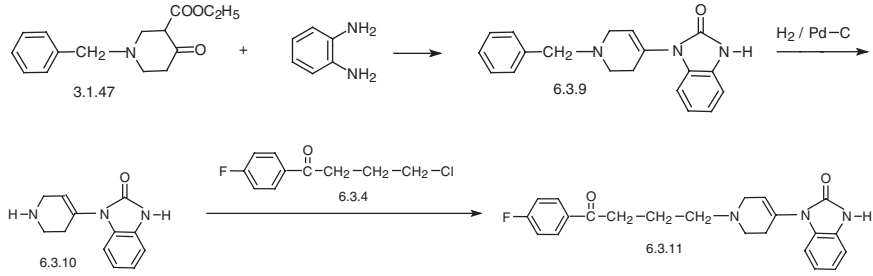
alcoholic psychoses. It surpasses other neuroleptics in terms of its ability to stop minor manic excitement. Synonyms of trifluperidol are triperidol, psychoperidol, trisedil, and others.

Haloperidol: Haloperidol, 4-[4-(*p*-chlorophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone (6.3.8), is synthesized by the alkylation of 4-(4-chlorophenyl)-4-hydroxypiperidine (6.3.7) using 4′-chloro-4-fluorobutyrophenone (6.3.4). 4-(4-Chlorophenyl) -4-hydroxypiperidine (6.3.7) is synthesized from 2-(4-chlorophenyl)propene, which on reaction with formaldehyde and ammonium chloride gives the intermediate 4-methyl-4-(4-chlorophenyl)-1, 3-oxazine (6.3.5), evidently through stages postulated for the Prince reaction. Treatment of the resulting product with hydrochloric acid leads to the formation of 4-(4-chlorophenyl)-1,2,3,6-tetrahydropiperidine (6.3.6), probably through a stage of opening of the hydrogenated 1,3-oxazine ring, followed by dehydration, and subsequent recyclization. Addition of hydrogen bromide to the double bond of 4-(4-chlorophenyl)1,2,3,6-tetrahydropipidine (6.3.6) and the subsequent alkaline hydrolysis of the 4-(4-chlorophenyl)-4-bromopiperidine formed during the reaction, gives 4-(4-chlorophenyl)-4-hydroxypiperidine (6.3.7), the reaction of which with 4′-chloro-4-fluorobutyrophenone (6.3.4) gives the desired haloperidol (6.3.6) [41–46].



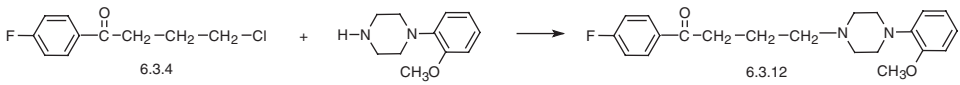
Haloperidol is one of the most actively used modern neuroleptics. Its high antipsychotic activity is combined with a moderate sedative effect. It effectively stops various types of psychomotor excitement. It is used for schizophrenic psychoses, manic, paranoid, and delirious conditions, depression, psychomotor excitement of various origins, and for delirium and hallucinations of different origin. The most common synonyms are haldol, vezadol, linton, and others.

Droperidol: Droperidol, 1-[1-[3-(*p*-fluorobenzoyl)propyl]-1,2,3,6,4-piridyl]-2-benzymidazolinone (6.3.11), is synthesized from 1-benzyl-3-carbethoxypiperidin-4-one (3.1.47), which is reacted with *o*-phenylendiamine. Evidently, the first derivative that is formed under the reaction conditions, 1,5-benzdiazepine, rearranges into 1-(1-benzyl-1,2,3,6-tetrahydro-4-piridyl)-2-benzymidazolone (6.3.9). Debenzylation of the resulting product with hydrogen over a palladium catalyst into 1-(1,2,3,6-tetrahydro-4-piridyl)-2-benzimidazolon (6.3.10) and subsequent alkylation of this using 4′-chloro-4-fluorobutyrophenone (6.3.4) yields droperidol (6.3.11) [47–49].



The neuroleptic droperidol possesses antipsychotic, sedative, and antishock action. It potentiates the action of drugs for narcosis. In psychiatric practice, droperidol is used for psychomotor excitement and hallucinations. The principal use of this drug lies in anesthesiology for neuroleptanalgesia in combination with fentanyl. It is used in premedication as well as in surgical operations and post-operational circumstances. Synonyms of this drug are talamonal, droleptan, leptofen, innovar, and others.

Fluanisone: Fluanisone, 4′-fluoro-4-[4-(*o*-methoxyphenyl)-1-piperazinyl]-butyrophenone (6.3.12), is synthesized by reacting 1-(2′-methoxyphenyl)-piperazine with 4′-chloro-4′-fluorobutyrophenone (6.3.4) [50].

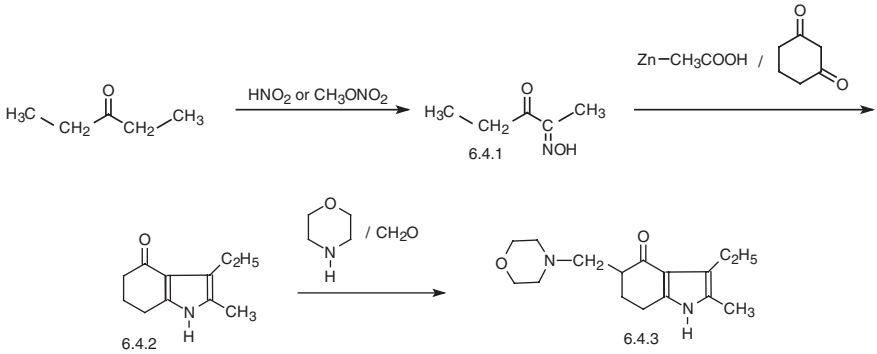


Fluanisone is a neuroleptic with sedative properties and relatively poorly expressed antipsychotic action. It is used as an independent or adjuvant drug for psychomotor excitement in severe and chronic schizophrenia and for manic-depressive disorder. Synonyms of this drug are sedalande, methorin, and others.

6.4 DIHYDROINDOLONE DERIVATIVES

Dihydroindolone derivatives do not structurally belong to any of the classes of drugs examined above. However, their mechanism of action, indications of use, and side effects are very similar to phenothiazine derivatives.

Molindone: Molindone, 3-ethyl-6,7-dihydro-2-methyl-5-(morpholinomethyl)indol-4(5*H*)-one (6.4.3), is synthesized by the nitrozation of diethylketone using nitric acid or methylnitrite into nitrozodiethylketone (6.4.1). Reduction of this product with zinc in acetic acid into 2-aminodiethylketone in the presence of cyclohexandion-1,3 gives 3-ethyl-2-methyl-4,5,6,7-tetrahydroindol-4-one (6.4.2). Aminomethylation of this product using morpholine and formaldehyde gives molindone (6.4.3) [51–52].

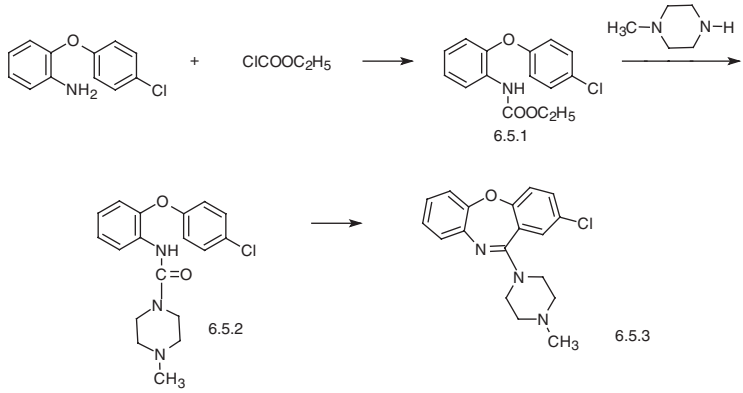


Molindone is a more active antipsychotic than chloropromzine. Its sedative effect is less expressed. Side effects are also expressed less than with powerful neuroleptics. It facilitates the reduction of spontaneous movements and aggressiveness, and is used for treatment of psychotic disturbances, particularly in cases of chronic and severe schizophrenia. A synonym of this drug is moban.

6.5 DIBENZOXAZEPINE AND DIBENZDIAZEPINE DERIVATIVES

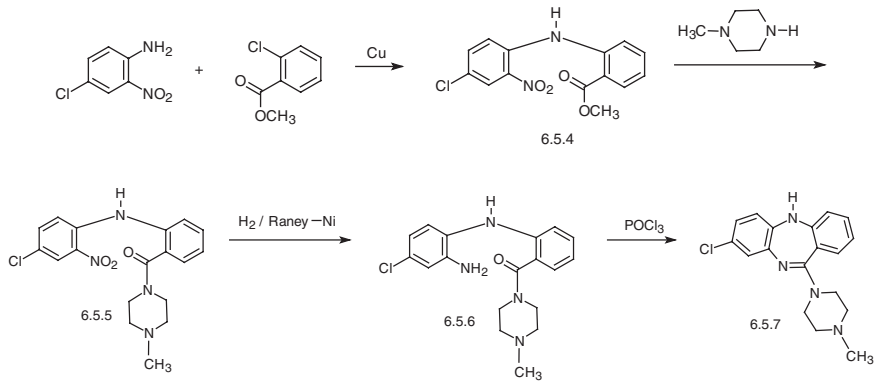
Dibenzoxazepine and dibenzdiazepines do not structurally belong to any of the classes of drugs listed above. However, their mechanism of action, indications for use, and side effects are analogous to phenothiazine derivatives.

Loxapine: Loxapine, 2-chloro-11-(4-methyl-1-piperazinyl)dibenz [b,f][1,4]exazepine (6.5.3), which is synthesized from 2-(4-chlorophenoxy)anyline. Acylation of the resulting product using ethylchloroformate forms *N*-ethoxycarbonyl-2-(4-chlorophenoxy)aniline (6.5.2). Treatment of this product with a mixture of phosphorous oxychloride and phosphorous anhydride gives loxapine (6.5.3) [53–55].

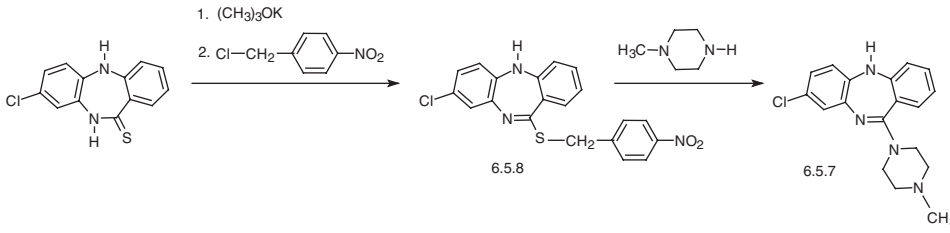


Loxapine is a more expressed, active antipsychotic than chlorpromazine. Its sedative effect is inferior to that of chlorpromazine. Indications for its use and side effects correspond with those of phenothiazine derivatives. Loxapine is used for treating psychotic disturbances, in particular cases of chronic and severe schizophrenia. Synonyms of this drug are loxapac and loxitane.

Clozapine: Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[b,e] [1,4]diazepine (6.5.7) is synthesized by two methods. According to the first, 4-chloro-2-nitroaniline in the presence of copper filings is acylated by the *o*-chlorobenzoic acid methyl ester, forming the corresponding diphenylamine (6.5.4). By reacting this with *N*-methyl piperazine, the ester group in the resulting polyfunctional diphenylamine is transformed into the amide (6.5.5). The nitro group in the resulting 4-chloro-2- nitro-2′-carb-(*N*′-methyl piperazino)amide (6.5.5) is further reduced into an amine group by hydrogen in the presence of Raney nickel. Reacting the resulting product (6.5.6) with phosphorous oxychloride yields in heterocyclization into the desired dibenzodiazepine, clozapine (6.5.7) [56–58].



The other way of synthesis of clozapine is from 8-chloro-10,11-dihydro-5*H*-dibenzo[b,e]1, 4-diazepin-11-thione, which is alkylated at the sulfur atom of the dibenzodiazepine ring by 4-nitrobenzylchloride in the presence of potassium *tert*-butoxide, giving *N*-methyl derivative (6.5.8). Reaction of this with *N*-methylpiperazine gives the desired clozapine (6.5.7) [59].



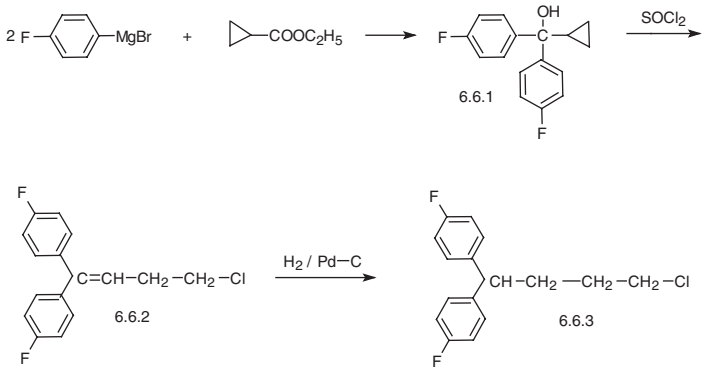
Clozapine is a neuroleptic, which expresses antipsychotic and sedative action. It does not cause general depression and extrapyramidal disorders. It is used for severe and chronic

forms of schizophrenia, maniacal conditions, manic-depressive psychosis, psychomotor excitement, and various other psychotic conditions. Synonyms of this drug are leponex, iprox, and others.

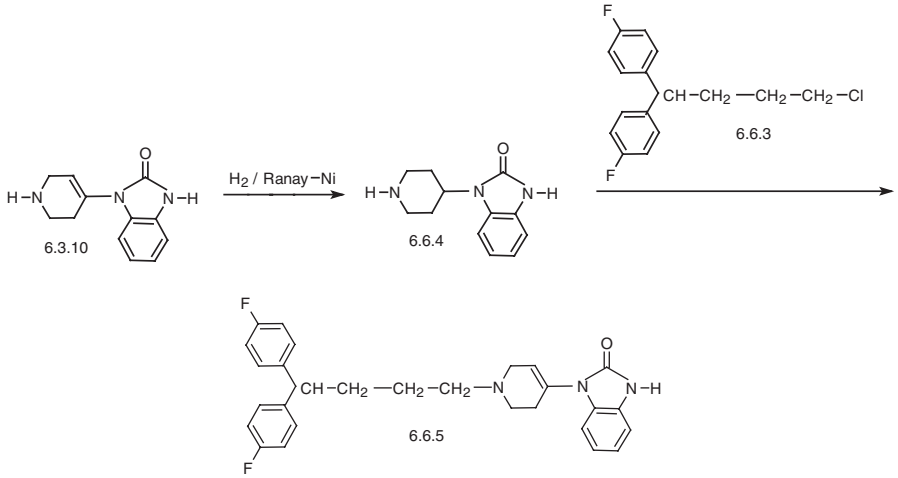
6.6 DIPHENYLBUTYLPIPERIDINE DERIVATIVES

Representatives of diphenylbutylpiperidines are pimozide, fluspirilene, and penfluridol, which belong to the powerful neuroleptic drugs with expressed antipsychotic properties similar to haloperidol. The principle distinctive feature of this series of drugs is their prolonged action. The mechanism of their action is not completely known; however, it is clear that they block dopaminergic activity.

Pimozide: Pimozide, 1-[1-[4,4-*bis*-(*p*-fluorophenyl)butyl]-4-piperidyl]-2-benzymidazolinone (6.6.5), is structurally very similar to droperidol with the exception of the presence of a double bond in the piperidine ring and the substitution of a *p*-fluorobutyrophenone group on the nitrogen atom of the piperidine ring with a 4,4-*bis*-(*p*-fluorophenyl)-butyl radical. 4,4-*bis*-(*p*-fluorophenyl)-butylchloride (bromide) (6.6.3), which is needed for the synthesis of pimozide as well as fluspirylene and penfluridol, is synthesized by reacting of two moles of 4-*p*-fluorophenylmagnesiumbromide with cyclopropancarboxylic acid ester, which results in the formation of *bis*-(4-*p*-fluorophenyl)cyclopropylcarbinol (6.6.1). Treatment of this with thionyl chloride (phosphorous tribromide) leads to opening of the cyclopropyl ring, forming 1,1-*bis*-(4-fluorophenyl)-4-chloro(bromo)-1-butene (6.6.2). Reduction of the double bond using hydrogen over a palladium catalyst leads to the formation of 1,1-*bis*-(4-fluoro- phenyl)butyl chloride (bromide) (6.6.3) [60–63].

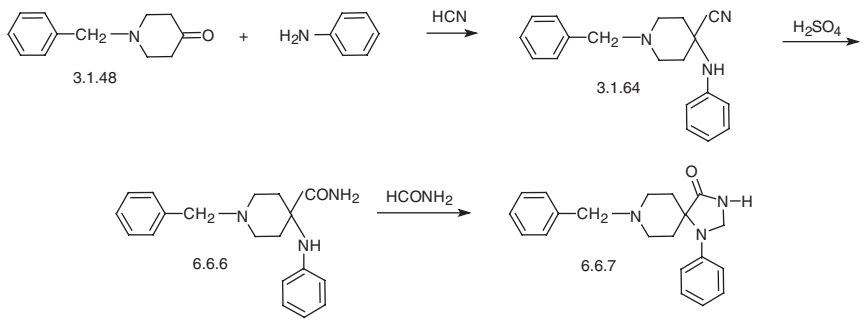


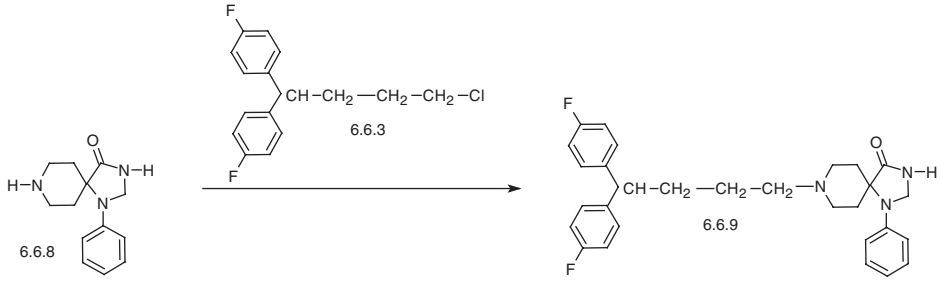
In essence, the synthesis of pimozide lies in the *N*-alkylation of 4-(2-benzimidazolinon)piperidine (6.6.4), which is synthesized by the reduction of 1-(1,2,3,6-tetrahydro-4-piridyl)-2-benzimideazolone (6.3.10) using hydrogen over Raney nickel of pimozide (6.6.5), by the earlier synthesized 4,4-*bis*-(4-fluorophenyl)butylchloride (6.6.3).



In terms of pharmacological action, pimozide is similar to haloperidol. It is used in hospitals as well as in outpatient settings for supportive therapy of patients suffering from schizophrenia, paranoid conditions, and mental and neurotic disorders with paranoid characteristics. It is unfit for use in severe psychoses because it does not possess psychomotor-sedative action. It is used for treating patients who suffer from Turretts's syndrome. Pimozide has a number of side effects, many of which are similar to those of phenothiazine and a number of others. A synonym of this drug is orap.

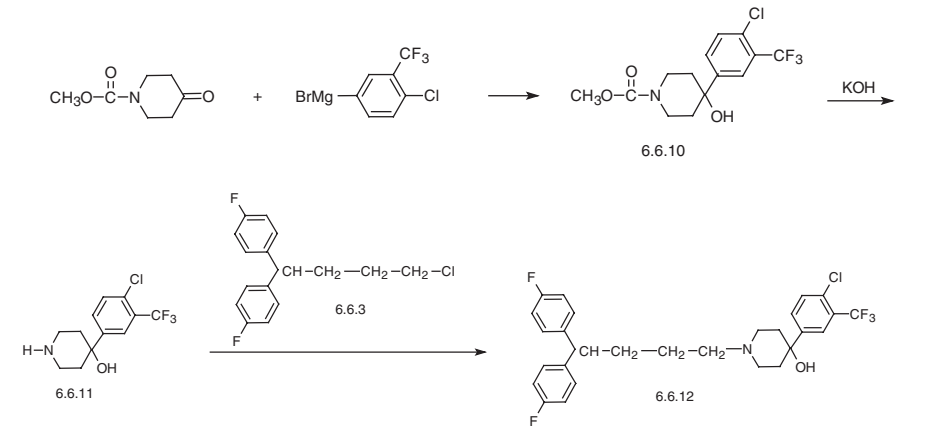
Fluspirilene: Fluspirilene, 8-[4,4-*bis*(*p*-fluorophenyl)butyl]-1-phenyl-1,3,8-triazaspiro [4,5]decan-4-one (6.6.9), is synthesized from 1-benzyl-4-anilino-4-cyanopiperidine (3.1.64) by the way of its acidic hydrolysis into the amide (6.6.6), and the subsequent heterocyclization of 4-aminocarbonyl and 4-aniline functional groups into imidazolone cycle, thus creating the desired spiroheterocyclic system, 8-benzyl-1-phenyl-1,3,8-triazaspiro[4,5] decan-4-one (6.6.7). Hydrogenation of this product using a palladium on carbon catalyst removes the *N*-benzyl protecting group, forming 1-phenyl-1,3,8-triazaspiro [4,5]decan-4-one (6.6.8). Alkylating this with 1,1-*bis*-(4-fluorophenyl)butyl bromide (6.6.3) gives fluspirilene (6.6.9) [64–66].





This drug is primarily used for supportive therapy of patients suffering from chronic mental illnesses after treatment in the hospital. It is suitable for use in ambulatory practice because of the lack of expressed hypno-sedative effects. Synonyms of this drug are imap, redeptin, and others.

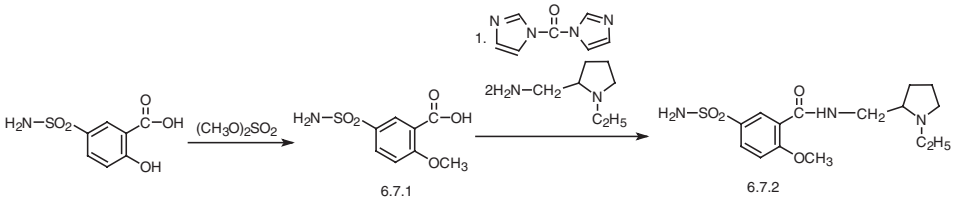
Penfluridol: Penfluridol, 4-(4-chloro-3-trifluoromethylphenyl)-1-[4,4-*bis*-(*p*-fluorophenyl) butyl]-4-piperidinol (6.6.12), is synthesized implementing a Grignard reaction between 1-carbomethoxypiperidin-4-one and 4-chloro-3-trifluoromethylphenylmagnesium bromide, giving 1-carbomethoxy-(4-chloro-3-trifluoromethylphenyl)-4-piperidinol (6.6.10). Upon alkaline hydrolysis of the carbomethoxy group, it turns into (4-chloro-3-trifluoromethylphenyl)-4-piperidinol (6.6.11), the alkylation of which with 1,1-*bis*(4-fluorophenyl)butyl bromide (6.6.3) gives penfluridol (6.6.12) [67–69].



In terms of pharmacological action, penfluridol is similar to pimozide; however, it is significantly longer lasting, which is connected to the slow metabolism of the drug. Penfluridol is used as a supportive therapy in ambulatory settings for patients suffering from schizophrenia as well as patients with paranoid, psychotic, and neuroleptic conditions. Synonyms of this drug are semap, longoperidol, and others.

6.7 OTHER NEUROLEPTICS

Sulpiride: Sulpiride, *N*-[(1-ethyl-2-pirrolidinylmethyl]-5-sulfamoyl-*O*-anizamide (6.7.2), is synthesized from 5-aminosulfosalycilic acid. Methylating this with dimethylsulfate gives 2-methoxy-5-aminosulfonylbenzoic acid (6.7.1), which is transformed into an amide using 2-aminomethyl-1-ethylpyrrolidine as amine components and carbonyl-1,1′-*bis*-imidazole as a condensing agent [70–74].



6.7.1 6.7.2

Sulpiride possesses moderate neuroleptic activity along with some stimulating and antidepressant effects. It has antiemetic, moderately cataleptogenic, and antiserotonin action. It facilitates increased blood flow in the stomach. It speeds up the restorative processes in tissues. It is used for schizophrenia, depression, migraines, disturbance of behavioral functions, and stomach and duodenal ulcers. Synonyms of this drug are arminol, dogmatil, confidan, eglonil, and many others.

6.8 LITHIUM DERIVATIVES

Lithium salts were proposed in medicine for treating gout and dissolving kidney stones. However, it was later discovered that lithium drugs were capable of stopping severe mania excitement in humans and preventing affective attacks. The mechanism of action of lithium drugs is not conclusively known; however, it is clear that lithium ions influence sodium transport ions in nerve and muscle cells, which results in lithium ions acting as antagonists to sodium ions.

Lithium carbonate: Lithium carbonate is synthesized by reacting lithium salts with soda or potash, followed by purification of the salt, which is not readily soluble [75].

$$2LiCl + Na_2CO_3 = 2NaCl + Li_2CO_3$$

The most common lithium drug is lithium carbonate, which possesses antimania action. It is presumed that lithium alters the transport of sodium ions in neurons, thus influencing the intercellular contents of catecholamines, normalizing the mental state and not causing general lethargy. It is used for mania conditions of various origins, preventative measures, and for treating affective psychoses. Synonyms of this drug are eskalith, carbolith, cibalith, lithane, and others.

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– 7 –

Antidepressants

Drugs used for treating mental disorders accompanied by depression are called antidepressants. They are drugs that can relieve a number of symptoms that are associated with number of known psychosomatic disorders such as depression.

In other words, antidepressants are capable of removing or alleviating a number of disorders in the psychoemotional realm referred to as "depressive syndrome" in psychoneurological practice.

In turn, conditions characterized by the term "depression" include affective disorders, which are frequently accompanied by a number of other disturbances including unmotivated sorrow, sleep disorders, changes in appetite, various psychomotor disturbances, loss of interest in things once pleasurable, feelings of worthlessness, and often suicidal thoughts.

There are sufficiently acceptable, although not universally accepted classifications of depression based on their etiology. Endogenous depression is characterized by loss of interest in things once pleasurable, loss of libido, minor restlessness, and trouble sleeping. Neurotic or anxious depression is distinguished by anxiety, stress, hyperactivity to unexpected events or loss, irritability, and helplessness. Situational depression usually originates upon influence of stressful outside factors. Manic-depressive disorder is characterized by alternating expression and unequal mood swings.

Despite the fact that the initial biochemical abnormalities responsible for depression and manic-depressive conditions have not been completely discovered, some facts suggest that depressive conditions may be caused by a lack of norepinephrine (noradrenaline) and serotonin. The majority of drugs used in treatment of such illnesses act by affecting the system of biogenic amines of the brain, thus leading to action of a mechanism that is capable of increasing their contents in respective parts of the brain.

There are four classes of antidepressants: tricyclic antidepressants (imipramine, trimipramine, amitriptyline, doxepin, desipramine, protriptyline, nortriptyline, amoxapine, maprotiline); monoaminooxidase (MAO) inhibitors (phenelzine, isocarboxazid, tranylcypromine); second-generation antidepressants or atypical antidepressants, which are a chemically dissimilar group of recently proposed drugs (bupropion, trazodone, fluoxetine); and amphetamines and other stimulators of the CNS (dextroamphetamine, methylphenidate).

The most frequent and widely used drugs for treating endogenous depression are tricyclic antidepressants. In terms of clinical action they are similar to the phenothiazine

antipsychotics. Second-generation antidepressants differ from the previous drugs in the number of side effects observed. MAO inhibitors exhibit less clinical efficacy than tricyclic antidepressants and they are usually used for treating severe depression that does not successfully respond to tricyclic antidepressants. Finally, some of the CNS stimulators, the majority of which are amphetamine derivatives, are used mainly in cases of moderate depression; however, their low efficacy in cases of severe depression and their evident ability to cause addiction limit their use.

In choosing drugs for pharmacotherapy, both the characteristics of the drugs themselves, the level of severity, and the symptomatology of the illness should be taken into consideration.

7.1 TRICYCLIC ANTIDEPRESSANTS

The most frequently used drugs are tricyclic antidepressants, which received their name from the organization of their chemical structures, in particular the systems consisting of two benzene rings joined to a central 7-membered ring with a dialkylaminoalkyl group connected to the central ring. Depending on the substituents on the terminal nitrogen atom in the amine-containing side chain, they in turn are subdivided into tertiary (imipramine, amitriptyline, trimipramine, doxepin) and secondary (desipramine, nortriptyline, protriptyline) amines. These classifications are very formal and are not based on the most essential structural variations of the examined drugs; however, they are accepted in pharmacology.

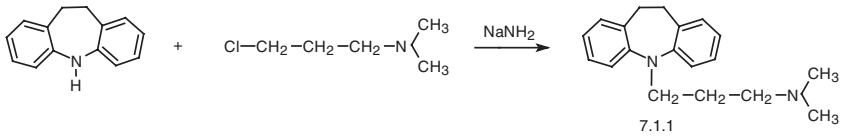
Tricyclic antidepressants are chemically, pharmacologically, and toxicologically very similar to antipsychotics of the phenothiazine series. The mechanism of action of tricyclic depressants is not conclusively known, and not one of the proposed hypotheses is currently capable of fully explaining their antidepressant effect.

It is believed that tricyclic antidepressants inhibit the (neuronal) reuptake of norepinephrine (noradrenaline) and/or serotonin by presynaptic nerve endings, thus blocking one of the leading mechanisms of their inactivation, and thereby increasing the concentration of the indicated amines potentiating their effects. It should be noted that, as a rule, secondary amines, which are representatives of tricyclic antidepressants, exhibit high activity, blocking the neuronal reuptake of norepinephrine, while tertiary amines act more on the neuronal reuptake of serotonin.

It is also possible that tricyclic antidepressants block presynaptic α_2 adrenoreceptors, thus increasing the quantity of releasable norepinephrine and/or serotonin. Tricyclic antidepressants are used for relieving symptoms of depression (especially of the endogenous type), for controlling anxiety associated with depressive conditions, for treating depression in patients with maniac-depressive psychosis, and so on.

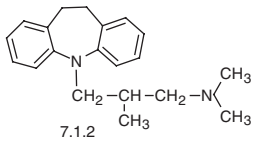
7.1.1 Tertiary amines—representatives of tricyclic antidepressants

Imipramine: Imipramine, 5-[3-(dimethylamino)propyl]-10,11-dihydro-5*H*-dibenz[b,f] azepine (7.1.1), is synthesized by the alkylation of 10,11-dihydro-5*H*-dibenz[b,f]azepine using 3-dimethylaminopropylchloride in the presence of sodium amide [1–3].



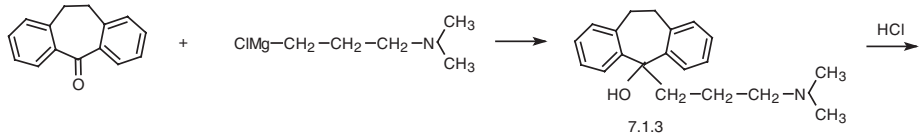
Imipramine is the primary representative of typical tricyclic antidepressants. It acts by blocking the mechanism of reuptake of biogenic amines. It does not inhibit MAO activity. Imipramine lessens sadness, lethargy, improves mood, and improves the mental and overall tone of the body. It is used in depression of various etiology accompanied by motor clumsiness and enuresis in children and Parkinson's disease. Primary synonyms of this drug are tofranil, surplix, imizin, melipramin, and others.

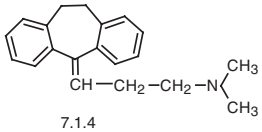
Trimipramine: Trimipramine, 5-[3-(dimethylamino)-2-methylpropyl]-10,11-dihydro-5*H*-dibenz[b,f]-azepine (7.1.2), is synthesized in the exact manner as imipramine, alkylating 10,11-dihydro-5*H*-dibenz[b,f]azepine with 3-dimethylamino-2-methylpropylchloride [4,5] instead of 3-dimethylaminopropylchloride, as it was in the case of imipramine.



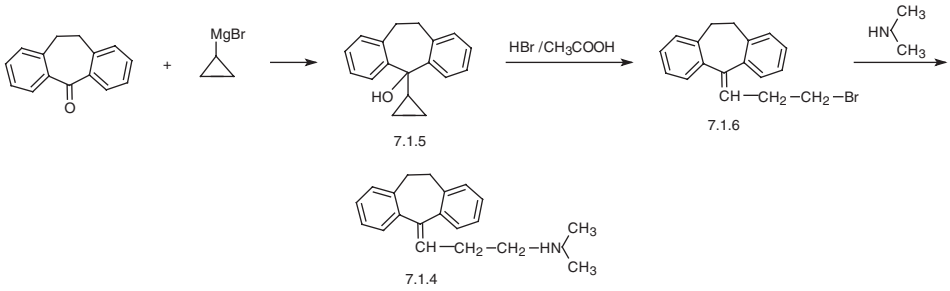
As with imipramine, it is used for depression of various etiology. In terms of efficacy, it is analogous to imipramine. Surmontil is a synonym of trimipramine.

Amitriptyline: Amitriptyline, 5-(3-dimethylaminopropyliden)-10,11-dihydrodibenzocycloheptene (7.1.4), differs from imipramine in that the nitrogen atom in the central part of the tricyclic system is replaced by a carbon, which is bound to a side chain by a double bond. Amitriptyline (7.1.4) is synthesized by interaction of 10,11-dihydro-*N*,*N*-dimethyl-5*H*-dibenzo[a,d]cyclohepten-5-one with 3-dimethylaminopropylmagnesium bromide and the subsequent dehydration of the resulting tertiary alcohol (7.1.3) using hydrochloric acid [6–11].





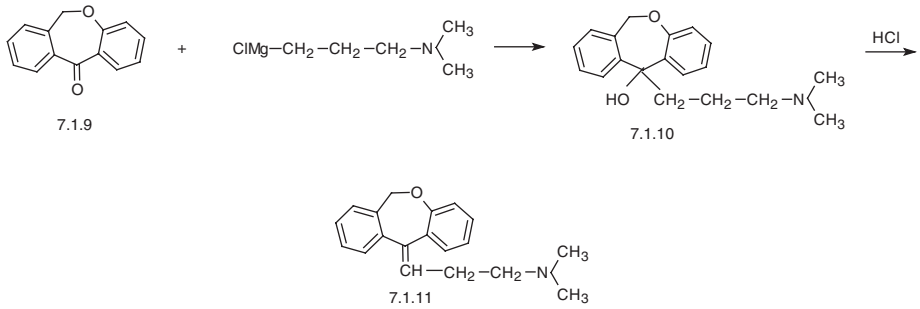
An alternative way of synthesis of amitriptyline is by interaction of 10,11-dihydro-*N*,*N*-dimethyl-5*H*-dibenzo[a,d]-cyclohepten-5-one with cyclopropylmagnesium bromide, giving 10,11-dihydro-*N*,*N*-dimethyl-5*H*-dibenzo[a,d]-cyclohepten-5-cyclopropyl-5-ol (7.1.5). Reacting this with hydrogen bromide in acetic acid results in an opening of the cyclopropyl ring, which forms 5-(3-bromopropyliden)-10,11-dihydro-5*H*-dibenzo[a,d]-cycloheptene (7.1.6). Alkylating this with dimethylamine gives amitriptyline (7.1.4) [12,13].



7.1.5 7.1.6 7.1.4

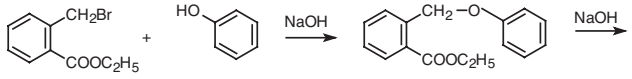
Amitriptyline is used for anxious-depressive conditions. It is easier to tolerate than imipramine. The most frequently encountered synonyms are triptizol and amiprin.

Doxepin: Doxepin, (11[16H]-(3-dimethylaminopropyliden)-6,11-dihydrobenz[b,e] oxepine) (7.1.11), is synthesized in an analogous manner by reacting 6,11-dihydrodibenz-[b,e]oxepin-11-one (7.1.9) with 3-dimethylaminopropylmagnesium bromide and the subsequent dehydration of the resulting tertiary alcohol (7.1.10) by hydrochloric acid [14–17].

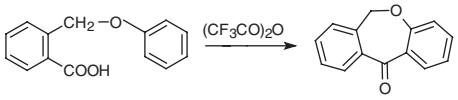


7.1.9 7.1.10 7.1.11

The initial 6,11-dihydrodibenz[b,e]oxepin-11-one (7.1.9) is synthesized from the ethyl ester of 2-phenoxymethyl benzoic acid (7.1.7), which is easily synthesized by reacting ethyl 2-bromomethylbenzoate with phenol in the presence of a base. The resulting ester (7.1.5) is hydrolyzed into 2-phenoxymethylbenzoic acid (7.1.8), which is cyclized to 6,11-dihydrodibenz[b,e]oxepin-11-one (7.1.9) by trifluoroacetic acid anhydride.



7.1.7



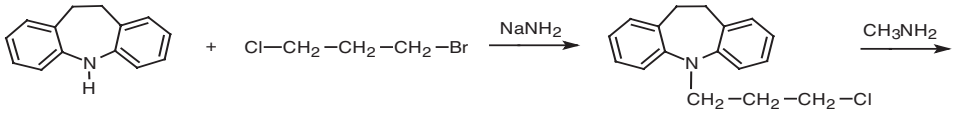
7.1.8 7.1.9

The mechanism of action of doxepin is presumable linked to the effect on the adrenergic transmission in the CNS, in particular to the blockage of neuronal norepinephrine uptake. Doxepin is used in anxious-depressive and anxious conditions, neuroses, alcoholism, organic illnesses of the CNS, and psychoses. The most frequently used synonyms are adapin and sinequan.

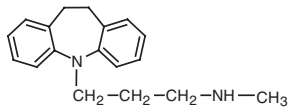
7.1.2 Secondary amines—representatives of tricyclic antidepressants

Desipramine: Desipramine, 10,11-dihydro-5-[3-(methylamino)propyl]-5*H*-dibenz[b,f] azepine (7.1.13), differs from imipramine in that it contains only one methyl group on the nitrogen atom of the propylamine side chain. The suggested methods of desipramine synthesis are very simple, and the difference lies only in the manner in which the secondary methylamine group is introduced into the structure of the drug.

The first way of synthesis is by the alkylation of 10,11-dihydro-5*H*-dibenz[b,f]azepine using 1-bromo-3-chloropropane in the presence of sodium amide into a chloro derivative (7.1.12) and the subsequent reaction of this with methylamine, giving desipramine (7.1.13) [18–20].

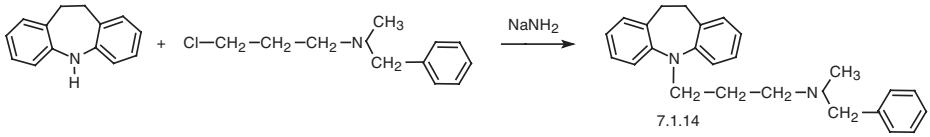


7.1.12

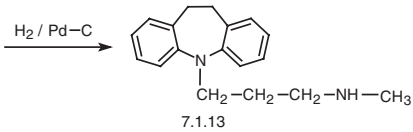


7.1.13

A second way is by alkylation of 10,11-dihydro-5*H*-dibenz[b,f]azepine with 3-(*N*-benzyl-*N*-methylamino)propyl chloride in the presence of sodium amide and the subsequent debenzylation of the resulting product (7.1.14) by hydrogenation using a palladium catalyst [21,22].

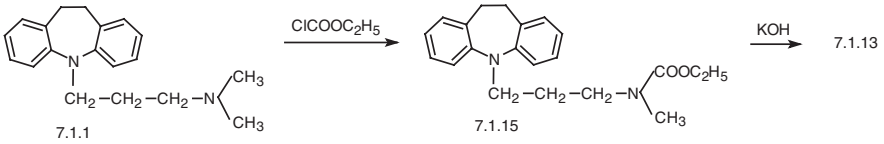


7.1.14



7.1.13

Finally, a third way of synthesis is from imipramine (7.1.1), which undergoes demethylation by successive reaction with ethyl chloroformate, giving 5-[3-(*N*-carbethoxy-*N*-methyl)aminopropyl]-10,11-dihydro-5*H*-dibenz[b,f]azepine (7.1.15), the alkaline hydrolysis of which leads to desipramine (7.1.13) [23,24].



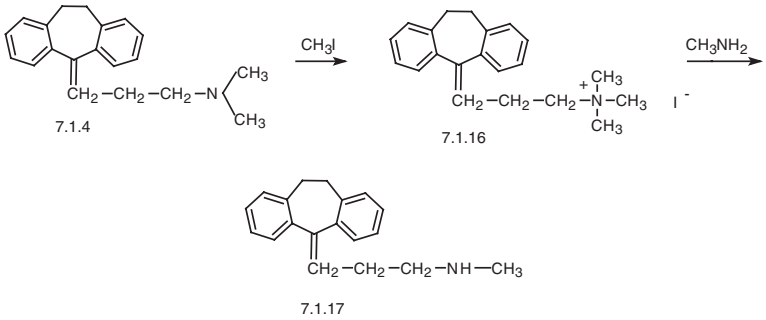
7.1.1 7.1.15

Desipramine is used for depression of various etiology and in particular for endogenous depression. Synonyms are norpramin and pertofrane.

Nortriptyline: Nortriptyline is 5-(3-methylaminopropyliden)-10,11-dihydrodibenzcycloheptene (7.1.17). Nortriptyline differs from desipramine in the same manner in which amitriptyline differs from imipramine. In nortriptyline, the nitrogen atom in the central part of the tricyclic system of desipramine is replaced by a carbon atom, which is bound to a side chain by a double bond.

Two suggested methods of nortriptyline synthesis are based on the *N*-demethylation of amitriptyline. The third way utilizes the reaction of methylamine with 5-(3-bromopropyliden)-10,11-dihydro-5*H*-dibenz[a,d]cycloheptene (7.1.18).

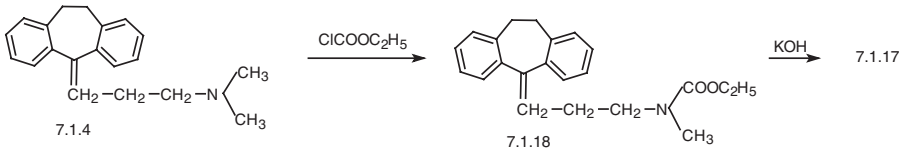
According to the first scheme, demethylation takes place by the reaction of amitriptyline (7.1.4) with methyliodide, which leads to the formation of a quaternary ammonium salt (7.1.16), the reaction of which with methylamine at a relatively high temperature gives the desired nortriptyline (7.1.17) [25].



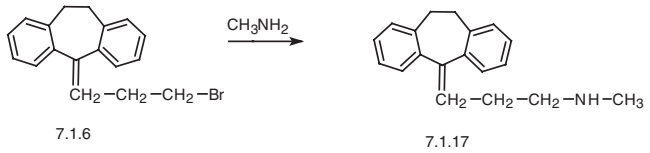
7.1.4 7.1.16

7.1.17

In the second scheme, the specified reaction of amitriptyline (7.1.4) with ethyl chloroformate leads to the substitution of a methyl group on the amino group with an ethoxycarbonyl group. Hydrolysis of the formed product leads to nortriptyline (7.1.17) [26].



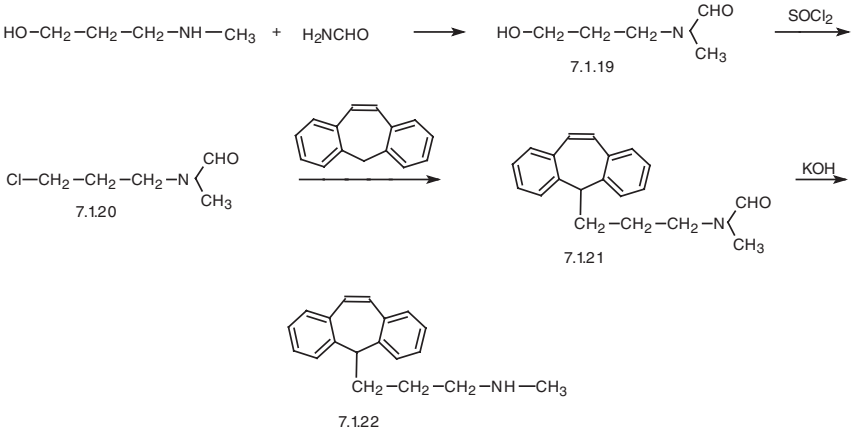
According to the third scheme, nortriptyline is synthesized by reacting methylamine with 5-(3-bromopropyliden)-10,11-dihydro-5*H*-dibenz[a,d]cycloheptene (7.1.6) [8].



A few modifications of the described methods have been suggested for making nortriptyline [27–32]. Nortriptyline is a drug with a relatively short latent period of action. It is practically devoid of sedative effects. It is used in manic-depressive psychoses, in all forms of endogenous depression, and also in major depressive conditions. The most common synonyms of nortriptyline are aventyl, nortrilen, motival, vivactil, and pamelor.

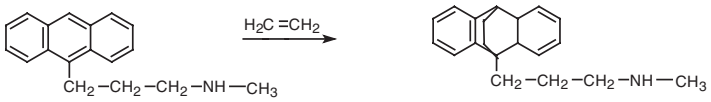
Protriptyline: Protriptyline, *N*-methyl-5-*H*-dibenzo[a,d]cyclohepten-5-propylamine (7.1.22), differs from all of the drugs described above in that there is present a double bond at the C_{10}–C_{11} position of the central 7-membered ring of the tricyclic part of the molecule. At the same time, a free electron pair on C_5 belonging to either a nitrogen atom or an exocyclic double bond are excluded, which undoubtedly changes both the architecture of the whole molecule as well as, the collocation of pharmacophore groups.

Protriptyline is synthesized by alkylation of 5-*H*-dibenzo[a,d]cycloheptene with 3-(*N*-phormyl-*N*-methylamino)propylchloride (7.1.20), which is synthesized from compound (7.1.19). The resulting intermediate product (7.1.21) undergoes alkaline hydrolysis, which leads to the formation of protriptyline (7.1.21) [33–38].



Protriptyline is a powerful antidepressant, the mechanism of action of which is not known. It is not a MAO inhibitor and does not stimulate the CNS. It begins to act much faster and acts much longer than imipramine or amitriptyline. Protriptyline does not possess sedative tranquilizing properties. It is used in clinical conditions for treating severe depression. The most common synonyms are concordin, triptil, and vivactil.

Maprotiline: Maprotiline, *N*-methyl-9,10-ethanoanthracen-9(10*H*)-propylamine (7.1.22), is synthesized by a 4+2 cycloaddition reaction of 9-(3-methylaminopropyl)anthracene with ethylene [39–41].



7.1.22

Maprotiline is frequently referred to as a tetracyclic antidepressant. This "hybrid" drug, containing both elements of "classic tricyclic antidepressants" and protriptyline elements, is pharmacologically and clinically more similar to imipramine.

It disrupts neuronal reuptake of monoamines in the CNS and possesses moderate tranquilizing and cholinergic activity. It improves mood significantly and relieves feelings of fear. Maprotiline is used in various forms of depression accompanied by a feeling of fear and irritability. Ludiomil is a synonym of maprotiline.

7.2 MONOAMINOOXIDASE INHIBITORS

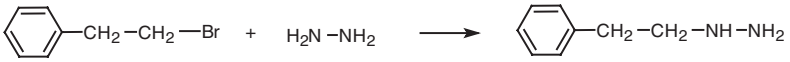
Monoaminooxidase is a complex enzymatic system that is present in practically every organ that catalyzes deamination or inactivation of various natural, biogenic amines, in particular norepinephrine (noradrenaline), epinephrine (adrenaline), and serotonin. Inhibition of MAO increases the quantity of these biogenic amines in nerve endings. MAO inhibitors increase the intercellular concentration of endogenous amines by inhibiting their deamination, which seems to be the cause of their antidepressant action.

These drugs, which form stable complexes with MAO and thereby inhibit its action have long been used in medicine as antidepressants, and are referred to as MAO inhibitors. It is possible, that MAO inhibitors act not by complexation with the enzyme, but by forming covalent bonds that is by irreversibly inactivating the enzyme.

The mechanism of antidepressive action of this series of drugs is likely associated with their inhibition of the oxidizing deamination process of the neurotransmitters norepinephrine, epinephrine, dopamine, and serotonin, which participate in the transmission of nerve excitement in the CNS. A major drawback of these drugs is the high toxicity associated with their inhibition of not only MAO, but also a number of other nonspecific enzymes.

MAO inhibitors are used in treating severe endogenous, exogenous, and reactive depressions that do not react to treatment with tricyclic antidepressants, as well as for controlling depressive phases in manic-depressive psychoses.

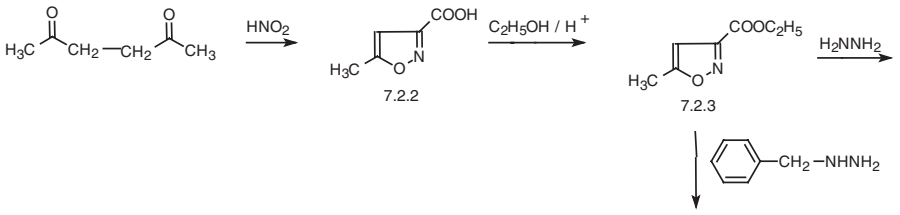
Phenelzine: Phenelzine, 2-phenylethylhydrazine (7.2.1), is synthesized by reacting 2-phenylethylbromide with hydrazine [42–45].



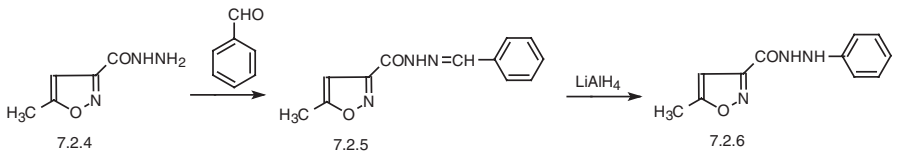
7.2.1

Phenelzine is a MAO inhibitor which is used for treating patients with depressive characteristics such as "atypical," "nonendogenous," or "neurotic" conditions in which a combination of anxiety, depression, or phobia are observed. Phenelzine is not a drug of first choice, and it is used in depressions that do not respond to other medicinal drugs. Nardil is a synonym of phenelzine.

Isocarboxazid: Isocarboxazid, 2-benzylhydrazid-5-methyl-3-isoxazolecarboxylate (7.2.6), can be synthesized from acetylacetone, which on nitrosation with nitrous acid gives 5-methyl-isoxazol-3-carboxylic acid (7.2.2). Esterification of this product gives the ethyl ester of 5-methyl-isoxazol-3-carboxylic acid (7.2.3). The synthesized ester (7.2.3) is further reacted with benzylhydrazine, to give isocarboxazide (7.2.6), or with hydrazine, which forms 5-methyl-isoxazol-3-carboxylic acid hydrazide (7.2.4). Reacting the latter with benzaldehyde gives hydrazone (7.2.5), which is further reduced to the isocarboxazide (7.2.6) [46,47].



7.2.2 7.2.3

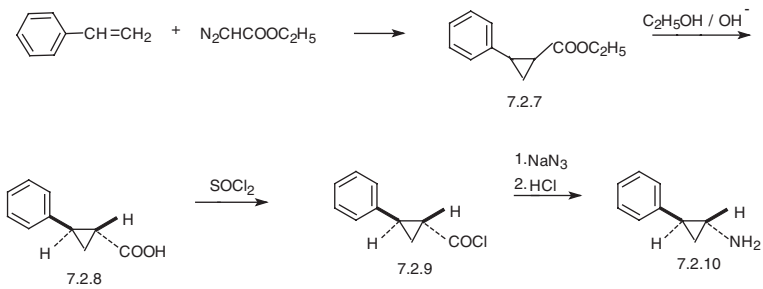


7.2.4 7.2.5 7.2.6

Isocarboxazid is a powerful MAO inhibitor. As with phenelzine, isocarboxazid is used for depressions that do not respond to other drugs. Marplan is a synonym of isocarboxazid.

Tranylcypromine: Tranylcypromine, (±)-*trans*-2-phenylcyclopropylamine (7.2.10), differs from the drugs described above in that it is not a derivative of hydrazine. It is synthesized from the ethyl ester of 2-phenylcyclopropan carboxylic acid (7.2.7), which

is synthesized by the reaction of styrene with ethyl diazoacetate. 2-phenylcyclopropancarboxylic acid ethyl ester (7.2.7) is hydrolyzed by alkali to 2-phenylcyclopropancarboxylic acid (7.2.8) and the *trans*-isomer is separated for further reactions. The reaction of the *trans*-isomer with thionyl chloride gives *trans*-2-phenylcyclopropancarboxylic acid chloride (7.2.9), which upon reaction with sodium azide gives the respective acid azide, which undergoes Curtius rearrangement to the transcyclopropylamine (7.2.10) [48,49].



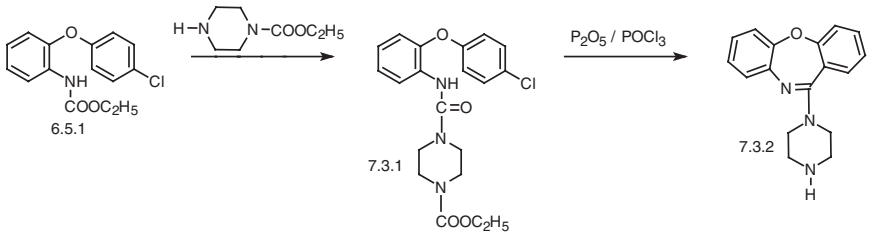
As with the MAO inhibitor drugs described above, tranylcypromine is also used for depressions that do not respond to other drugs. Synonyms of this drug are transamin, parmodalin, parnate, and others.

7.3 SECOND-GENERATION ANTIDEPRESSANTS (ATYPICAL ANTIDEPRESSANTS)

A number of chemically dissimilar compounds that are not classified and do belong to either the class of tricyclic antidepressants or to the class of MAO inhibitors, exhibit very effective antidepressant activity.

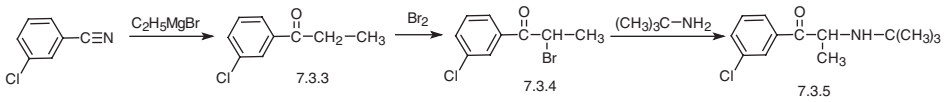
It is very likely that their action is also due to the ability to inhibit the intake of norepinephrine or serotonin. However, because of the diversity of this group, the mechanism of action of each drug will be examined separately.

Amoxapine: Amoxapine, 2-chloro-11-(1-piperazinyl)-dibenz[b,f]oxazepine (7.3.2), is a direct analog of the neuroleptic loxapine (6.5.3), differing only in the absence of a methyl group in the piperazine region of the molecule. On the other hand, it could be included in the class of tricyclic antidepressants, the main difference being the presence of a side chain on the central 7-membered ring of the tricyclic system. Amoxapine, like loxapine, is synthesized from 2-(4-chlorobenzoxy)aniline, which as in loxapine synthesis is acidified with chlorocarbonic acid into (6.5.1) and further transformed into ureide (7.3.1) upon reaction with 1-carboethoxypiperazine. Cyclization by a mixture of phosphorous pentoxide and phosphorous oxychloride into the dibenzoxazepine and subsequent alkaline hydrolysis gives amoxapine (7.3.2) [50–53].



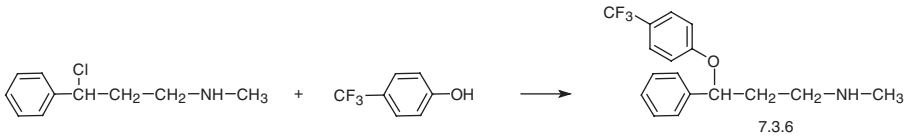
The antidepressant action of amoxapine is comparable to that of imipramine and amitriptyline. It exhibits antagonistic activity on dopamine (D_2) receptors. Amoxapine is intended more for relieving symptoms in patients with neurotic or situational depression. It has a number of serious side effects. Synonyms of this drug are asendin, amoxan, moxadil, and others.

Bupropion: The synthesis of bupropion, 1-3(-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone (7.3.5), begins with the reaction of 3-chlorobenzonitrile, with ethylmagnesium bromide to give 3-chloropropiophenone (7.3.3). Brominating this with bromine gives 3-chloro-α-bromopropiophenone (7.3.4), which on reaction with *tert*-butylamine gives bupropion (7.3.5) [54–58].



Bupropion is an α-aminoketone that is structurally related to amphetamines, and it exhibits unique activity comparable to that of other antidepressants. It is believed that bupropion restores the total amount of norepinephrine in the body. This compound is a poor reuptake inhibitor of dopamine, and does not exhibit anticholinergic activity or inhibit MAO. Its efficacy as an antidepressant is comparable to that of tricyclic antidepressants, and as a serotonin uptake inhibitor it is comparable to fluoxetine. It is preferable to use amoxapine. Synonyms of bupropion are amphebutamon and wellbutrin.

Fluoxetine: Fluoxetine, 3-[p-(trifluoromethyl)-phenoxy]-N-methyl-3-phenylpropylamine (7.3.6), is synthesized by reaction of p-trifluoromethylphenol with 3-(chloro)-N-methyl-3-phenylpropylamine in the presence of potassium carbonate [59,60].

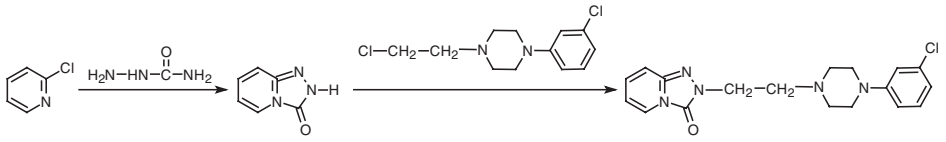


Fluoxetine is a phenylpropylamine that inhibits the neuronal reuptake of serotonin, which presumably has a direct relationship on antidepressant activity. This compound has either

no effect or a small effect on the neuronal reuptake of norepinephrine and dopamine. In addition, it does not bind to cholinergic, histaminergic, or α-adrenergic receptors, which is believed to be the cause of tricyclic antidepressant side effects.

The efficacy of fluoxetine in treating patients with moderate depression is comparable to the efficacy of tricyclic antidepressants. It is capable of elevating mood and removing feelings of fear and stress. It does not have a sedative effect. Fluoxetine is used in depression as well as in bulemic neuroses. Use of fluoxetine is preferred in cases when sedative, hypotensive, and anticholinergic side effects caused by other antidepressants are contraindicative to patients. Prozac is a synonym for fluoxetine.

Trazodone: Trazodone, 2-[3-[4-(*m*-chlorophenyl)-1-piperazineyl]propyl]-s-triazolo[4,3-a] piridine-3(2H)-one (7.3.8), is synthesized from 2-chloropiridine, the reaction of which with semicarbazide gives s-triazolo-3-one[4,3-a]pyridine (7.3.7). Alkylation of this product using 1-(3-chloropropyl)-4-(3-chlorophenyl)piperazine gives trazodone (7.3.8) [61,62].

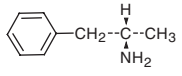


7.3.7 7.3.8

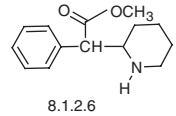
It is believed that trazodone, in therapeutic doses, inhibits the neuronal reuptake of serotonin. It is not a MAO inhibitor or a CNS stimulator. It has a minor influence on the reuptake of norepinephrine and dopamine. In addition, it does not bind with cholinergic or α-adrenergic receptors. Synonyms of this drug are thrombran, pragmarel, desyrel, and others.

7.4 AMPHETAMINES AND OTHER CNS STIMULATORS

Amphetamines are synthetic sympthetomimetic amines that are powerful CNS stimulators, of few of which, in particular dextroamphetamine (8.1.2.2) and methylphenidate (8.1.2.6), are sometimes used for treating depressive conditions. They elevate mood, stimulate motor activity, vigilance, and allow one to concentrate better. However, depending on the dosage and personality of the patient, it may cause various degrees of euphoria, which frequently leads to dependence and addiction.



8.1.2.2



8.1.2.6

The quantity of amphetamines competent for medicinal use is seriously limited, and their synthesis and properties will be examined in detail in Chapter 8, “Central Nervous System Stimulants.”

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– 8 –

Central Nervous System Stimulants

A huge number of physiologically active substances exhibit stimulatory action on the central nervous system (CNS); however, the number of drugs used for this purpose in medicine is extremely limited. Substances that increase vigilance and reduce the need for sleep are considered as CNS stimulants or psychostimulants. In other words, there are drugs capable of temporarily keeping one awake, elevating mood and maintaining adequate perception of reality, reducing outer irritability and the feeling of fatigue, and elevating the physical and mental capacity of work.

Some CNS stimulants such as amphetamines and methylphenidate are sometimes used for elevating mood in patients with depression. However, unlike the antidepressants examined in Chapter 7, these compounds only elevate the level of excitement of the CNS and cannot affect depression, and therefore the terms antidepressant and psychostimulant should be differentiated.

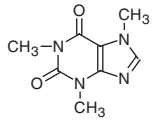
CNS stimulants can be classified as: *Psychomotor stimulants:* compounds that display a stimulatory effect primarily on brain functions and which activate mental and physical activity of the organism. They are made up of: methylxanthines (caffeine, theophylline, pentoxifyllin), amphetamines (dextroamphetamine, methamphetamine), and also methylphenidate and pemoline. *Respiratory stimulants or analeptics:* compounds, which cause certain activations of mental and physical activity of the organism, and primarily excite the vasomotor and respiratory centers of the medulla (doxapram, almitrine).*Drugs that suppress appetite or anorectics:* drugs that activate mental and physical activity of the organism, but primarily accentuate the excitatory center of satiation in the hypothalamus (phentermine, diethylpropion).In order to increase mental capability, *nootropics* — drugs that increase the functional state of the brain — are sometimes used, the effect of which is associated with blood flow and metabolism of the brain.

8.1 PSYCHOMOTOR STIMULANTS

8.1.1 Methylxanthines

Caffeine: Caffeine, 1,3,7-trimethylxanthine (23.3.6), is the most widely used CNS stimulant. It is an alkaloid in tea leaves (*Thea sinensis*), in coffee beans (*Coffea arabica*), in

cocoa beans (*Theobroma cocao*), in cola seeds (*Cola acuminata*), and in other plants whose synthesis will be described in Chapter 23, "Drugs for treating pulmonary diseases."



23.3.6

A cup of coffee can contain 50–150 mg of caffeine, and cola drinks can have 35–55 mg. Theophiline,1,3-dimethylxanthine, a principal, characteristic alkaloid of tea, and theobromine, 3,7-dimethylxanthine (23.3.19), a principal alkaloid of cocoa, are among a number of methylxanthines. In small doses, caffeine is a relatively weak psychostimulant and is used for increasing awareness as well as for relieving headaches associated with blood flow disorders of the brain. Caffeine has a stimulatory effect on the respiratory and vasomotor centers, and it stimulates centers of the vagus nerve. It has a direct stimulatory effect on the myocardium, and in large doses can cause tachycardia and arrhythmia.

Caffeine displays dual action on the level of blood pressure. It raises blood pressure by a central mechanism of stimulating the vasomotor center, but lowers it by facilitating the widening of blood vessels by directly affecting the smooth muscle of the vascular walls. In a person with regular blood pressure, caffeine causes practically no changes; however, introducing it into a patient with hypotension causes the blood pressure to rise (normalize). Secretion of stomachic glands increases under the influence of caffeine. It is believed that the stimulatory effect of caffeine is connected to its ability to competitively bind to adenosine receptors, a factor which lowers the excitatory processes in the brain. Replacing them with caffeine leads to a stimulatory effect, since methylxanthines and adenosine cause opposite effects. According to another point of view, by inhibiting phospodiesterase, caffeine increases the concentration of cyclic adenosinemonophosphate (cAMP), which serves as a second messenger by which physiological effects of several biologically active substances are carried out. In particular, glycogenolic processes are strengthened under the influence of cAMP, and metabolic processes are stimulated in various organs and tissues, the CNS included.

Caffeine is used for stimulating metal activity, for fatigue, migraines, and hypotension. Synonyms of caffeine are not popular. They are cafecon, coffan, and a few others.

8.1.2 Amphetamines, methylphenidate, and pemoline

Amphetamines are powerful synthetic psychostimulants with a high potential of addiction. They increase vigilance and the ability to concentrate, temporarily elevate mood, and stimulate motor activity. However, depending on the dosage and more importantly on the person's personality, they can cause various levels of euphoria, raise blood pressure, and facilitate contraction of the sphincter of the urinary bladder as well as facilitate the development of mydriasis.

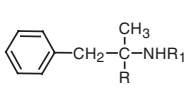
Prolonged amphetamine use often leads to irritability, insomnia, and hyperhidrosis. Changing drugs can result in depression. Attempting to overcome the depressive state by using higher doses of the same amphetamines leads to a vicious cycle of addiction and

dependence. Taking even higher doses of the drug causes euphoria, hallucinations, and other psychotic effects with symptoms very similar to the clinical symptoms of the paranoid form of schizophrenia.

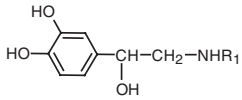
It is believed that the mechanism of action of amphetamines lies in their ability to release epinephrine (adrenaline) and dopamine from presynaptic nerve endings, which stimulate the corresponding receptors in the CNS. It is also possible that they reduce neuronal uptake of amines as well as inhibit their degradation by monoaminoxidase (MAO). Characteristic of this series of compounds is the effect on the respiratory center, on the satiation center located in the hypothalamus, which leads to suppression of feelings of hunger, thus allowing analog of the examined compounds to be used as anorectics.

Together with the CNS, compounds of this group affect the nervous system. They indirectly stimulate α- and β- adrenoreceptors. The adrenomimetic properties of these compounds are similar to the properties of norepinephrine (noradrenaline); however, they are quite inferior to them in terms of activity.

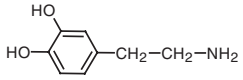
In terms of chemical structure, amphetamines are very close to epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine, differing in the absence of a hydroxyl group in the aromatic ring and in the aliphatic chain.



amphetamines



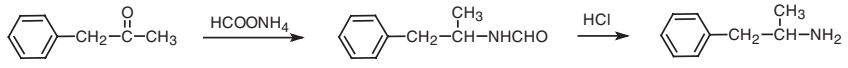
epinephrines



dopamine

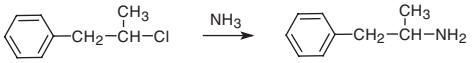
Amphetamines are used in treating narcolepsy, to increase the capacity to work, in treating attention-deficit disorder in children, and also in treating obesity. The effects of amphetamines can be potentiated by tricyclic antidepressants, MAO inhibitors, acetozolamide, cocaine, furazolidone, propoxyphene, sodium bicarbonate, and other drugs which alkylize urea. At the same time, antagonists of amphetamines are drugs which acidify urea: ascorbic and glutaminic acid, phenothiazines, haloperidol, methenamine, lithium drugs, and fruit juices.

Dextroamphetamine: Dextroamphetamine, D-2-amino-1-phenylpropane (8.1.2.2), is synthesized by various methods. One of them consists of uses of the Leucart reaction, in particular, the reaction between methylbenzylketone and ammonium formate, giving the formamide (8.1.2.1), which is hydrolyzed to 2-amino-1-phenylpropane (8.1.2.2) by hydrochloric acid [1]. An analogous method has been suggested using formamide instead of ammonium formate [2].



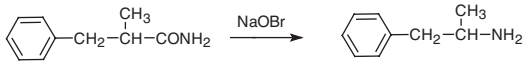
8.1.2.1 8.1.2.2

The other method consists of monoalkylation of ammonia using 2-chloro-1-phenylpropane [3].



8.1.2.2

2-Amino-1-phenylpropane (8.1.2.2) is also synthesized in a Hofmann reaction from α-benzylpropionic acid amide [4,5].



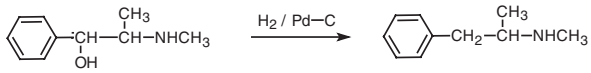
8.1.2.2

The product of either of the outlined methods, 2-amino-1-phenylpropane (amphetamine) is separated into isomers using D-tartaric acid, and separating the necessary dextroamphetamine, D-2-amino-1-phenylpropane (8.1.2.2) [6,7].

Dextroamphetamine is a powerful stimulant of the nervous system that manifests its effects by releasing dopamine and norepinephrine from presynaptic nerve endings, thus stimulating central dopaminergic and noradrenergic receptors. In certain doses it strengthens the excitatory process in the CNS, reduces fatigue, elevates mood and the capacity to work, reduces the need for sleep, and decreases appetite.

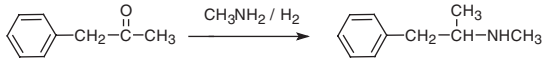
Dextroamphetamine should be used with caution and only upon medicinal indication in treating narcolepsy, consequences of encephalitis, and other illnesses accompanied by apathy, drowsiness, asthenia, for temporary increase of physical and mental capacity, in treating attention deficit disorder in children, and in treating obesity.Synonyms of this drug are D-amphetamine, dexamphetamine, dexalone, tempodex, zenidex, and many others.

Methamphetamine: Methamphetamine, (+)-N-α-dimethylphenylethylamine (8.1.2.3), can be synthesized by the reduction of (−)-ephedrine by hydrogen using a palladium on carbon catalyst [8].



8.1.2.3

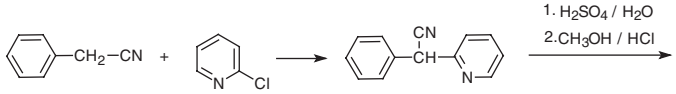
Another way of making methamphetamine is by the reduction of methylbenzylketone by hydrogen in the presence of methylamine [9].



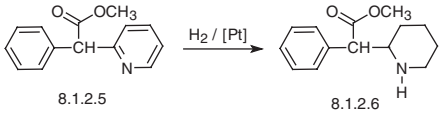
8.1.2.3

It possesses the same properties as dextroamphetamine and is used for the same indications.Synonyms of this drug are peritin, filopon, desoxyn, methampex, and others.

Methylphenidate: Methylphenidate, the methyl ester α-phenyl-2-piperidilacetic acid (8.1.2.6), is synthesized in the following manner. Arylation of benzylcyanide by 2-chloropyridine in the presence of a base gives α-phenyl-α-(2-pyridil) acetonitrile (8.1.2.4). Sulfuric acid hydrolysis of the nitrile group and subsequent esterification with methanol gives the methyl ester of α-phenyl-α-(2-pyridylacetic acid) (8.1.2.5). The pyridine moiety is reduced into a piperidine by hydrogen over platinum, giving methylphenidate (8.1.2.6) [10–12].



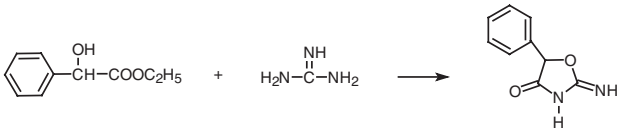
8.1.2.4



8.1.2.5 8.1.2.6

Methylphenidate is a CNS stimulant similar to amphetamine; however, in usual doses it has a more expressed action on mental activity rather than physical or motor activity. In therapeutic doses it does not raise blood pressure, respiratory rate, or increase heart rate. All of these effects as well as a number of others are associated with general excitement of the CNS. Tremor, tachycardia, hyperpyrexia, and a state of confusion can result from using large doses. It is used in treating moderate depression and apathetic conditions, and also as an adjuvant drug for treating attention deficit disorder in children.Synonyms of this drug are meridil, ritalin, and others.

Pemoline: Pemoline, 2-amino-5-phenyl-2-oxazolin-4-one (8.1.2.7), is synthesized by the condensation of the ethyl ester of mandelic acid with guanidine [13,14].



8.1.2.7

Pemoline is a structurally unique CNS stimulant that exhibits minimal sympatomimetic effects, and possesses the same pharmacological properties as amphetamines and methylphenidate, yet it has less potential to cause addiction than other CNS stimulators. It enhances vigilance and motor activity, and causes weak euphoria, which is possibly linked to an increase in dopaminergic transmissions in CNS structures.

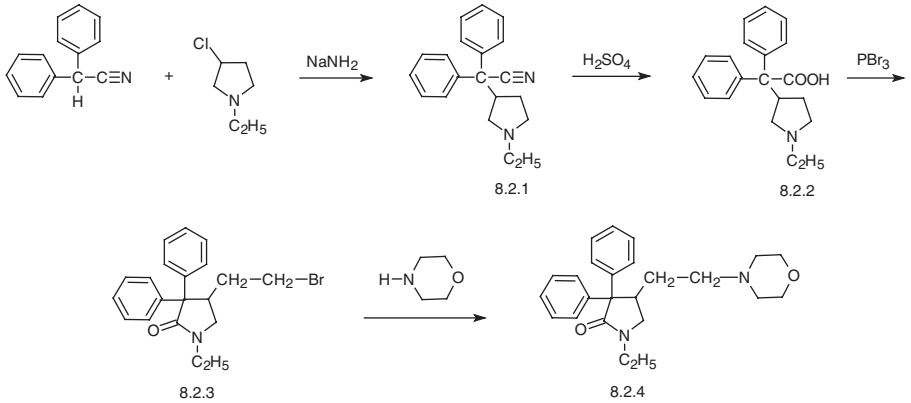
Pemoline is used for narcolepsy and for relieving drowsiness, as well as in treating attention-deficit disorder in children. Synonyms of this drug are tradon, deltamine, volital, phenoxazole, antimeran, cylert, and others.

8.2 RESPIRATORY STIMULANTS OR ANALEPTICS

Analeptics are drugs that have a stimulatory effect on the respiratory and vasomotor centers of the medulla. Analeptics are primarily used as antagonists in depressant drug overdose (hypnotics, narcotics). Having a relatively small range of therapeutic action, they can stimulate other parts of the CNS even in minor overdoses, causing a number of undesirable side effects such as stimulation of the cardiovascular system, hyperreflexia, vomiting, and seizures.

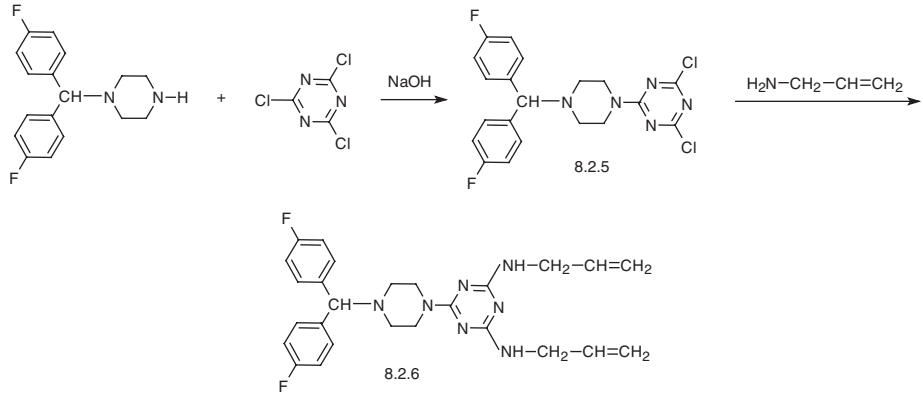
Doxapram: Doxapram, 1-ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone (8.2.4), is synthesized in the following manner. Diphenylacetonitrile in the presence of sodium amide is alkylated with 1-ethyl-3-chlorpyrrolidine, giving (1-ethyl-3-pyrrolidinyl) diphenylacetonitrile (8.2.1). Acidic hydrolysis of the nitrile group gives (1-ethyl-3 pyrrolidinyl)diphenylacetic acid (8.2.2). Reacting this with phosphorous tribromide

(thionyl chloride, thionyl bromide, acetic anhydride) leads to rearrangement with an opening of the pyrrolidine ring and the subsequent closing of the pyrrolidinone ring, forming 1-ethyl-4-(2-bromoethyl)-3,3-diphenyl-2-pyrrolidinone (8.2.3). Substitution of the bromine atom with a morpholine group gives doxapram (8.2.4) [15–18].



Doxapram increases the rate and depth of respiration. It is used for post-anesthetic respiratory depression, and for respiratory depression caused by drug use. Synonyms of this drug are doxapril, dopram, and others.

Almitrine: Almitrine, 2,4-*bis* (allylamino)-6-[4-[*bis*-(*p*-fluorophenyl)methyl]-1-piperazinyl]-*s*-triazine (8.2.6), is synthesized by reacting 1-[*bis*-(p-fluorophenyl)methyl]piperazine with cyanuric chloride, which gives 2,4-dichloro-6-[4-[*bis*-(*p*-fluorophenyl) methyl]-1-piperazinyl]-*s*-trazine (8.2.5). Reacting this with allylamine gives almitrine (8.2.6) [19–22].



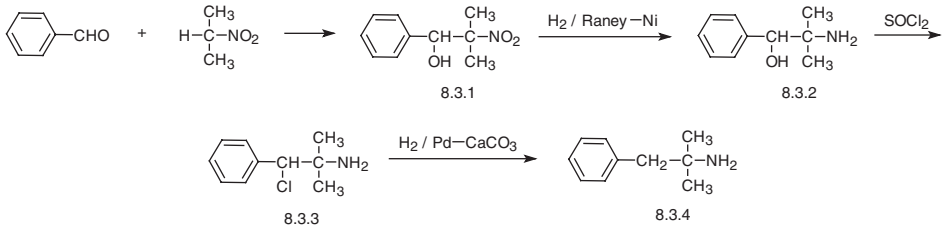
Almitrine, like doxapram, increases the rate and depth of respiration. In addition, it is believed that it redistributes pulmonary blood circulation, increasing it in alveoli, which leads to relatively better pulmonary ventilation. It has a more prolonged effect than doxapram.Synonyms are vectarion, duxil, and others.

8.3 APPETITE SUPPRESSANTS OR ANORECTICS

A group of drugs structurally related to amphetamines that suppress appetite and which are used in treatment of obesity are called analeptics.

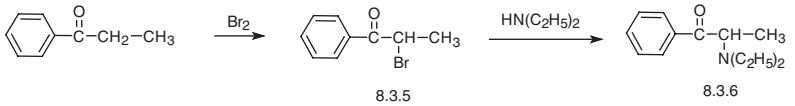
Compounds of this group exhibit a range of pharmacological and toxicological action analog to that of amphetamines, and are used as adjuvant drugs in the treatment of obesity,which is accomplished through an individually structured program of limiting caloric intake. Not one of the substances used exceeds amphetamines in terms of activity; however, the lesser likelihood of dependence makes its use preferable. The mechanism of action of these drugs is similar to that of amphetamines. They activate satiation centers of the hypothalamus, thus reducing appetite. Anorectics can enhance the effects of narcotics, barbiturates, alcohol, and other CNS depressants.

Phentermine: Phentermine, α,α-dimethylphenylethylamine (8.3.4), differs from amphetamine in the presence of an additional methyl group in the α-position of the amino group. It is synthesized from benzaldehyde, the condensation of which with 2-nitropropane gives carbinol (8.3.1). Reduction of the nitro group of this product gives 2-amino-2-methyl-1-phenylpropanol (8.3.2). The hydroxyl group is replaced with a chlorine atom upon reaction with thionyl chloride, giving 2-amino-2-methyl-1-phenylpropylchloride (8.3.3). Reducing this with hydrogen using a palladium on calcium carbonate catalyst gives phentermine (8.3.4) [23,24].



The action of this drug consists of the activation of the satiation center of the hypothalamus and the reduction of appetite, which by limiting caloric intake leads to weight loss.Synonyms of this drug are ionamin, linil, lipopill, teramine, and others.

Diethylpropion: Diethylpropion, 1-phenyl-2-diethylaminopropanon (8.3.6), is synthesized by the bromination of propiophenone into α-bromopropiophenone (8.3.5) and the subsequent substitution of the bromine atom with a diethylamino group [25,26].



Diethylpropion possess basically the same pharmacological properties as amphetamines and is used in treating obesity by limiting caloric intake.Synonyms of this drug are amphepramone, anorex, adiposon, regenon, tenuate, tepanil, and others.

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– 9 –

Antiepileptic Drugs

Epilepsy is a brain disorder in which clusters of nerve cells, or neurons, in the brain sometimes signal abnormally. In epilepsy, the normal pattern of neuronal activity becomes disturbed, causing strange sensations, emotions, and behavior or sometimes convulsions, muscle spasms, and loss of consciousness. Epilepsy is a chronic disease that is characterized by paroxysmal attacks caused by pathologic excitation of cerebral neurons. Epilepsy is accompanied by various degrees of disturbance of consciousness. There are both convulsive and non-convulsive forms of epileptic attacks, each of which is characterized by distinctive clinical features. Moreover, there are specific changes in the electro-encephalogram for practically all varieties of epilepsy. Seizures are generated in the epileptogenic center of the brain and can be nothing more than shaking of the extremities. If the convulsive discharge begins to spread and the excitation encompasses both hemispheres of the brain, seizures begin. Discharges induce major epileptic convulsive seizures (grand mal) and minor epileptic attacks (petit mal). Generally speaking, however, seizures are involuntary muscle contractions that can take place as a result of pathologic processes both inside and outside the brain. They can occur in response to toxins, trauma, hyperthermia, medicinal overdose, or upon discontinuation of medication.

Various drugs including barbiturates and benzodiazepines, which are used for relieving the severe, convulsive conditions that originate as a result of conditions other than epilepsy, are used in treating epilepsy. It is believed that various mechanisms may be operating within the genesis of epilepsy, and it is possible to influence these mechanisms medicinally.

From the clinical point of view, antiepileptic drugs are primarily divided into two categories; those effective in treating major attacks (phenytoin, carbamazepine, mephobarbital, and also primidone), and those effective in treating minor attacks (ethosuximide, acetazolamide, clonazepam, trimethadione, and valproic acid).

Treatment in each individual case of epilepsy is carried out by specific drugs, beginning with one type of drug. However, sometimes a second and often third drug is required for complete control of the illness. Frequent changes of dosage or drugs is not recommended.

From the chemical point of view, formally, antiepileptic drugs could be classified as derivatives of hydantoins (phenytoin, mephenytoin, ethotoin), barbiturates (phenobarbital, mephobarbital, and primidone), succinimides (ethosuximide, methosuximide, phensuximide), benzodiazepines (diazepam, chlorodiazepoxide, clonazepam, lorazepam), oxazolidines (trimethadione, paramethadione), and also valproic acid, carbamazepine, and acetazolamide.

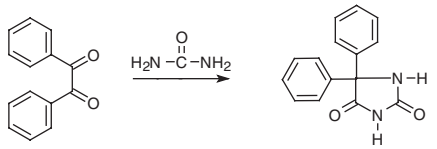
The mechanism of antiepileptic drugs is not sufficiently clear, as the etiology of epilepsy is not yet completely understood.

Some drugs block sodium channels, while others act on the GABA system. They enhance the GABA-dependent CNS inhibition. They also change the intracellular ratio of calcium and potassium ion concentrations, and block the *N*-methyl-D-aspartate (NMDA) receptor responsible for high-frequency discharges that appear during epilepsy.

9.1 HYDANTOIN DERIVATIVES

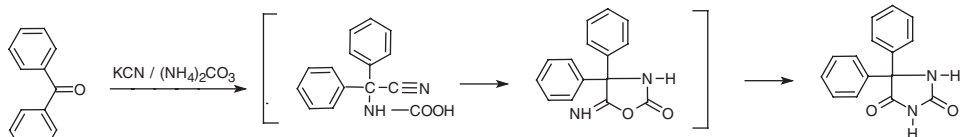
The mechanism of action of hydantoins is not yet conclusive. According to one hypothesis, hydantoins prevent high-frequency activation of the epileptogenic center and also facilitate secretion of sodium ions, which reduces excitation of neurons and prevents their activation upon contact with impulses from the epileptogenic center.

Phenytoin: Phenytoin, 5,5-diphenylimidazolidinedione (9.1.1) is synthesized in two different ways. The first involves a rearrangement on the reaction of benzil with urea to form the desired product (9.1.1) [1].



9.1.1

The second method involves the reaction of benzophenone with sodium cyanide in the presence of ammonium carbonate, followed by the simultaneous cyclization of the resulting product (carboxyaminonitrile) and its rearrangement under the reaction conditions to form phenytoin [2].

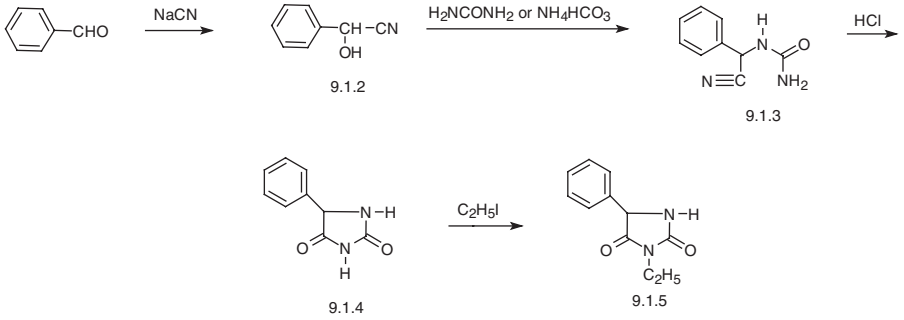


9.1.1

In terms of its effect on the CNS, phenytoin is considered an excellent antiepileptic drug with insignificant sedative effects. Even in large doses it does not cause hypnosis. It is presumed that phenytoin facilitates secretion of sodium ions from nerve cells, which reduces the stimulation of neurons. This in turn prevents the activation of neurons upon receiving impulses from the epileptogenic center. In addition, phenytoin reduces the incoming flow of potassium ions during repolarization. It is possible that phenytoin significantly slows the distribution of excitation in the brain as a direct result of the redistribution of the ion flow.

Phenytoin is used primarily in the treatment of major epileptic attacks. Difhydan, alepsin, dilantin, and solantin are the primary synonyms for phenytoin.

Ethotoin: Ethotoin, 3-ethyl-5-phenylimidazolidine-2,4-dione (9.1.5), is synthesized in basically the same manner as described above, which in this case involves the reaction of benzaldehyde oxynitrile (9.1.2), with urea or ammonium hydrocarbonate, which forms the intermediate urea derivative (9.1.3) which on acidic conditions (9.1.3) cyclizes to 5-phenylhydantoin (9.1.4). Alkylation of this product using ethyliodide leads to the formation of ethotoin (9.1.5) [3,4].



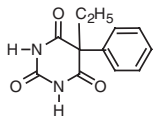
Ethotoin is less active and less toxic than phenytoin. It is used for the same indications as is phenytoin, i.e. for control of major and complex epileptic attacks.

Peganone is the primary synonym of this drug.

9.2 BARBITURATES

The efficacy of barbiturates as antiepileptic drugs can be attributed to their effect on the stimulation of epileptogenic neurons, and also on the GABA-ergic channel in the CNS by elevating of the inhibitory action of GABA. Furthermore, barbiturates can reduce the excitatory effects of glutamate at synapses. It is not presently known which of these proposed mechanisms is more important for the development of antiepileptic activity.

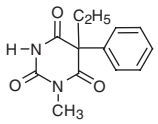
Phenobarbital: Phenobarbital is 5-ethyl-5-phenylbarbituric acid (4.1.4). The methods of synthesis have already been described in Chapter 4. This drug is widely used independently as well as an ingredient in various composite medicinal drugs.

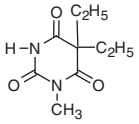


4.1.4

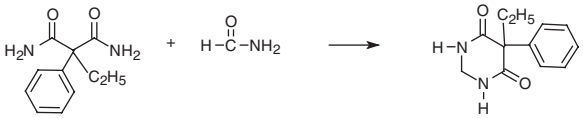
Phenobarbital noticeably reduces the excitation of motor centers of the brain, and therefore is used in treating both minor and major epileptic attacks, chorea, and spastic paralysis. Luminal, adonal, seconal, and many others are synonyms for this drug.

Other drugs described above, such as mephobarbital (4.1.8) and metharbital (4.1.9) are also used in treating epilepsy.


4.1.8


4.1.9

Primidone: Primidone, 5-ethyl-5-phenylhexahydropyrimidinedione-4,6 (9.2.1) is synthesized by reacting ethylphenylmalonic acid diamide with formamide [5,6]. An alternative method is the electrolytic reduction of phenobarbital or the catalytic reduction of the appropriate 2-thiobarbituric acid [7].


9.2.1

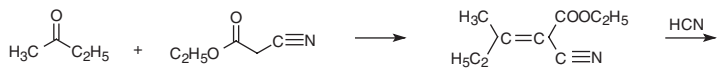
Primidone is chemically and structurally similar to phenobarbital with the exception that the carbonyl group on C_2 is replaced by a methylene group. This modification leads to the production of a drug with strong anticonvulsant properties without expressed soporific effects.

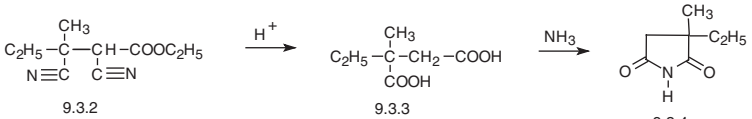
Primidone is mainly used for major attacks. Hexamidine and mylepsin are the primary synonyms.

9.3 SUCCINIMIDES

Succinimides are a group of drugs that are derived from the amide of succinic acid. They are used in minor forms of epilepsy in which attacks are not observed.

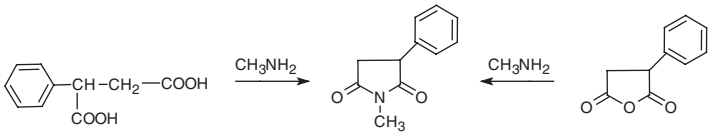
Ethosuximide: Ethosuximide, 3-ethyl-3-methypyrrolidine-2,5-dione (9.3.4) is synthesized from methylethylketone and cyanoacetic ester, which are condensed in Knoevanagel reaction conditions. Then hydrogen cyanide is added to the resulting product (9.3.1). After acidic hydrolysis and decarboxylation of synthesized dinitrile (9.3.2), 2-methyl-2-ethylsuccinic acid (9.3.3) is formed. Reacting this product with ammonia gives the diammonium salt, and heterocyclization into the ethosuximide (9.3.4) takes place during subsequent heating [8,9].


9.3.1


9.3.2 9.3.3 9.3.4

Ethosuximide is an anticonvulsant drug that is used in minor forms of epilepsy. It is also prescribed under the name aximide, suxilene, rontone, and pyknolepsinum.

Phensuximide: Phensuximide, 1-methyl-3-phenylpyrrolidine-2,5-dione (9.3.5) is synthesized by the reaction of phenylsuccinic acid or its anhydride with methylamine [10,11].

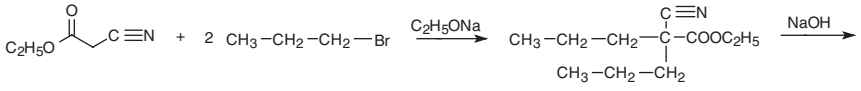


9.3.5

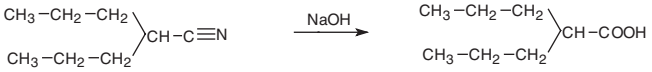
Phensuximide, like ethosuximide, is an anticonvulsant drug used in minor forms of epilepsy. It is also prescribed under the name milontin.

9.4 VALPROIC ACID

Valproic acid, 2-propylvaleric acid (9.4.3), is synthesized by the alkylation of cyanoacetic ester with two moles of propylbromide, to give dipropylcyanoacetic ester (9.4.1). Hydrolysis and decarboxylation of the carbethyoxy group gives dipropylacetonitrile (9.4.2), which is hydrolyzed into valproic acid (9.4.3) [12–15].



9.4.1



9.4.2 9.4.3

Valproic acid and its salts are a new group of antiepileptic drugs that differs from the known drugs both structurally and in terms of its mechanism of action. It is believed that it acts on the metabolism of the GABA system. Valproic acid has been shown to elevate the level of GABA in the brain by means of competitive inhibition of GABA transaminase and the dehydrogenase of succinic semialdehyde.

This drug not only exhibits anticonvulsant action, but also betters the mental condition of the patient.

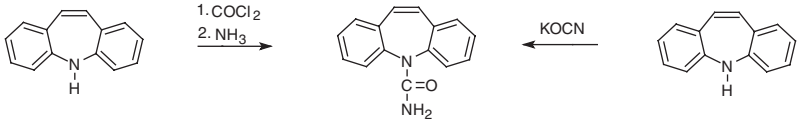
Valproic acid, like the succinimides, is used for epilepsy in the absence of attacks, but its clinical efficacy exceeds that of the succinimides.

Depakine and convulex are the most common synonyms of this drug.

9.5 CARBAMAZEPINE

Carbamazepine: Carbamazepine, 5*H*-dibenz[b,f]azepine-5-carboxamide (9.5.2), is synthesized by reacting 5*H*-dibenz[b,f]azepine and phosgene, which forms 5-chlorcarboxy-5*H*-dibenz-[b,f]azepine (9.5.1), and its subsequent reaction with ammonia to give the

desired carbamazepine (9.5.2) [16]. An alternative method of synthesis is the direct reaction of 5*H*-dibenz[b,f]azepine with potassium cyanate [17].

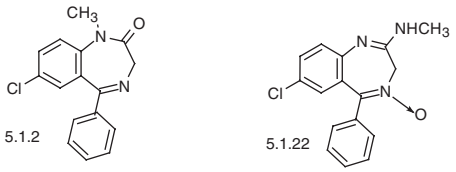


9.5.1

Carbamazepine is used principally for major epileptic attacks. It is not effective enough for minor attacks. There are data showing a number of side effects. A synonym of carbamazepine is tegretol.

9.6 BENZODIAZEPINES

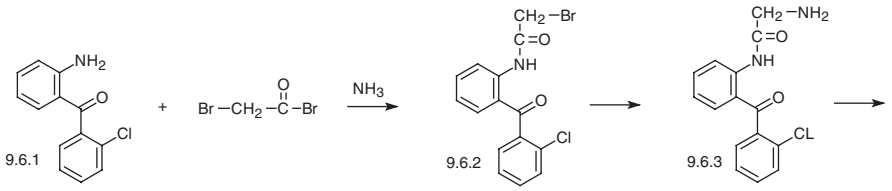
Benzodiazepines are primarily used in medicine as tranquilizers. However, they also have been successfully used for epilepsy in controlling long-lasting convulsions. The most widely used is diazepam (5.1.2) and chlordiazepoxide (5.1.22). The synthesis of these was described in Chapter 5.



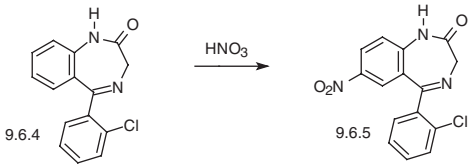
5.1.2 5.1.22

The third drug of the benzodiazepine family used for epilepsy is called clonazepam.

Clonazepam: Clonazepam, 5-(2-chlorphenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepine-2-one (9.6.5), is synthesized by following a standard scheme of making derivatives of 1,4-benzodiazepines, with the exception that the acceptor nitrile group (in this example) on C_7 of the benzodiazepine system is introduced at the last stage of synthesis. The synthesis of clonazepam begins with 2-chloro-2′nitrobenzophenon, which is reduced to 2-chloro-2′-aminobenzophenon (9.6.1) by hydrogen over Raney nickel. The amino derivative is amidated by 2-bromoacetyl bromide to give the bromacetamide (9.6.2) and is further converted into aminoacetamide (9.6.3) upon reaction with ammonia. Upon reaction this with pyridine, it is cycled into 5-(2-chlorophenyl)-2,3-dihydro-1*H*-1,4-benzodiazepine-2-one (9.6.4). The nitration of the resulting product in mild conditions (potassium nitrate in sulfuric acid) results in clonazepam (9.6.5) [18–23].



9.6.1 9.6.2 9.6.3

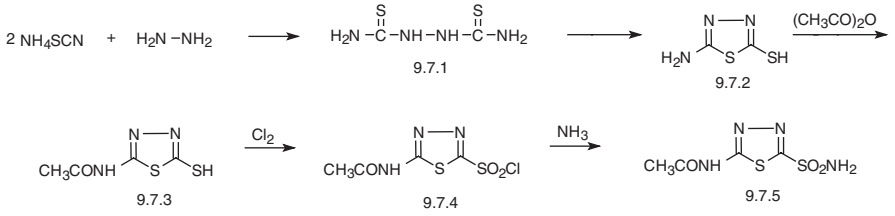


This drug exhibits expressed anticonvulsant as well as anxiolytic, sedative, and central muscle relaxant action.

Clonazepam is used in somnambulic epilepsy, various forms of muscular tonus, insomnia (especially in patients with structural brain lesions), and psychomotor agitation. Synonyms of this drug are clonopin and rivotril.

9.7 ACETAZOLAMIDE

Acetazolamide: Acetazolamide is 5-acetamido-1,3,4-thiadiazole-2-sulfonamide (9.7.5). The synthesis of acetazolamide is based on the production of 2-amino-5-mercapto-1,3,4-thiadiazole (9.7.2), which is synthesized by the reaction of ammonium thiocyanate and hydrazine, forming hydrazino-N,N′-*bis*-(thiourea) (9.7.1), which cycles into thiazole (9.7.2) upon reaction with phosgene. Acylation of (9.7.2) with acetic anhydride gives 2-acetylamino-5-mercapto-1,3,4-thiadiazol (9.7.3). The obtained product is chlorinated to give 2-acetylamino-5-mercapto-1,3,4-thiadiazol-5-sulfonylchloride (9.7.4), which is transformed into acetazolamide upon reaction with ammonia (9.7.5) [24,25].



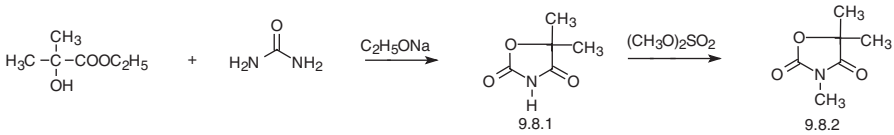
Acetazolamide is used for epilepsy in the absence of attacks and also in conjunction with other antiepileptic drugs. The most common synonym of this drug is diamox.

9.8 OXAZOLIDINES

This group of compounds is represented by two drugs that are used only in minor forms of epilepsy and in the absence of attacks.

Trimethadione: Trimethadione, 3,5,5-trimethyloxazolidine-2,4-dione (9.8.2), is synthesized by methylating 5,5-trimethyloxazolidine-2,4-dione (9.8.1) with dimethylsulfate.

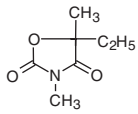
Starting 5,5-trimethyloxazolidine-2,4-dione (9.8.1) is in turn synthesized by the cyclocondensation of the ester of 2-hydroxyisobutyric acid with urea [26–28].



9.8.1 9.8.2

Trimethadione is used in minor forms of epilepsy that does not respond to treatment of other drugs.Synonyms of this drug are trimethinum and troxidone.

Paramethadione: Paramethadione, 5-ethyl-3,5-dimethyloxazolidine-2,4-dione (9.8.3), differs from trimethadione only in the substitution of one methyl group with an ethyl group. It is synthesized in a completely analogous manner, except that it comes from 2-hydroxy-2-methylbutyric acid instead of 2-hydroxyisobutyric acid [29].



9.8.3

Paramethadione is also used in minor forms of epilepsy. Paradione is a synonym of this drug.

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– 10 –

Antiparkinsonian Drugs

Parkinson's disease is a degenerative, slowly progressing illness of the CNS characterized by bradykinesia, shuffling gait, postural instability, tremor, and loss of automatic movement, which is associated with damaged basal ganglions. The etiology of this illness is not known. The most likely cause of the aforementioned motor problems could be a lack of dopamine, which has an inhibitory effect on the regulatory function of the spinal cord. On the other hand, cholinergic neurons act in regulating the extrapyramidal system. For more than a century, treatment of Parkinsonism was based on use of central anticholinergic substances. Up until recent times, various alkaloid drugs of belladonna, which have a characteristic cholinergic action (i.e. the ability to reduce sensitivity to acetylcholine, a neurotransmitter of cholinergic synapses) have been used for Parkinsonism. Currently, a sufficient quantity of facts have been established that support the idea that Parkinsonism is a consequence of an imbalance between dopaminergic and cholinergic systems, and that treatment of Parkinsonism should consist of either blocking excessive stimulation of the cholinergic system, or normalizing functional activity of the dopaminergic system. Consequently, one of the approaches of Parkinsonism pharmacotherapy may include eliminating the deficit of dopamine. Because dopamine itself does not penetrate through the blood–brain barrier, either a dopamine precursor (levodopa), drugs that release dopamine, dopamine receptor agonists, or inactivation inhibitors of dopamine are used. On the other hand, during treatment of Parkinsonism, anticholinergic drugs should be used. From the information cited above, treatment of Parkinsonism should be based on using two groups of substances: drugs which stimulate the dopaminergic system of the brain and substances which inhibit the cholinergic system of the brain.

10.1 DRUGS AFFECTING THE DOPAMINERGIC SYSTEMS OF THE BRAIN

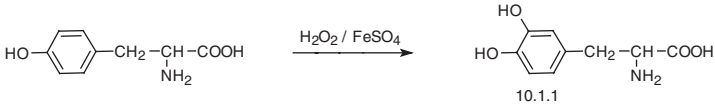
In medical practice, four types of dopaminergic drugs are used, and they can be characterized as dopamine precursors (levodopa), dopamine-releasing drugs (amantadine), dopamine receptor agonists (bromocriptine), and dopamine inactivation inhibitors (selegiline).

Dopamine precursors elevate the concentration of dopamine. Another group, dopamine-releasing drugs, was discovered accidentally while making the antiviral drug amantadine. It can be beneficial to patients who have a depot of dopamine. The third group, dopamine receptor agonists, is a group of adjunct drugs, which allows for treatment with smaller

doses than levodopa. Finally, the fourth group of drugs, which is represented by selegiline, are inhibitors of a variety of monoaminooxidases (MAO-B), enzymes that ensure the intercellular inactivation of dopamine in presynaptic nerve endings.

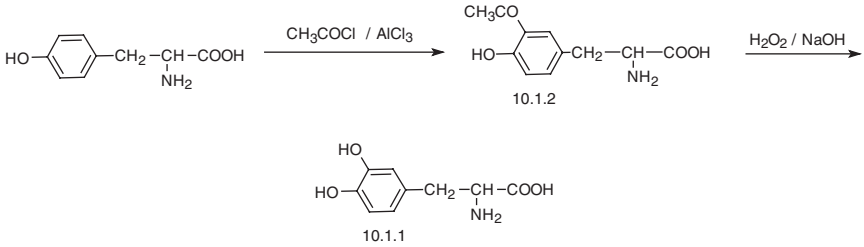
Levodopa: Levodopa, (−)-3-(3,4-dihydroxyphenyl)-L-alanine (10.1.1), is a levorotatory isomer of dioxyphenylalanine used as a precursor of dopamine. There are a few ways of obtaining levodopa using a semisynthetic approach, which consists of the microbiological hydroxylation of L-tyrosine (10.1.1) [1,2], as well as implementing a purely synthetic approach.

Oxidation of L-tyrosine, for selective introduction of a hydroxyl group at C_3 of the tyrosine ring, can be accomplished in a purely synthetic manner by using a mixture of hydrogen peroxide and iron(II) sulfate mixture in water as an oxidant with permanent presence of oxygen [3].



10.1.1

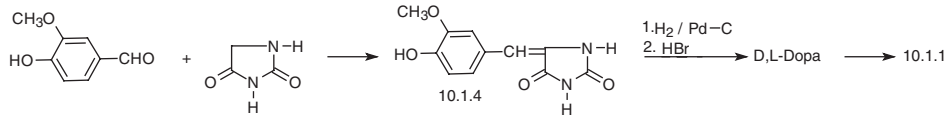
The third method of levodopa synthesis consists of the acetylation of tyrosine using acetylchloride in the presence of aluminum chloride and the subsequent oxidative deacylation of the formed 3-acetyltyrosine (10.1.2) using hydrogen peroxide in sodium hydroxide solution [4–7].



10.1.2

10.1.1

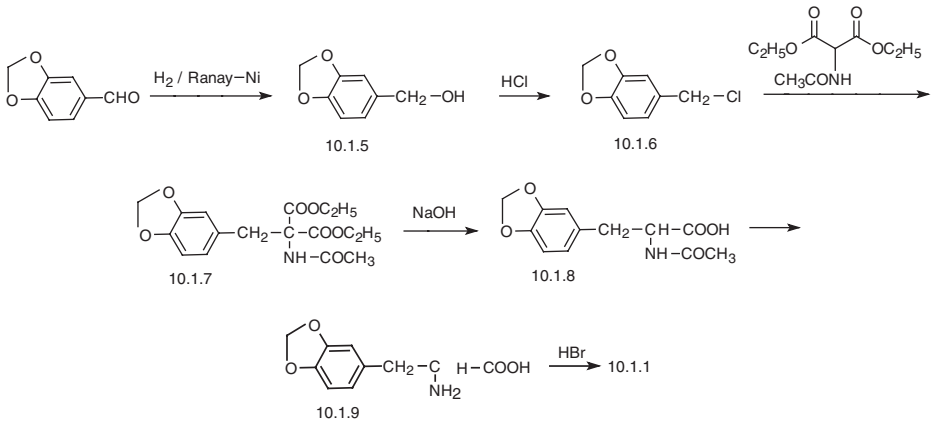
Methods of synthesis of levodopa from vanillin [8–14] have been suggested. According to one of them, condensation of vanillin with hydantoin and the subsequent reduction of the double bond in the formed product (10.1.4), after hydrolysis, gives racemic DOPA from which levodopa is isolated [8].



10.1.4

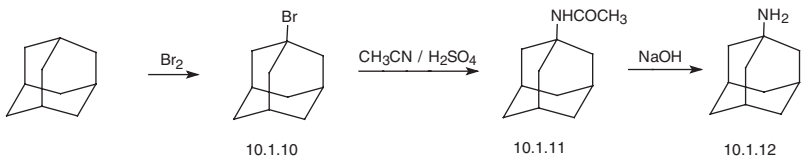
Levodopa also is synthesized from piperonal, the aldehyde group of which is reduced by hydrogen over Raney nickel, forming a piperonyl alcohol, 3,4-methylendioxyphenylmethanol (10.1.5). Upon reaction with hydrochloric acid, the product is transformed into 3,4-methylendioxyphenylmethylchoride (10.1.6). Reacting this compound with acetamidomalonic ester gives (3,4-methylendioxyphenylmethyl)-acetamidomalonic ester (10.1.7). Alkaline hydrolysis and partial decarboxylation of this product leads to the formation of the product (10.1.8) in which two hydroxyl groups and the amino group still

are protected. The hydrolysis of the amide-protecting group using the enzyme takadiastase allows one to isolate directly only the L-3-(3,4-methylendioxyphenyl)alanine (10.1.9). Removing the methylendioxy-protecting group of the last using hydrogen bromide gives levodopa (10.1.1) [15].



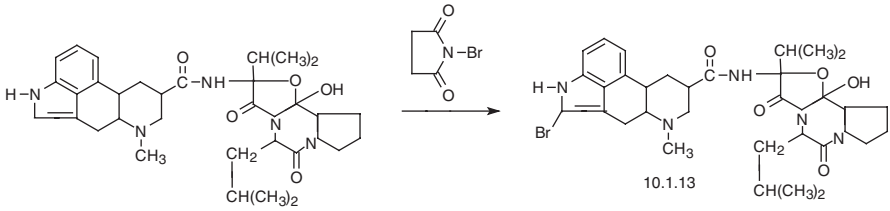
In a number of attempts to fix the deficit of dopamine in Parkinsonism, the introduction of a direct precursor of dopamine—levodopa—into the patient is considered a very logical therapy since levodopa diffuses across the blood–brain barrier, where it turns into dopamine and normalizes the level of dopamine. In this manner, levodopa stops or slows the development of Parkinsonism. Levodopa belongs to a group of the most effective drugs for treating the type of Parkinsonism not caused by medicinal agents. Unfortunately, it posesses a number of undesirable side effects. The most common synonyms are 1-dopa, madopar, dopar, sinemet, larodopa, and others.

Amantadine: Amantadine, 1-adamantanamine (10.1.12), is synthesized from adamantane. It is directly brominated to 1-bromadamantane (10.1.10), which in Ritter reaction conditions when heated with a mixture of acetonitrile and concentrated sulfuric acid transforms into 1-acetylaminoadamantane (10.1.11). Hydrolysis of this product using alkali leads to the formation of amantadine (10.1.12) [16,17].



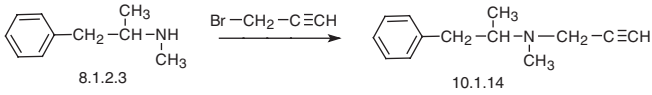
Amantadine is an agent that raises the concentration of dopamine in the synaptic cleft by releasing it from neurons and suppressing the process of reuptake. Amantadine is an antiviral drug. The properties in amantadine, which relieve symptoms of Parkinsonism were discovered by accident. Treatment of Parkinsonism with a combination of levodopa, anticholinergic drugs, and amantadine gives better results than using any of these drugs individually. Synonyms are midantan and simmetrel.

Bromocriptine: Bromocriptine, 2-bromoergocriptine (10.1.13), is a semisynthetic derivative of a natural ergot alkaloid, ergocriptin (a derivative of lysergic acid), which is synthesized by bromination of ergocriptin using *N*-bromosuccinimide [18,19].



Bromocriptine, a dopaminomimetic that is a dopamine D_2 receptor agonist, possesses expressed antiparkinsonian activity. It is used for treating all phases of idiopathic and postencephalic Parkinsonism. However, it has a number of undesirable side effects, even causing mental disturbances in long-term use. The most common synonyms are parlodel, bromergon, and others.

Selegiline: Selegiline, *N*-methyl-*N*-(2-propinyl)-2-methyl-1-phenylethylamine (10.1.14), is synthesized by the alkylation of (−)methyamphetamine (8.1.2.3) using propargylbromide [20–23].



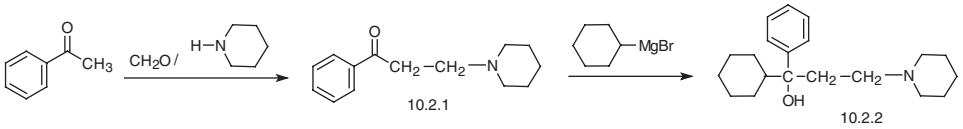
8.1.2.3 10.1.14

This drug is a selective inhibitor of monoaminooxidase B, which suppresses dopamine-inactivation processes and facilitates an increase of its level in the brain. In treating Parkinsonism, selegiline is usually used in combination with levodopa. The most common synonyms of selegiline are deprenyl, eldepryl, eldopal, and others.

10.2 ANTICHOLINERGIC DRUGS (CENTRAL CHOLINOBLOCKERS)

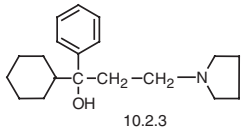
The first drugs used in treating parkinsonism were the alkaloids, atropine and scopolamine, and over the course of many years they were the only drugs used for this purpose. However, in treating Parkinsonism today, these alkaloids are used extremely rarely and have been practically replaced by synthetic drugs that exhibit central anticholinergic properties (central cholinoblockers). They suppress stimulatory cholinergic effects by suppressing cholinoreceptors. It is believed that they do not affect the synthesis, release, or hydrolysis of acetylcholine. Their action facilitates the reduction or alleviation of motor disturbances associated with damage to the extrapyramidal system. They reduce rigidity and to a lesser extent akinesia, and have a minimal effect on tremors. The therapeutic value of such drugs is relatively small and they are used either in combination with levodopa, or in cases of minor Parkinsonism, primarily for alleviating rigidity. In addition, they cause a number of side effects, including general weakness, headaches, and so on.

Trihexyphenidyl: Trihexyphenidyl, 1-cyclohexyl-1-phenyl-3-piperidineopropan-1-ol (10.2.2), is synthesized by the reaction of 2-(1-piperidino)propiophenone (10.2.1) with cyclohexylmagnesiumbromide. The initial 2-(1-piperidino)propiophenone is synthesized in turn by the aminomethylation of benzophenone using paraformaldehyde and piperidine [24–27].



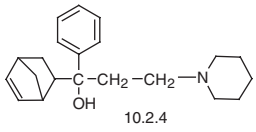
Trihexyphenidyl, an antiparkinsonian drug, possesses central and peripheral anticholinergic actions, as well as a direct relaxant effect on smooth muscle. It reduces muscle rigidity and general stiffness, and has a relatively minor effect on tremors. It is used in Parkinsonism in the form of monotherapy as well as in combination with levodopa. The most common synonyms are parkopan, parkinsan, and cyclodol.

Procyclidine: Procyclidine, 1-cyclohexyl-1-phenyl-3-pirrolidinopropan-1-ol (10.2.3), is synthesized in the exact same manner, except beginning with 2-(1-pyrrolidino) propiophenone [28–32].



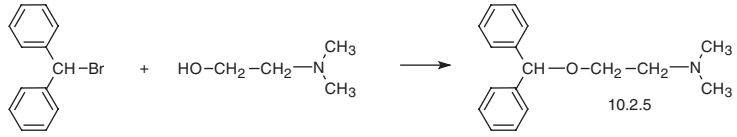
In terms of pharmacological properties, it basically does not differ from trihexyphenidyl. The most common synonym of procyclidine is cemadrin.

Biperiden: Biperiden, 1-(5-norbornen-2-yl)-1-phenyl-3-piperidinopropan-1-ol (10.2.4), is also synthesized according to the method of making trihexyphenidyl, except by reacting 2-(1-piperidino)propiophenone (10.2.1) with 5-norbornen-2-ylmagnesiumbromide [33,34].



Biperiden has the same properties as the aforementioned drugs. A synonym of this drug is akineton.

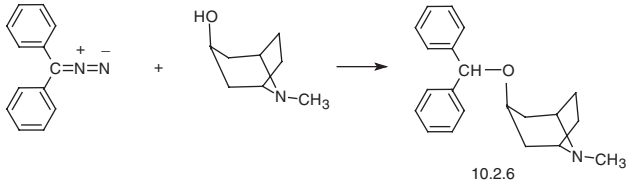
Diphenhydramine: Diphenhydramine, 2-diphenylmethoxy-*N*,*N*-dimethylamine (10.2.5), is synthesized by the esterification of 2-dimethylaminoethanol with benzhydrylbromide [35–37].



Diphenhydramine also reduces muscle rigidity and general stiffness, and has a relatively minor effect on tremors.

Synonyms of this drug are benadryl and benylin.

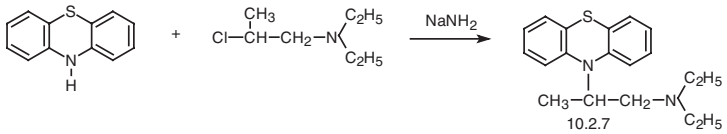
Benztropine: Benztropine, 3-(diphenylmethoxy)tropane (10.2.6), is synthesized by the reaction of tropin and diphenyldiazomethane [38].



10.2.6

This drug is used for quick relief of severe distonic reactions in Parkinsonism. It does not relieve tremors. A synonym is congentin.

Ethopropazine: Ethopropazine, 10-(2-diethylaminopropyl) phenothiazine (10.2.7), is synthesized by alkylation of phenothiazine using 1-diethylamino-2-propylchloride in the presence of sodium amide [39,40].



10.2.7

Ethopropazine is a derivative of phenothiazine with expressed anticholinergic activity. It effectively reduces muscle rigidity and general stiffness, including tremors. It is used in Parkinsonism as well as in other situations of extrapyramidal disorders, including situations caused by phenothiazine drugs. Synonyms of this drug are parsidol, lizivan, parcin, and others.

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– 11 –

Adrenergic (Sympathomimetic) Drugs

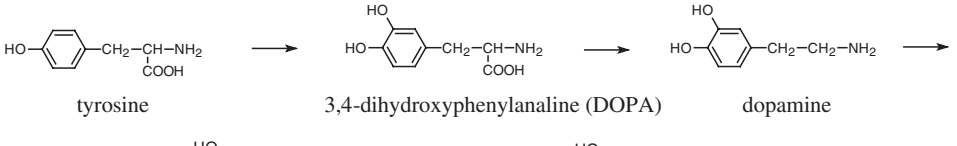
Adrenergic drugs are natural or synthetic compounds that either partially or completely replicate the effects of norepinephrine (noradrenaline), epinephrine (adrenaline), and dopamine, and which cause a biological response similar to the activation of the sympathetic nervous system. They are also referred to as sympathomimetics because they mimic the stimulation of the sympathetic nervous system.

As such they increase cardiac output, dilate bronchioles, and usually produce constriction of blood vessels. In medicine, they are commonly prescribed in cardiac emergencies including shock and anaphylaxis, in some cases for weight loss, and in cold remedies, where they shrink swollen membranes in the upper respiratory tract.

The sympathetic nervous system plays an important role in the involuntary regulation of cardiac activity, vascular tonicity, functional activity of smooth muscle, and glands by releasing endogenic adrenergic substances, catecholines, from peripheral nerve endings into the synapses of the central nervous system (CNS).

These compounds are dispersed in the body in large quantities during physical or emotional stress, and they play a huge role in the adaptation of the body to stressful situations.

Within the body itself, catecholines (β-arylethylamines containing hydroxyl groups at C_3 and C_4 of the aromatic ring) such as dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline) are primarily produced by the adrenal glands from a general precursor, tyrosine, which is initially hydroxylated into the *meta*-position of the aromatic ring by the enzyme tyrosine hydroxylase. The resulting 3,4-dihydroxyphenylanaline (DOPA) is further decarboxylated by the enzyme L-decarboxylase of aromatic acids, forming dopamine. Dopamine is further hydroxylated by the enzyme dopamine-β-hydroxylase, which forms norepinephrine (noradrenaline). Finally, the terminal primary amine group is methylated by the enzyme phenylethanolamine-*N*-methyltransferase, forming epinephrine (adrenaline).



tyrosine — 3,4-dihydroxyphenylanaline (DOPA) — dopamine

norepinephrine (noradrenaline) — epinephrine (adrenaline)

Adrenergic drugs are used because of their ability to act on the cardiovascular system, causing a broncholytic effect, stimulating the CNS, and displaying mydriatic and anorectic action. On the other hand, the wide range of activity is due to an evidently high affinity to the various receptors other than adrenergic receptors, limits their use because of a number of undesirable side effects.

Adrenergic or sympathomimetic drugs comprise a large group of substances that can be subdivided into drugs with direct action, which directly react with adrenergic receptors. Epinephrine, phenylephrine, isoproterenol, dobutamine, terbutaline, albuterol, metaproterenol, isoetharine, clonidine, naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline belong to this group.

Nondirect-acting drugs exhibit sympathomimetic effects by causing the release of endogenic catecholamines. Sympathomimetic activity of these drugs depends on the presence of catecholines in the organism. Tyramine, a compound used primarily as an analyzer in experimental research, belongs to this group.

Finally, a few drugs have dual action—both direct and indirect. Dopamine, ephedrine, phenylpropanolamine, metaraminol, and amphetamines all belong to this group.

The initial reaction between adrenomimetics and effector cells occurs through adrenergic receptors, which are exceptionally numerous in the brain, various organs, and tissue. The structure of adrenoreceptors is not known.

The concept of receptors, as is well known, is based on the presence of certain structures that are responsible for binding biologically active compounds. The molecular structure of a ligand-binding region of the receptor determines the specific physiological response of the organism. The binding of an adrenergic agonist, as with any other drug using substrate–receptor interaction, with the appropriate receptor on the surface of the membrane causes a cascade of biochemical reactions in the cell, which ultimately lead to a change in its functional-metabolic condition. Accordingly, drugs contain an informational message that is transmitted into the cell and when appropriately diffused, causes measurable effects at the tissue or organ level. Specific binding of the drug activates certain biological processes, which can culminate in gland secretion, regulation of ion channels, changes in enzyme activity, and so on.

Each adrenergic drug independently exhibits significant qualitative and quantitative differences of both a pharmacodynamic and pharmacokinetic character, which permits their sensible therapeutic use.

Two main classes of receptor proteins that bind adrenergic drugs have been postulated, and they have historically been defined as α- and β-receptors, which have even been broken down into four subtypes: α_1, α_2, β_1, and β_2.

Despite a few differences, activation of α_1-receptors generally leads to excitement, while β_2-receptors generally are responsible for relaxation of tissue. Activation of β_1-receptors results in a stimulatory effect on the heart and kidneys, while activation of presynaptic α_2 adrenergic receptors possibly suggests a feedback mechanism, which is the inhibition of neuronal norepinephrine release. At the same time, stimulation of postsynaptic α_2-receptors, as with α_1-receptors, causes tissue excitement.

On the basis of anatomical, pharmacological, biological, and other criteria, it has been shown that: α_1-receptors are located primarily in effector organs; α_2-receptors in adrenergic neurons and presynaptic regions; β_1-receptors are located predominantly in cardiac and

renal tissue; β_2-receptors are found in many other organs (bronchi, vessels, uterus, among others).

A variety of responses in the body to different adrenergic drugs are based on their relative selectivity when binding with various receptors, which are exclusively found in and unevenly distributed in effector structures (heart, cardiovascular system, lungs, brain, peripheral nervous system, etc.).

In general, the response of effector organs to epinephrine (adrenaline) and/or norepinephrine (noradrenaline) is directly determined by the type of adrenoreceptor, as well as by the ratio of α- and β-adrenoreceptors.

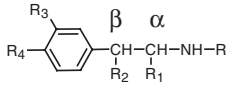
Typical pharmacological action of adrenergic drugs consists of the following: stimulation of cardiac action—an elevation of frequency and strength of cardiac contractions; vasomotor effects—vasodilation, vasoconstriction; regulation of endocrine conditions—modulation of insulin, renin, and a number of hormones; regulation of metabolic conditions—increased glycogenolysis in the liver and muscles, release of fatty acids from tissues; and from the CNS—psychomotor excitement.

A myriad of cardiovascular, respiratory, hormonal, metabolic, and neuropsychic responses, which can be caused by adrenergic drugs, are generally very similar to many of the adaptive reactions of the organism such as increased physical activity and physical stress.

From the clinical point of view, adrenergic drugs are formally classified in the following manner, although some of them can appear in various groups at the same time.

Endogenic (epinephrine, norepinephrine, and dopamine) and synthetic catecholamines (isoproterenol, dobutamine).
Vasopressor amines (metaraminol, methoxamine, and methentermine).
Antiedematic (tetrahydrozoline, phenylephrine, naphazoline, and ephedrine).
Bronchiolytics (ephedrine, metaproterenol, isoetharine, and terbutaline).
Smooth muscle relaxants (ritodrine, arlidin, and isoxyprine).
CNS stimulants (amphetamines).

From the chemical point of view, adrenergic drugs have a lot in common, and are examined as substituted phenylethylamines.



Some correlations have been made between the structure of sympathomimetics and the biological activity exhibited by them.

1. Sympathomimetic activity is maximal when there are two carbon atoms between the aromatic ring and the amino group.
2. The lesser the degree of substitution at the amino group, the greater selectivity of the compound in activating α-adrenoreceptors, and vice versa, an increase in volume of substituents at the primary amino group adds to the selectivity in relation to β-receptors.
3. Substitution at the α-carbon atom prevents oxidative deactivation of the drug molecules by monoaminooxidase, thus considerably increasing the duration of action. At

the same time, substitution at the α-carbon atom facilitates indirect action of the drug—the ability to release endogenous catecholamines from neuronal reserves.

4. Activity of the drug depends considerably on the presence of hydroxyl groups at C_3 and C_4 of the aromatic ring. These conditions are necessary for activation of both α- and β-adrenoreceptors. Compounds with hydroxyl groups at C_3 of the aromatic ring display a high ratio of direct/indirect agonistic activity. Compounds with hydroxyl groups on C_4 of the aromatic ring display a high ratio of direct/indirect activity. Phenylethylamines that do not contain hydroxyl groups in the aromatic ring (noncatecholamines) exhibit more of a stimulatory effect on the CNS than catecholamines.

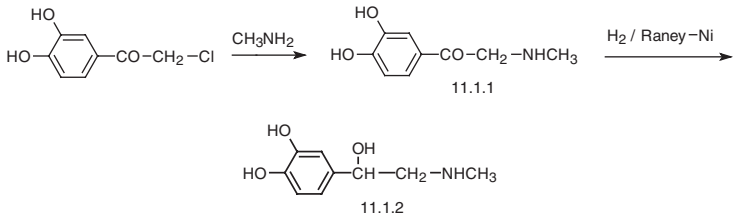
11.1 DIRECT-ACTING AGONISTS

11.1.1 Drugs stimulating α- and β-adrenoreceptors

Endogenic and synthetic catecholamines

The three main endogenic catecholamines, epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine are responsible for the function of the sympathetic nervous system, and they are found in every part of the body. In addition, a large number of other drugs display activity by modifying action of one or more of these endogenous substances, and thereby catecholamines turn out to be able to exhibit results of a relatively wide range of drugs. In medicine, synthetic direct-acting sympathomimetic drugs are widely used in treating many pathologies. Therapeutic indications of catecholamine use are based on their vasoconstrictor, broncholytic, and cardiac-stimulating action.

Epinephrine: Epinephrine, L-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol (11.1.2), is obtained from the adrenal glands tissue of livestock [1,2] as well as in a synthetic manner. Epinephrine is synthesized from ω-chloro-3,4-dihydroxyacetophenone—chloroacetylpyrocatechine—the reaction of which with excess of methylamine gives ω-methylamino-3,4-dihydroxyacetophenone (11.1.1). Reduction of this using hydrogen over Raney nickel, or action of aluminum amalgam, or electrolytic reduction gives D,L-epinephrine (11.1.2) [3–9], which is separated into isomers using (+) tartaric acid [10].



Epinephrine, and endogenic catecholamine, is better known by its official English name adrenaline. Epinephrine is a powerful agonist of both α- and β-adrenergic receptors. Its action is very complex and depends not only on the relative distribution of adrenergic receptors in

regions of various tissues and organs, but also on the dosage and method of introduction. The natural isomer of epinephrine (−) is 50 times more active than the (+) isomer. It directly and nonspecifically activates both α- and β-adrenergic receptors. Activation of α-adrenoreceptors leads to constriction of most blood vessels. Activation of β_1-adrenoreceptors increases the heart rate and strength of contractions of cardiac muscle. Activation of β_2-adrenoreceptors leads to a dilation of bronchi and skeletal muscle blood vessels. The level of blood glucose increases, and intraocular pressure also increases. Despite the fact that the primary pharmacological action is reflected on the cardiovascular and respiratory systems, the complete spectrum of its effects shows its physiological significance as a systemic neurohormone involved in the activation of a large number of protective functions.

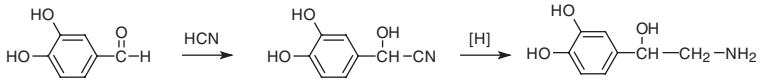
As a matter of fact, it is a prototype of many adrenergic drugs, and therefore its action on individual organ systems should be examined more carefully. A typical reaction upon intravenous introduction of epinephrine is the dramatic increase mainly in systolic blood pressure. A similar effect of epinephrine results from a combined action: first, contraction of the majority of blood vessels, and second, stimulation of the myocardium, which is expressed by the elevation of the strength of contractions and frequency of heartbeats. Epinephrine and other sympathomimetic drugs with β_2-adreno-agonist properties are responsible for relaxation of bronchial muscles and an increase in bronchodilatation. Moreover, the α-adrenergic agonist activity of epinephrine is exhibited through the contraction of pulmonary vessels and the development of antiedema effects.

It is used in anaphylactic, allergic, and other hypersensitive reactions, as an agent to increase blood pressure in hypotension, as a broncholytic in pulmonary edema, as an antiedema agent in othorinolaringology (LOR) and in ophthalmological practice, and also to prolong the action of local anesthetics.

Epinephrine is used for relieving bronchial asthma, revival from anaphylactic shock, in hyperglycemic coma, and allergic reactions. It is used as a local vasoconstrictor, in particular, in ophthalmology for reducing intraocular pressure.

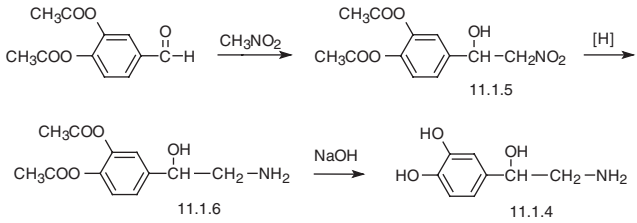
There is a large number of synonyms for epinephrine: adnephrine, adrenat, biorenin, epinal, hemostatin, nieralin, syndernin, and others. However, the main synonym of epinephrine is adrenaline.

Norepinephrine: Norepinephrine, L-1-(3,4-dihydroxyphenyl)-2-aminoethanol (11.1.4), is synthesized by two methods starting from 3,4-dihydroxybenzaldehyde. According to the first method, the indicated aldehyde is transformed into the cyanohydrin (11.1.3) by reaction with hydrogen cyanide, which is then reduced into norepinephrine (11.1.5) [11,12].



11.1.3 11.1.4

The second method consists of the condensation of diacetate of the same aldehyde with nitromethane, which forms (3,4-diacetoxyphenyl)-2-nitroethanol (11.1.5). Then the nitro group is reduced and the product (11.1.6) is hydrolyzed into the desired norepinephrine (11.1.4) [4,9,13,14].

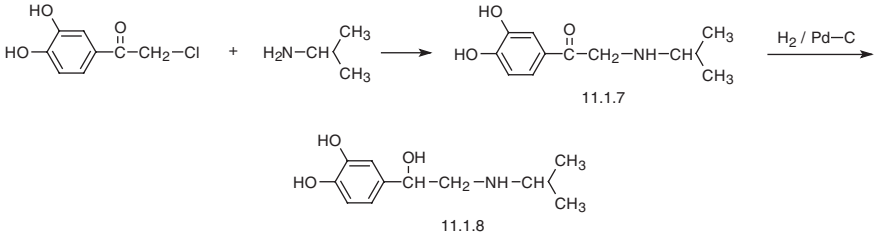


Norepinephrine is the primary neurotransmitter produced and released by adrenergic neurons, and in literature it is also described as and called (−) noradrenaline or levarterenol. This vasopressor catecholamine reduces both the resistance and capacity of blood vessels by stimulating α-adrenoreceptors and having a direct cardiostimulatory effect, which is accomplished by activation of β_1-adrenoreceptors. Norepinephrine exhibits significantly less activity than epinephrine as a drug for widening blood vessels through the activation of β_2-adrenoreceptors. Elevation of both stylistic and diastolic blood pressure is a typical reaction to intravenous introduction of norepinephrine.

Norepinephrine is used for increasing cardiac constriction and for the necessary elevation of blood pressure after sharp decline, which can result from surgical intervention or trauma. Synonyms of noradrenaline are arterenol, levarterenol, levophed, and others.

11.1.2 Drugs stimulating predominantly β-adrenoreceptors

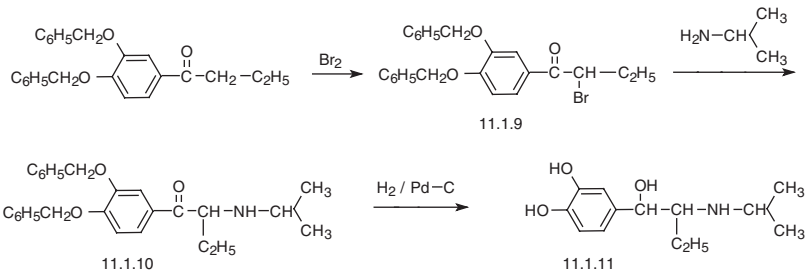
Isoproterenol: Isoproterenol, 1-(3,4-dihydroxyphenyl)-2-iso-propylaminoethanol (11.1.8), is synthesized by an analogous scheme of making epinephrine. Interaction of ω-chloro-3,4-dihydroxyacetophenone (chloroacetylpyrocatechol) with isopropylamine gives ω-isopropylamino-3,4-dihydroxyacetophenone (11.1.7), reduction of the carbonyl group of which by hydrogen using a palladium on carbon catalyst gives isoproterenol (11.1.8) [11,12].



Isoproterenol is a representative of the sympathomimetic drugs with high selectivity to β-adrenoreceptors. As was already noted, the addition to compounds of a bulky *iso*-propyl or *tert*-butyl group at the nitrogen atom of the β-phenylethylamino skeleton is associated with higher affinity to β-adrenergic receptive regions than to α-adrenergic. Isoproterenol is devoid of significant α-adrenergic agonistic action. Activation of β_1-adrenergic receptors in the heart increases positive chronotropic and ionotropic action. Peripheral vascular resistance is increased by the widening of blood vessels, primarily in skeletal muscle, but also in renal and mesenteric blood circulation, which is caused by the β_2-adrenergic system.

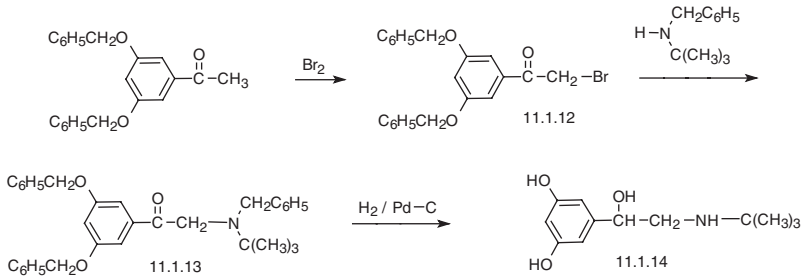
This complex, cardiostimulatory and vasodilating action is expressed by a significant increase of cardiac output and stroke volume. In response to activation of β_2-adrenoreceptors, bronchodilation also increases. Isoproterenol is used in bronchospasms, asthma, cardiac block, and shock. Synonyms of isoproterenol are proternol, isoprenaline, isadrine, norisodrine, novodrin, and others.

Isoetharine: Isoetharine, 3,4-dihydroxy-α-[1-(*iso*-propylamino)propyl]benzylic alcohol (11.1.11), differs from isoproterenol in the presence of an additional ethyl group in the ethylamino side chain—and is synthesized by bromination of 3,4-dibenzyloxybutyrophenone and the subsequent reaction of the resulting bromo derivative (11.1.9) with isopropylamine. The product (11.1.10) undergoes reduction by hydrogen using a palladium catalyst, during which the carbonyl group is simultaneously reduced and the benzyl-protecting group is removed, forming isoetharine (11.1.11) [15].



Isoetharine is a direct-acting sympathomimetic with relatively low selectivity with β_2-adrenoreceptors. However, it quickly calms bronchospasms better than more selective bronchodilators. It is used in treating chronic obstructive illnesses of outer respiratory tract. Synonyms of this drug are asthmalitan and bronkosol.

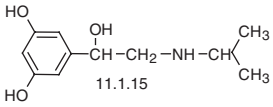
Terbutaline: Terbutaline, α-[(*tert*-butylamino)methyl]-3,5-dihydroxybenzylic alcohol (11.1.14), differs from the examined compounds mainly in the location of hydroxyl groups in the benzene ring, and is synthesized by brominating 3,5-dibenzyloxyαcetophenone into the appropriate 3,5-dibenzyloxybromoacetophenone (11.1.12), which is reacted with N-benzyl-N-*tert*-butylamine, giving the aminoketone (11.1.13). Reduction of this product by hydrogen over a palladium catalyst leads to terbutaline (11.1.14) [16–18].



Terbutaline is a synthetic sympathomimetic amine. It is one of the most selective direct–acting stimulants of β_2-adrenoreceptors. It stimulates smooth muscle β_2-adrenoreceptors in the bronchi, relaxing them and relatively minutely acting on the β_1—receptors of the heart.

It is used for preventing and relieving bronchospasms in bronchial asthma, chronic bronchitis, pulmonary emphysema, and other broncho-pulmonary diseases. Synonyms are bretin and bricanyl.

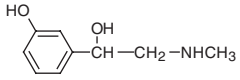
Metaproterenol: Metaproterenol, α-[(isopropylamino)methyl]-3,5-dihydroxybenzylic alcohol (11.1.15), is an analogue of terbutaline, in which the tert-butylamine group is replaced with an iso-propylamine group. Synthesis is accomplished in the same manner as terbutaline synthesis [19–21].



11.1.15

Metaproterenol is less selective than terbutaline and albuterol; however, it is widely used in treating chronic obstructive illnesses of the outer respiratory tract. Synonyms of this drug are orsiprenaline, metaprel, and alupent.

Phenylephrine: Phenylephrine, 1-(3-hydroxyphenyl)-2-methylaminoethanol (11.1.16), which differs from epinephrine, in that it does not have a hydroxyl group at C_4 of the aromatic ring, is synthesized by an analogous scheme of making epinephrine; however, instead of using ω-chloro-3,4-dihydroxyacetophenone, ω-chloro-3-dihydroxyacetophenone is used [11,22,23].



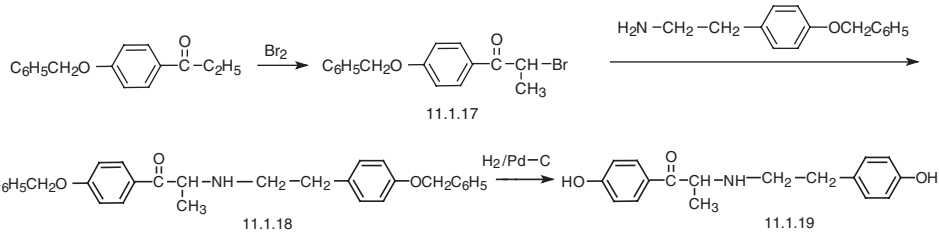
11.1.16

This synthetic drug has both chemical and pharmacological similarities to norepinephrine. A characteristic quality of phenylephrine is the distinctly expressed selectivity to α-adrenoreceptors, especially α_1-adrenoreceptors. Although phenylephrine increases the contractibility of blood vessels, in practical terms it is not considered a cardiostimulant.

Phenylephrine is used in hypotension, paroxysmal supraventricular tachycardia, and shock. It is also used locally, particularly in the form of nasal spray, for relieving edema. Synonyms of this drug are almefrine, degest, neoxedrin, metaoxedrin, and many others.

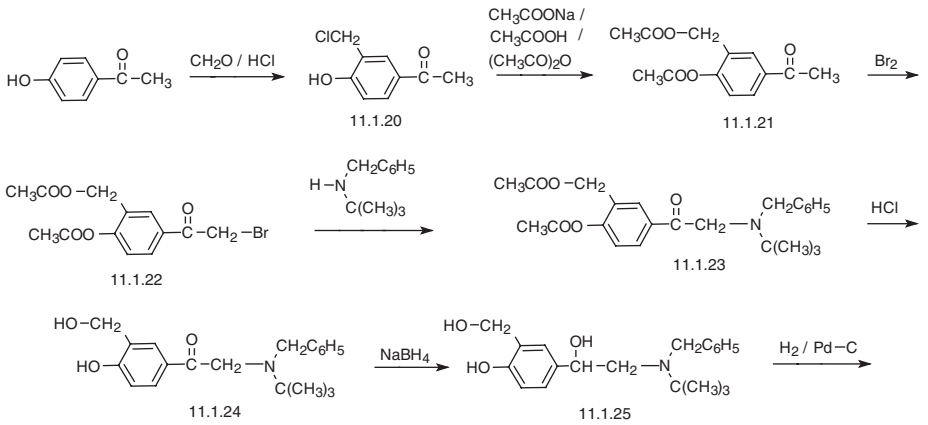
Ritodrine: Ritodrine, 4-hydroxy-α-[1-[(4′-hydroxyphenethyl)amino]ethyl]benzylic alcohol (11.1.19), differs slightly from epinephrine, and in the given example only one hydroxyl group has been added to the aromatic ring of the phenylethylamino region of classic sympathomimetics. The second major difference between the examined series is the replacement of the traditionally terminal *iso*-propyl or *tert*-butylamine region with a p-hydroxyphenylethylamine. Finally, the third difference is the presence of a methyl group at the α-atom of the phenylethylamine region of sympathomimetics, which makes it similar to isoetharine.

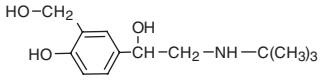
It is synthesized from 4-benzyloxypropiophenone, which undergoes bromination into 4-benzyloxy-α-bromopropiophenone (11.1.17). This is reacted with 2-(4-benzyloxyphenyl)ethylamine, forming an intermediate product (11.1.18), which undergoes further debenzylation by hydrogen using a palladium catalyst, giving ritodrine (11.1.19) [24,25].



Ritodrine is a selective β_2-adrenoreceptor stimulant, predominantly of the urino-genital system. It is used as a tocolytic agent for problems associated with premature miscarriages, and only in specialized medical facilities. Synonyms of ritodrine are yutopar and pre-par.

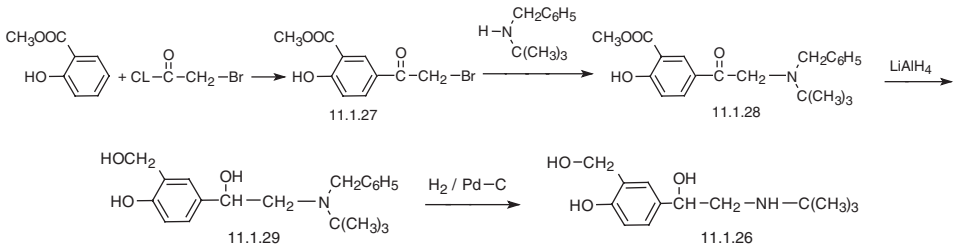
Albuterol: Albuterol, 2-*tert*-butylamino-1-(4-hydroxy-3-hydroxymethylphenyl)ethanol (11.1.26), basically differs from all of the aforementioned sympathomimetics in that the hydroxyl group at C_3 of the aromatic ring is replaced with a hydroxymethyl group. It is synthesized in two ways. According to the first, it is prepared from 4-hydroxyacetophenone, the chloromethylation of which gives 4-hydroxy-3-hydroxymethylacetophenone (11.1.20). This is acetylated into a diacetyl derivative (11.1.21), which is further brominated into the corresponding bromoacetophenone (11.1.22). Reacting this with N-benzyl-N-*tert*-butylamine gives a derivative of aminoacetophenone (11.1.23), the acetyl group of which is hydrolyzed by hydrochloric acid, and the resulting product (11.1.24) undergoes a reduction—first by sodium borohydride for transforming the keto group into a hydroxyl group to give 11.1.25, and then by hydrogenation over a palladium catalyst for removing the benzyl-protecting group, giving albuterol (11.1.26) [26–30].





11.1.26

The second way differs little from the previous, and consists of the initial formation of 4-hydroxy-3-acetoxybromoacetophenone (11.1.27) by acylation of methyl ester salicylic acid using bromoacetyl chloride. This is also reacted with *N*-benzyl-*tert*-butylamine, and the resulting product (11.1.28) is completely hydrolyzed by lithium aluminum hydride into the *N*-benzyl substituted albuterol (11.1.29), the benzyl group of which is removed by hydrogen over a palladium catalyst to give the desired albuterol (11.1.26) [31].



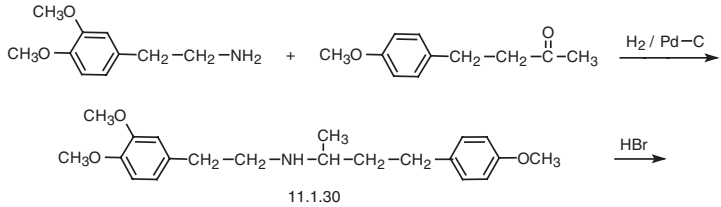
11.1.27 11.1.28 11.1.29 11.1.26

Albuterol is a β_2-adrenergic sympathomimetic amine with pharmacological similarities to terbutaline. It has almost no effect on β_1-adrenoreceptors of the heart. It has expressed broncholytic effects—prevention or relief of bronchi spasms, lowering respiratory tract resistance, and increasing the vital capacity of the lungs.

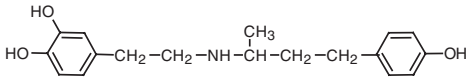
It is widely used for severe and chronic bronchial asthma and other illnesses of the respiratory tract that result in a spastic condition of the bronchi. Synonyms of albuterol are aloprol, ventolin, volma, salbutamol, salbuvent, spreor, and others.

Dobutamine: Dobutamine, (±) 4-[2(4′-hydroxyphenyl)-1-methylpropyl]-3,4-dihydroxyphenylethylamine (11.1.31), differs significantly from all of the presented drugs in terms of structure, the main difference being the absence of a hydroxyl group at the β-carbon atom of the phenylethylamine moiety of classic sympathomimetics. The second considerable difference from the examined drugs is the presence of p-hydroxyphenyl-iso-butylamine group as a terminal amine substituent.

It is synthesized by the reaction of 3,4-dimethoxyphenyl-2-amine and 1-(4-methoxyphenyl)-3-butanone with a simultaneous reduction of formed imine, giving the product (11.1.30), the methoxyl-protecting groups of which are cleaved by hydrogen bromide, giving dobutamine (11.1.31) [32,33].



11.1.30



11.1.31

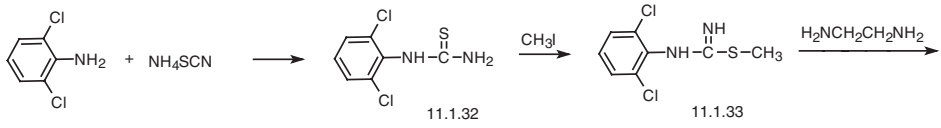
Dobutamine is a selectively activating drug at cardiac β_1-adrenoreceptors, as well as β_2-adrenoreceptors of the blood vessels and α_1-adrenoreceptors of the myocardium. The mechanism of its action is very complex.

Dobutamine is used in situations where, during severe cardiac decompensation, it is necessary to temporarily strengthen contractions of the myocardium, and in particular during decompensation of cardiac activity associated with surgical intervention on the heart or in organic diseases. A synonym of dobutamine is dobutrex.

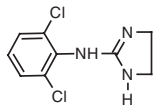
11.1.3 Drugs stimulating predominantly α-adrenoreceptors

The direct-acting adrenomimetics described next are α-adrenergic agonists that are structurally very different from the drugs described above.

Clonidine: Clonidine, 2-(2,6-dichlorophenylamino)imidazoline (11.1.34), is synthesized from 2,6-dichloroaniline, the reaction of which with ammonium thiocyante gives N-(2,6-dichlorophenyl)thiourea (11.1.32). Methylation of this product into (11.1.33) by the subsequent reaction with ethylendiamine gives clonidine (11.1.34) [34–39].



11.1.32 11.1.33



11.1.34

Clonidine is a selective α_2-adrenergic agonist. Clonidine has expressed hypotensive action, which is associated with a reduction of general peripheral vascular resistance, reduced frequency of cardiac beats, and a reduction of cardiac output. The mechanism of action of clonidine is caused by stimulation of α_2-adrenoreceptors of the inhibitory structures of the brain as well as a reduction of sympathetic impulses to the blood vessels and brain.

Clonidine raises systemic blood pressure and heart rate by stimulating α_2-adrenoreceptors in certain parts of the CNS, and it is used mainly as an antihypertensive agent. Clonidine is used in various forms of hypertonic illnesses and for stopping hypertensive attacks. It is also used in ophthalmological practice for open-angle glaucoma. Synonyms of clonidine are hemiton, catapres, and clofelin.

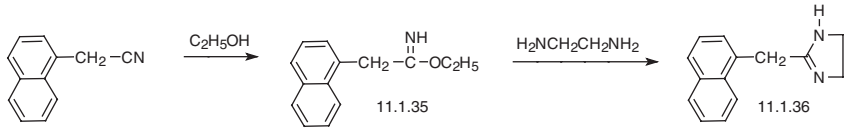
11.1.4 Antiedema sympathomimetics

Currently, the most popular antiedema agents for the mucous membranes are the drugs naphazoline, oxymethazoline, tetrahydrozoline, and xylomethazoline, which are derivatives of

imidazoline. They are solely α-adrenoreceptor agonists that exhibit a draining effect by constricting blood vessels in the mucous membranes.

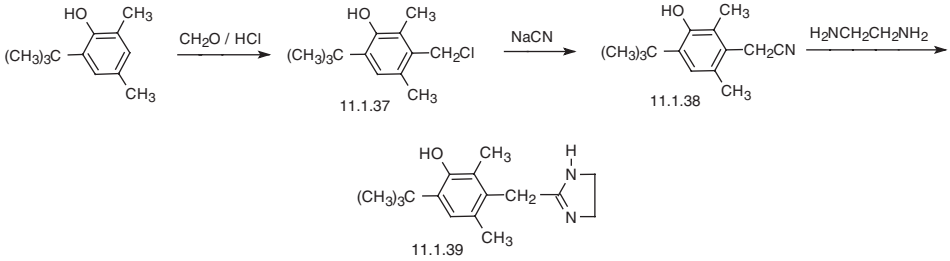
Phenylephrine and phenylpropanolamine, which are sympathomimetics of mixed action, are also used in medicine for reducing edema in the mucous membranes.

Naphazoline: Naphazoline, 2-(1-naphthylmethyl)-2-imidazoline (11.1.36), is synthesized from (1-naphthyl)acetonitrile, which upon reaction with ethanol transforms into iminoester (11.1.35), and undergoes further heterocyclization into the desired imidozoline derivative (11.1.36) upon reaction with ethylendiamine [40].



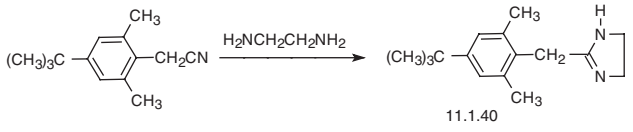
Naphazoline is used in severe rhinitis associated with colds, allergic reactions, and severe and chronic inflammatory conditions, in particular for inflammation of the antrum of Highmore as well as for stopping nosebleeds. Synonyms of naphazoline are nafazair, sanorin, rinazin, and privine.

Oxymetazoline: Oxymetazoline, 6-*tert*-butyl-3(2-imidazolin-2-ilmethyl)-2,4-dimethylphenol (11.1.39), is synthesized by chloromethylation of 6-*tert*-butyl-2,4-dimethylphenol and the further transformation of the resulting chloromethyl derivative (11.1.37) into a nitrile (11.1.38). The reaction of this with ethylendiamine gives oxymetazoline (11.1.39) [41,42].



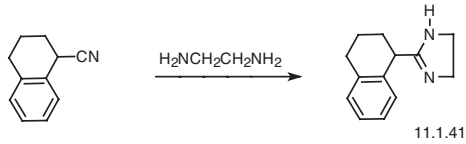
Oxymetazoline is used for the same indications as naphazoline, primarily for rhinitis. Synonyms of this drug are afrin and duramist.

Xylometazoline: Xylometazoline, 2-(4-*tert*-butyl-2,6-dimethylbenzyl)-2-imidazoline (11.1.40), is also synthesized in a single reaction by cyclocondensation of 4-*tert*-butyl-2,6-dimethylbenzylcyanide with ethylendiamine [43,44].



Xylometazoline is used for rhinitis, laryngitis, sinusitis, inflammation of antrum of Highmore, and allergic illnesses of the nasal cavity and throat. Synonyms of this drug are halazoline and otrivin.

Tetrahydrozoline: Tetrahydrozoline, 2-(1,2,3,4-tetrahydro-1-naphthalenyl)-2-imidazoline (11.1.41), is synthesized in one step by the heterocyclization of 1-cyanotetraline with ethylenediamine [45].



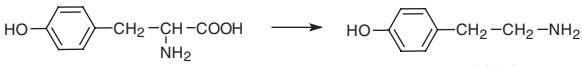
11.1.41

Tetrahydrozoline is generally used in the form of eye drops for constriction of blood vessels as well as locally for minor inflammations and bites. The main synonyms of tetrahydrozoline are visine and tyzine.

11.2 INDIRECT-ACTING AGONISTS

Tyramine, the only indirect–acting compound, exhibits sympathomimetic effects by causing the release of endogenic norepinephrine, and it has only found practical use in experiments. It inactivates monoaminooxidase very quickly. It has no practical clinical use.

Tyramine: Tyramine, 4-(2-aminoethyl)phenol (11.2.1), can be synthesized in various ways, in particular by the decarboxylation of tyrosine [46–48]. It is also isolated from the tissues of livestock.



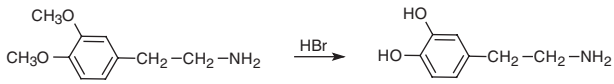
11.2.1

Synonyms of this drug are mydrial, uteramin, and others.

11.3 AGONISTS OF MIXED ACTION

Practically every examined substance of mixed action has indirect action (such as that of tyramine), in addition to a direct action (activation of adrenoreceptors), and all are α- and β-adrenomimetics of indirect (mediated) action.

Dopamine: As a medicinal agent, dopamine, 2-(3,4-dihydroxyphenyl)-ethylamine (11.3.1), is synthesized by demethylation of 2-(3,4-dimethoxyphenyl)ethylamine (19.4.3) using hydrogen bromide [49–51].

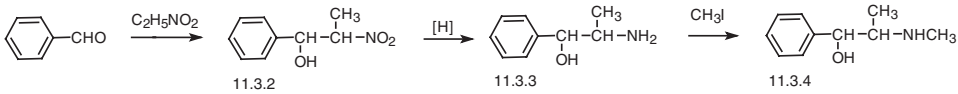


19.4.3 11.3.1

Dopamine is found in every sympathetic neuron and ganglion in the CNS. As a drug, and in addition to stimulation of dopaminergic receptors, dopamine indirectly stimulates both α- and β-adrenoreceptors. Dopamine also causes a release of endogenous norepinephrine. The mechanism of action is based on the excitatory effect on β-adrenoreceptors (in low and moderate doses), as well as on α-adrenoreceptors (in large doses). It has a positive inotropic effect on the heart, increases blood supply, selectively widens renal and mesenteric blood vessels, does not elevate blood pressure, and slightly increases the frequency of heartbeats.

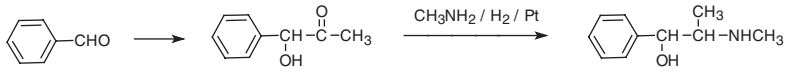
Dopamine exhibits its primary action of the cardiovascular system, kidneys, and mesentery. It is used as a temporary agent for treating hypotension and circulatory shock caused by myocardial stroke, trauma, kidney rejection, and endogenous septicemia. The main indication for use of this drug is shock of various origins (cardiogenic, postoperational, infectious-toxic, anaphylactic), severe hypotension, and imminent renal insufficiency. Synonyms of dopamine are dopamin and inotropin.

Ephedrine: Ephedrine, L-erythro-1-phenyl-2-methylaminopropanol-1 (11.3.4), is synthesized from benzaldehyde in a few different ways. According to the first, benzaldehyde is condensed with nitroethane, giving 2-methyl-2-nitro-1-phenylethanol (11.3.2), which is reduced to 2-methyl-2-amino-1-phenylethanol (11.3.3). The necessary L-isomer is isolated from the mixture of isomers by crystallization. Methylation of this gives ephedrine (11.3.4) [52,53].



11.3.2 11.3.3 11.3.4

The second method consists of the fermentation of glucose by yeast carboligase in the presence of benzaldehyde, which during the process turns into (−)-1-phenyl-2-ketopropanol (11.3.5). This is reduced by hydrogen in the presence of methylamine, to give the desired ephedrine (11.3.4) [54,55].



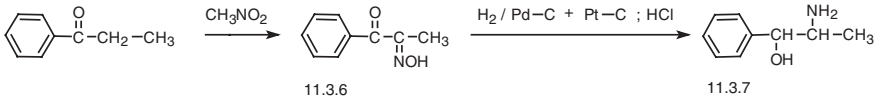
11.3.5 11.3.4

Ephedrine is an alkaloid that is present in various forms of the ephedrine family, and which is still extracted from *Ephedra sinica* and *Ephedra equisetina*. Because of the presence of two asymmetric atoms, there are four isomeric forms. Pseudoepinephrine (d-isoephrine) is a stereoisomer with pharmacological action that differs slightly from ephedrine. The pharmacological action of ephedrine is typical of noncatecholamine sympathomimetics of mixed action. It stimulates both α- and β-adrenoreceptors, and simultaneously causes a release of norepinephrine from synaptic neurons. Its vasoconstrictive ability is approximately 100 times weaker than that of epinephrine; however, the duration of action is approximately 10 times longer. It is much less toxic than epinephrine, which allows it to be used widely in medicine.

It is mainly used for bronchial asthma, allergic illnesses, as an antiedemic for mucous membranes in rhinitis, and also as a drug to increase blood pressure during surgical

interventions. It is used locally in ophthalmology as a vasoconstricting agent for dilating pupils. Synonyms of this drug are epipen, ephedrol, manadrin, calcidrin, and others.

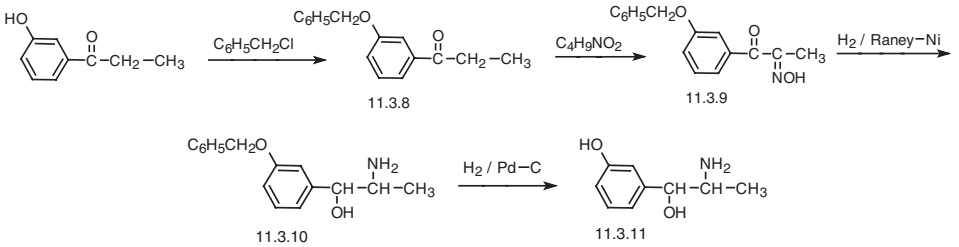
Phenylpropanolamine: Phenylpropanolamine, D,L-erythro-1-phenyl-2-methylaminopropanol-1 (11.3.7), is synthesized from propiophenone by nitrosation into an isonitroso derivative (11.3.6). Reduction of this by hydrogen in hydrochloric acid while simultaneously using two catalysts, palladium on carbon and platinum on carbon, gives norephedrine (11.3.7) [56–59].



11.3.6 11.3.7

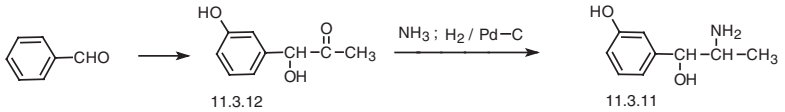
The pharmacological action of phenylpropanolamine is similar to the action of ephedrine. This sympathomimetic can temporarily elevate blood pressure, and it is used for the same indications as is ephedrine, which is primarily in combination with other drugs for catarrhal illnesses. In addition, it possesses weak central-stimulatory and anorectic action. The primary synonym is norephedrine.

Metaraminol: Metaraminol, L-1-(3-hydroxyphenyl)-2-aminopropan-1-ol (11.3.11), is synthesized in two ways. The first way is synthetic, and it is from 3-hydroxypropiophenone. The hydroxyl group is protected by alkylation with benzyl chloride, giving 3-benzyloxypropiophenone (11.3.8). Upon reaction with butylnitrite, it undergoes nitrosation into the isonitrosoketone (11.3.9), which by reduction using hydrogen over Raney nickel turns into 1-(3-benzyloxyphenyl)-2-aminopropan-1-ol (11.3.10), the protecting benzyl group is removed by reduction using hydrogen over palladium catalyst, to give racemic metaraminol (11.3.11). The desired L-isomer is isolated with the help of (+)- tartaric acid [60,61].



11.3.8 11.3.9 11.3.10 11.3.11

The second way is semisynthetic, consisting of fermentation of D-glucose in the presence of 3-acetoxybenzaldehyde, which forms (-)-1-hydroxy-1-(3-hydroxyphenyl)-acetone (11.3.12), the carbonyl group of which is reduced by hydrogen over a palladium catalyst in the presence of ammonia, giving metaraminol (11.3.11) [62–65].

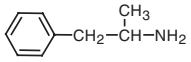


11.3.12 11.3.11

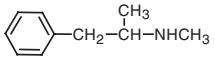
Metaraminol is a sympathomimetic amine of both direct and indirect action that has hemodynamic characteristics similar to norepinephrine. It has the ability to elevate both systolic and diastolic blood pressure.

It is used in hypotensive shock for the purpose of elevating blood pressure, which can result from spinal anesthesia, surgical complications, and head trauma. Synonyms of metaraminol are aramine, isophenylephrin, metaradine, and others.

Amphetamines: The term amphetamines is usually used in relation to racemates of amphetamine, dextroamphetamine (8.1.2.2), and methamphetamine (8.1.2.3).



8.1.2.2



8.1.2.3

As drugs of mixed action, amphetamines activate adrenergic receptors and simultaneously release endogenic catecholamines (norepinephrine and dopamine) from neurons of the brain and periphery. Sympathomimetic effects on the periphery are very similar to those of ephedrine. Amphetamine elevates systolic and diastolic blood pressure and has weakly expressed, broncholytic action. These effects are more prolonged, yet less expressed, than with epinephrine. The distinctive feature of amphetamines is their psychostimulatory activity. Larger doses can cause hallucinations and mental conditions similar to paranoid schizophrenia. As a sympathomimetic, amphetamine is sometimes used for uterine inertia. Synonyms of amphetamine are phenamine and benzedrine.

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– 12 –

Adrenoblocking Drugs

The adrenergic receptors (or adrenoceptors) are a class of G-protein coupled receptors, which are the targets of catecholamines. Adrenergic receptors specifically bind their endogenous ligands, the catecholamines, epinephrine, and norepinephrine (also called adrenaline and noradrenaline), and are activated by these.

The term adrenoblocker refers to drugs that are capable of competing with catecholamines and other adrenomimetics for binding with adrenergic receptors, thus blocking effects of sympathetic nerves caused by either stimulation by endogenic sympathomimetics or generated by adrenergic drugs of exogenic origin. True adrenoblockers do not affect the process of norepinephrine (noradrenaline) synthesis in the organism.

Adrenoblocking drugs are classified as α-adrenoblockers, β-adrenoblockers, and adrenergic neuron blockers depending on the response brought about in the organism. α-Adrenoreceptors cause dilation of peripheral blood vessels, and a few of them relax smooth muscles.

On the other hand, β-adrenoblockers have a minor effect on vascular tonicity. In addition, β-adrenoblockers prevent the vasodilatory effect of epinephrine. In organs such as the heart, which are regulated mainly by β-adrenoreceptors, β-adrenoblockers counteract the excitatory effect of norepinephrine.

In turn, α- and β-adrenoblockers are subdivided into selective and nonselective groups. Nonselective β-adrenoblockers exhibit affinity for both β_1- and β_2-adrenoreceptors. Included in this category are propranolol, nadolol, timolol, and labetalol (a combined α- and β-adrenoblocker). Selective β_1-blockers are acebutol, atenolol, esmolol, and metoprolol, which in therapeutic doses predominantly binds to β_1-adrenoreceptor regions.

Currently, there are no therapeutically useful selective β_2-adrenoblockers, although a number of experimental compounds with expressed β_2-adrenoblocking activity already exist.

β-Adrenoblockers are most widely used in treating angina, hypertonic diseases, tachycardia, and arrhythmia.

Likewise, α-adrenoblockers also are subdivided into selective and nonselective groups. Examples of nonselective α-adrenoblockers are phentolamine and phenoxybenzamine, as well as the ergo alkaloids, ergotamine, and ergonovine. Despite the fact that their practical use in medicine is not connected to their α-blocking ability, historically they were the first investigated α-adrenoblockers. In therapeutic doses, selective α-adrenoblockers show a

greater degree of affinity with both α_1-adrenoreceptor regions (prazosin, terazosin), and α_2-adrenoreceptor regions (yochimbin).

In medical practice, α-adrenoblockers are drugs that block α_1- and α_2-adrenoreceptors, and they are used relatively rarely. The most important effect of α-adrenoblockers is the dilation of blood vessels, for which they are used in various disturbances of peripheral blood flow, and hemorrhagic and cardiogenic shock, in which the typical effect is a spasm of the arterioles.

Conventionally called adrenergic neuron blockers, the last group of adrenoblockers are drugs that suppress synthesis, storage, and release of biogenic amines (norepinephrine, dopamine, or serotonin) in nerve endings.

Included in this series of drugs are rezerpin, guanadrel, guanethidine, and metyrosine, and they are used mainly as antihypertensive drugs.

12.1 β-ADRENOBLOCKERS

Drugs that exhibit reversible competitive blocking action on β-adrenoreceptive receptor system and that counteract effects of catecholamines are called β-adrenoblockers.

These drugs selectively reduce cardiostimulatory, vasodilating, broncholytic, and metabolic (glycogenolytic and lipolytic) action of catecholamines released from adrenergic nerve endings and adrenal glands.

β_1-Receptors are present in heart tissues, and cause an increased heart rate by acting on the cardiac pacemaker cells. Many β-blockers used for treatment of angina will mainly affect these receptors and the β_2-receptors to a lesser extent. These are referred to as 'cardio-selective' β-blockers.

β_2-Receptors are in the vessels of skeletal muscle, and cause vasodilation, which allows more blood to flow to the muscles, and reduces total peripheral resistance. These tend to work with epinephrine (adrenaline), but not norepinephrine (noradrenaline).

β_2-Receptors are also in bronchial smooth muscle, and cause bronchodilation when activated. Some antiasthma drugs, such as the bronchodilator salbutamol work by binding to and stimulating the β_2-receptors.

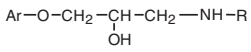
Nonselective β-blocking drugs, such as propranolol, can represent a risk to people with asthma by blocking the β_2-receptors, causing bronchoconstriction.

Introduction of β-adrenoblockers into medicine was one of the main advancements of pharmacology of the cardiovascular system. Initially these drugs were used only in treating essential hypertension. Currently, they are used in treating angina, arrhythmia, migraines, myocardial infarctions, and glaucoma.

Their efficacy in many illnesses is explained by the competitive binding of β-adrenoreceptors in the autonomic nervous system by basically any of the employed drugs of the 1-aryloxy-3-aminopropanol-2 class, which result in reduction of heart rate and strength of cardiac beats, slowing of atrioventricular conductivity, reduction of the level of renin in the plasma, and reduction of blood pressure. The main effects of β-adrenoblockers are expressed at the level of the vasomotor center in the hypothalamus, which result in a slowing of the release of sympathetic, tonic impulses. Included in the main group of

β-adrenoblockers are the drugs propranolol, metoprolol, nadolol, atenolol, timolol, acebutol, pindolol, esmolol, and a combinded α- and β-adrenoblocker, labetalol.

In terms of chemical structure, β-adrenoblockers have much in common. Practically, all of them are derivatives of 1-aryloxy-3-aminopropanol-2, the C_1 position of which always possesses a substituted or nonsubstituted aromatic or heteroaromatic group connected by an ether bond to a three-carbon chain. An R group at the nitrogen atom of the propanoic region must be represented as either a tertiary butyl group (nadolol, timolol), or an *iso*-propyl group (the remainder of the drugs).



It should be mentioned that the substituted ethanolamine group in the structure of β-adrenoblockers is similar to that of many compounds with agonistic adrenergic activity (isoproterenol (11.1.9), albuterol (11.1.21), and others), and therefore it is possible that it may be responsible for high affinity of the examined adrenoblockers with β-adrenergic receptors.

Levorotatory isomers of these drugs are much more powerful adrenoblockers than dextrorotatory isomers; however, all of these drugs are made and used as racemic mixtures.

The examined drugs reversibly bind with β-adrenergic receptive regions and competitively prevent activation of these receptors by catecholamines released by the sympathetic nervous system, or externally introduced sympathomimetics.

As was already noted, β-adrenoreceptors are subdivided into β_1-adrenoreceptors, which are predominantly found in cardiac muscle, and β_2-adrenoreceptors, which are predominantly found in bronchial and vascular muscles. Thus, β-adrenoblocking substances are classified by their selectivity in relation to these receptors.

Compounds that exhibit roughly the same affinity to β_1- and β_2-receptors independent of dosage such as nadolol, propranolol, pindolol, timolol, and labetalol (combined α- and β-adrenoblocker) are classified as nonselective blockers. Drugs which in therapeutic doses have higher affinity to β_1-receptors than to β_2-receptors such as acebutol, atenolol, metoprolol, and esmolol, are called selective or cardioselective β-adrenoblockers.

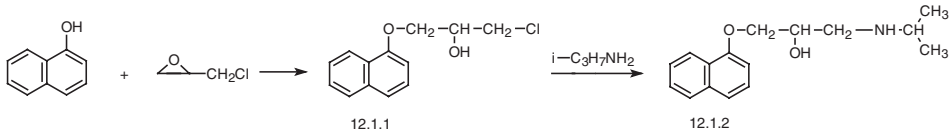
It is important to note that selectivity is not absolute, and it depends on the administered dose. In large doses, selectivity is even and both subtypes of β-adrenoreceptors are inhibited equally. In addition to blocking β-adrenoreceptors, these drugs affect the cardiovascular system in a different manner.

So, drugs that block β_1-receptors lower the heart rate and blood pressure and hence are used in conditions when the heart itself is deprived of oxygen. They are routinely prescribed in patients with ischemic heart disease. In addition, β-blockers prevent the release of renin, which is a hormone produced by the kidneys which leads to constriction of blood vessels.

Drugs that block β_2-receptors generally have a calming effect and are prescribed for anxiety, migraine, esophageal varices, and alcohol withdrawal syndrome, among others.

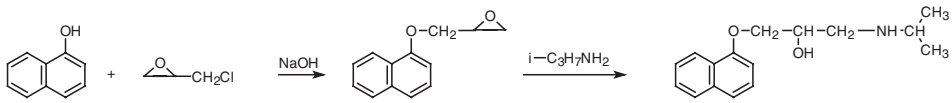
Propranolol: Propranolol, 1-(*iso*-propylamino)-3-(1-naphthyloxy)-2-propanol (12.1.2), is synthesized in two ways from the same initial substance. The first way consists of reacting

1-naphthol with epichlorohydrin. Opening of the epoxide ring gives 1-chloro-3-(1-naphthyloxy)-2-propanol (12.1.1), which is reacted further with *iso*-propylamine, giving propranolol (12.1.2).



12.1.1 12.1.2

The second method uses the same reagents in the presence of a base and consists of initially making 3-(1-naphthyloxy)propylenoxide (12.1.3), the subsequent reaction with *iso*-propylamine which results in epoxide ring opening leading to the formation of propranolol (12.1.2) [1–6].



12.1.3 12.1.2

Propranolol is a prototype of this series of drugs and is the oldest and most widely used nonselective β-adrenoblocker. It possesses antianginal, hypotensive, and antiarrhythmic action. Propranolol is a cardiac depressant that acts on the mechanic and electrophysiological properties of the myocardium. It can block atrioventricular conductivity and potential automatism of sinus nodes as well as adrenergic stimulation caused by catecholamines; nevertheless, it lowers myocardial contractility, heart rate, blood pressure, and the myocardial requirement of oxygen.

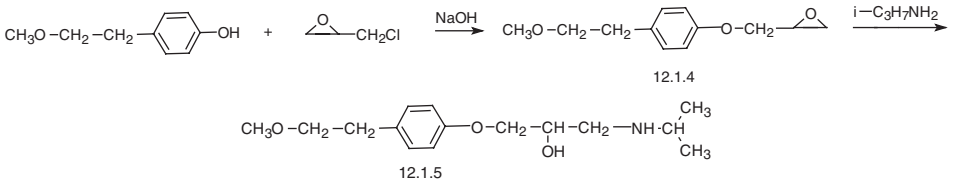
All of these properties make propranolol and other β-adrenoblockers useful antiarrhythmic and antianginal drugs.

Propranolol lowers blood pressure in the majority of patients with essential hypertension. These effects can be caused by a number of possible mechanisms, including lowering cardiac output, inhibiting the release of renin, lowering sympathetic release from the central nervous system, inhibiting the release of norepinephrine from sympathetic postganglionic nerves, and others.

However, not one of the suggested mechanisms adequately describes the antihypertensive activity of propranolol and other β-blockers.

Propranolol is used in treating arterial hypertonicity, angina, extrasystole, superventricular arrhythmia, ventricular tachycardia, migraines, hypertrophic subaortic stenosis, and pheochromocytoma. It also is used in the postanginal phase of myocardial infarctions. Universally accepted synonyms of this drug are anaprilin, inderal, and many others.

Metoprolol: Metoprolol, 1-(*iso*-propylamino)-3-[4′(2-methoxyethyl)phenoxy]-2-propanol (12.1.5), is synthesized by reacting 4-(2-methoxyethyl)phenol with epichlorhydride in the presence of a base, isolating 1,2-epoxy-3-[4′(2-methoxyethyl)phenoxy] propane (12.1.4), the subsequent reaction of which, analogous to that described before, with *iso*-propylamine, gives an opening of the epoxide ring and leads to the formation of metoprolol (12.1.5) [7,8].

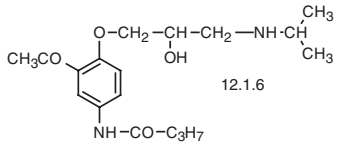


Unlike propranolol, which blocks both β_1- and β_2-adrenoreceptors, metoprolol exhibits cardioselective action, i.e in therapeutic doses, it blocks β_1-adrenoreceptors with insignificant reaction on β_2-adrenoreceptors.

Metoprolol is used in moderate hypertension, serious conditions of myocardial infarction, for preventing death of cardiovascular tissue, in angina, tachycardia, extrasystole, and for secondary prophylaxis after a heart attack. The most common synonyms are lopresor, betaloc, and others.

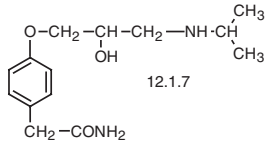
Other β-adrenoblockers whose syntheses differ slightly from those above also are used widely in medicine. Therefore, only their names, structural formulas, pharmacological properties, and synonyms are listed below.

Acebutol: Acebutol is 3′-acetyl-4′-[2-hydroxy-3-(*iso*-propylamino)propoxy] butyranilide (12.1.6) [9,10].



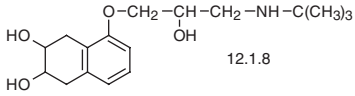
Acebutol is a selective β_1-adrenoblocker. It possesses antianginal, antihypotensive, and antiarrhythmic action. It is used for arterial hypertension, preventing attacks of angina, and cardiac rhythm disturbances. Synonyms of this drug are acebutolol, sectral, and others.

Atenolol: Atenolol is 2-[4′[2-hydroxy-3-(*iso*-propylamino)propoxy]phenyl]acetamide (12.1.7) [11–13].



Atenolol is a selective β_1-adrenoblocker, or in other words, a cardioblocker. Like acebutol, atenolol possesses antianginal, antihypotensive, and antiarrhythmic action. It is used for arterial hypotension, preventing attacks of angina, sinus tachycardia, and preventing supraventricular tachyarrhythmia. Synonyms of this drug are tenormin, calten, ibinol, and others.

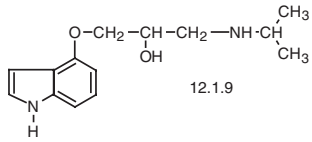
Nadolol: Nadolol is 1-(*tert*-butylamino)-3-[(5,6,7,8-tetrahydro-*cis*-6,7-dihydroxy-1-naphthyl)-oxy]-2-propanol (12.1.8) [14–16].



12.1.8

Nadolol is a nonselective β-adrenoblocker of prolonged action. Like the other β-adrenoblockers above, it possesses antianginal, antihypotensive, and antiarrhythmic action. It is used for arterial hypertension, for preventing attacks of angina, and for sinus tachycardia. Synonyms of this drug are corgard, solgol, corzid, and others.

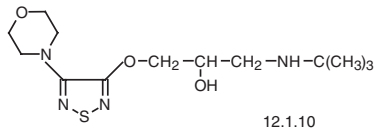
Pindolol: Pindolol is 1-(indol-4-yloxy)-3-(*iso*-propylamino)-2-propanol (12.1.9) [17,18].



12.1.9

Pindolol, like nadolol, is a nonselective β-adrenoblocker. It possesses antianginal, antihypotensive, and antiarrythmic action. It is used for arterial hypertension, angina stress (preventing attacks), supraventricular tachycardia, tachsystolic form of atrial fibrillation, and superventricular extrasystole. Synonyms of this drug are carvisken, visken, and others.

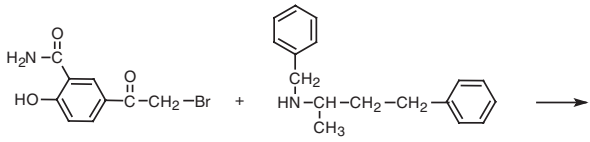
Timolol: Timolol is 1-(*tert*-butylamino)-3-[(4-morpholine)-1,2,5-thiadiazol-3-yl)oxy]-2-propanol (12.1.10) [19–27].

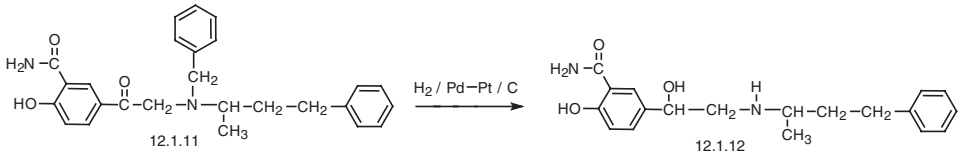


12.1.10

Timolol is a nonselective β-adrenoblocker that prevents action of catecholamines. When used locally in the form of eye drops, intraocular pressure decreases. It is used for chronic open-angle glaucoma as well as closed-angle glaucoma. Synonyms of this drug are moducrine, thiamicor, timoptol, blocadren, timolide, and others.

Labetalol: Labetalol, 2-hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropanol)amino)] ethyl] benzamide (12.1.12) is synthesized by the *N*-alkylation of *N*-benzyl-*N*(4-phenyl-2-butyl)amine 5-bromacetylsalicylamide and forming aminoketone (12.1.11), which is further debenzylated by hydrogen using a palladium–platinum on carbon catalyst into labetalol (12.1.12) [28–30].





12.1.11 12.1.12

Structurally, labetalol differs from other β-adrenoblockers even though it is a derivative of ethanolamine and not a 1-aryloxy-3-aminopropanol-2, which does not have an aryloxyl group, and is a derivative of phenylpropyamine, but not isopropyl or *tert*-butylamine. The aminoethanol region is not joined with the aromatic region by an ether bond. At the same time, the aromatic part of the molecule, unlike the typical structures of β-adrenoblockers described above, is sufficiently functionalized and constitute a substituted salicylamide. It is structurally similar to dobutamine (11.1.31); however, minor structural differences make it an antagonist of dobutamine. Pharmacologically, it is a selective, competitive α_1-blocker and a nonselective blocker of β-adrenergic receptors, which leads to a decrease in blood pressure in hypertensive patients.

Labetalol is used to treat essential hypertension. The main synonyms of this drug are trandate, avetol, aimpress, pressalol, and others.

12.2 α-ADRENOBLOCKERS

Compounds capable of blocking α-adrenergic receptive regions by preventing various agonists from acting on them are called α-blockers.

The distinctive feature of α-adrenoblockers is their ability to reduce the pressor effect of pharmacological doses of epinephrine (adrenaline).

α_1-Receptors act by phospholipase C activation, which, in turn, forms inositol trisphosphate, which together with diacylglycerol, are second messenger molecules used in signal transduction in biological cells.

In blood vessels these cause vasoconstriction. Blood vessels with α_1-receptors are present in the skin and the gastrointestinal system, and during the flight-or-fight response there is decreased blood flow to these organs. This is the reason people can appear pale when they have been frightened.

α_2-Receptors act by inactivation of adenylate cyclase; cyclic AMP (adenosine-monophosphate) levels within the cell decrease.

These are found on presynaptic nerve terminals.

In particular, postsynaptic α_1-blockers act on the α-receptive regions located on the smooth muscle of blood vessels and counteract the pressor, vasoconstricting effect of epinephrine and norepinephrine. In addition, they exhibit a direct relaxant effect on smooth muscle, which leads to peripheral dilation of blood vessels, which in turn raises blood pressure. However, they also exhibit a cardiostimulatory effect, which is frequently a cause of tachycardia.

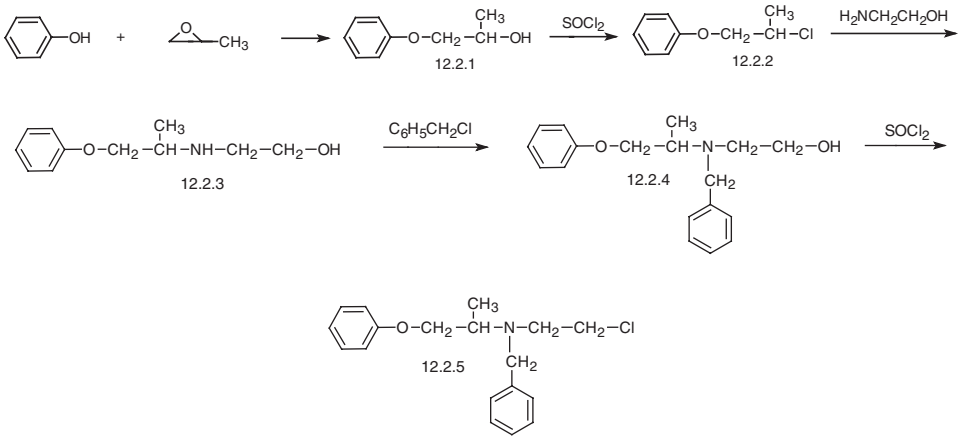
Presynaptic α_2-receptive regions are located on sympathetic nerve endings, and their blockage, evidently by a mechanism of reversible binding, increases output of epinephrine

from nerve endings. Such pharmacological action has extremely limited clinical use; however, it is a valuable laboratory instrument. The alkaloid yohimbin is a selective α_2-adrenoblocker.
Clinically useful α-blockers are:

1. Long-acting, noncompetitive antagonists (phenoxybenzamine), which form strong chemical bonds with α-receptor regions, can block α-receptors for days and even weeks.
2. Reversible competitive antagonists, nonselective (phentolamine, tolazoline), and α_1-selectively acting (prazosin, terazosin) that reversibly and competitively block α-receptive regions; terazosin can last a few hours. At the same time, blockage of α-receptors can be interrupted and stopped by large doses of an agonist such as norepinephrine.
3. Ergot alkaloids (ergotamine, ergonovine) also exhibit certain nonselective α-adrenoblocking activity; however, they primarily exhibit spasmogenic action on smooth muscle, causing a constriction of blood vessels.
4. Selective α_2-adrenoblockers such as the alkaloid yohimbin have limited clinical use.

12.2.1 Long-lasting noncompetitive antagonists

Phenoxybenzamine: Phenoxybenzamine, *N*-(2-chloroethyl)-*N*-(1-methyl-2-phenoxyethyl) benzylamine (12.2.5), is synthesized by reacting phenol with propylenoxide, which forms 1-phenoxy-2-propanol (12.2.1), the chlorination of which with thionyl chloride gives 1-phenoxy-2-propylchloride (12.2.2). Reacting this with 2-aminoethanol leads to formation of 1-phenoxy-2-(2-hydroxyethyl)aminopropane (12.2.3). Alkylation of the secondary amino group gives *N*-(2-hydroxyethyl)-*N*-(1-methyl-2-phenoxyethyl)benzylamine (12.2.4), the hydroxyl group of which is chlorinated using thionyl chloride, giving phenoxybenzamine (12.2.5) [31].

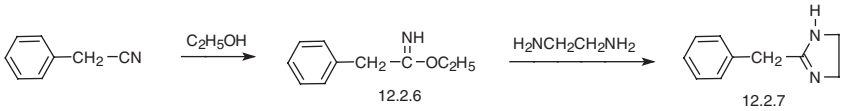


Phenoxybenzamine is a β-chloroamine that is structurally related to alkylating agents used in chemotherapy. The mechanism of its long-lasting blockage of α-adrenoreceptors can evidently be explained by its irreversible alkylation. The irreversible blockage most likely occurs after briefly affecting α_1- and α_2-adrenoreceptors. It is possible that the β-chlorethylamine region in tissue of the organism forms a highly reactive ethylenimonium intermediate, which then alkylates the receptor. Such blockages are irreversible and are called nonequilibrium receptor blockers.

Phenoxybenzamine is used in treating pheochromocytoma, swelling of the medullary layer of the adrenal glands, during which a large quantity of epinephrine is produced, which leads to a significant elevation of blood pressure. A synonym of this drug is dibenzyline.

12.2.2 Nonselective, reversible competitive adrenoblockers

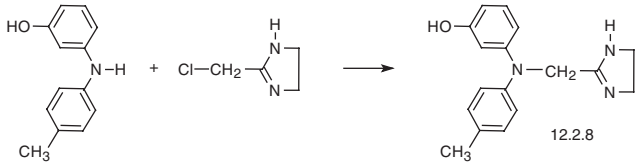
Tolazoline: Tolazoline, 2-benzyl-2-imidazoline (12.2.7), is synthesized by the heterocyclation of the ethyl ester of iminophenylacetic acid with ethylendiamine (12.2.6), which forms the desired product (12.2.7) [32–35]. The structure of tolazoline is strikingly similar to α-adrenergic agonists, which are antiedema sympathomimetics.



Tolazoline is a weak, reversible α-adrenoblocker that lowers resistance of peripheral blood vessels and elevates venous capacity. However, it also exhibits β-adrenomimetic activity, which consists of the stimulation of cardiac work and is manifest as tachycardia, cholinergic activity, which consists of stimulation of the gastrointestinal tract, and histamine-like activity, which consists of stimulation of gastric secretion.

It is used for treating stable forms of pulmonary hypertension in newborns, and in cases where systemic arterial oxygenation cannot be achieved in the usual manner under careful observation of professionals. Synonyms of this drug are prixol, prixofen, imadalin, and others.

Phentolamine: Phentolamine, 2-[[*N*-(3′-hydroxyphenyl)-*para*-toluidion]methyl]-2-imidazoline (12.2.8), is synthesized by alkylation of 3-(4-methylanilino)phenol using 2-chloromethylimidazoline [36, 37].



Phentolamine is also a derivative of imidazoline that exhibits a direct α-adrenoblocking, muscle-relaxant effect on smooth muscle as well as cholinomimetic, histamine, and sympathomimetic effects. The chemical variation of its structure permits a few of its properties to be more expressed. For example, the aforementioned tolazoline, 2-benzyl-2-imidazoline, a structural analog of phentolamine, has more of an expressed muscle-relaxant effect on smooth muscle than an α-adrenoblocking effect.

Phentolamine's action is exhibited by competing with catecholamines for binding with α-adrenoreceptors—for which reason it is called a competitive blocker—that has high affinity, yet minimal activity with these receptive regions. This type of substrate–receptor blocker lowers the ability of α-adrenoreceptors to react with sympathomimetic amines, and consequently lowers the significance of the response brought about by endogenic or exogenic amines. The duration of the blockage of α-adrenoreceptors by phentolamine is significantly less than that of phenoxybenzamine.

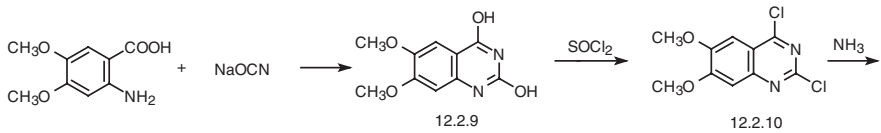
Phentolamine is used for peripheral blood circulation disorders, in particular in the beginning stages of gangrene, for treatment of trophic ulcers of the extremities, bedsores, and frostbite. Synonyms of this drug are regitine and dibazin.

12.2.3 Reversible, competitive α_1-selective adrenoblockers

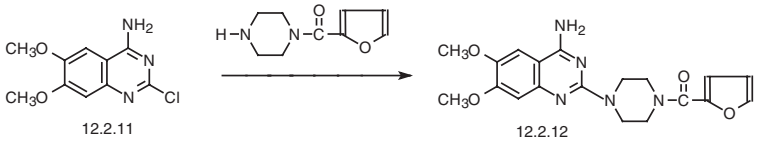
These drugs are peripheral coronary vasodilating drugs with α-adrenoblocking activity that differ only in specificity to α_1-adrenoreceptors. Unlike phenoxybenzamine and phentolamine (described above), they selectively block α_1-receptors and have little affinity with α_2-adrenergic receptors.

It is well known that norepinephrine regulates its own release from adrenergic nerve endings through a negative feedback mechanism by means of α_2-receptors on the postsynaptic membrane. At the same time, prazosin and terazosin are the only known selective α_1-adrenoblockers, which, in therapeutic doses, do not block α_2-adrenergic receptors. Thus, a feedback mechanism for releasing norepinephrine is not used when using such drugs.

Prazosin: Prazosin, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)-piperazine (12.2.12), is synthesized from 2-amino-4,5-dimethoxybenzoic acid, which upon reaction with sodium cyanate undergoes heterocyclation into 2,4-dihydroxy-6,7-dimethoxyquinazoline (12.2.9). Substituting hydroxyl groups of this compound with chlorine atoms by reaction with thionyl chloride, or a mixture of phosphorous oxychloride with phosphorous pentachloride gives 2,4-dichloro-6,7-dimethoxyquinazoline (12.2.10). Upon subsequent reaction with ammonia, the chlorine atom at C_4 of the pyrimidine ring is replaced with an amino group, which leads to the formation of 4-amino-2-chloro-6,7-dimethoxyquinazoline (12.2.11). Introducing this into a reaction with 1-(2-furoyl)piperazine gives prazosin (12.2.12) [38–47].



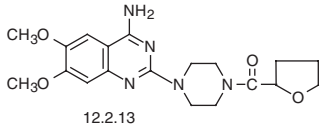
12.2.9 12.2.10



12.2.11 12.2.12

Prazosin is used for treating mid-to-moderate hypertension. When using this drug, blood pressure is reduced without any significant change in indicators of cardiac function such as frequency, coronary flow, or cardiac output. Synonyms of this drug are minipress and minizide.

Terazosin: Terazosin, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-tetrahydrofuroyl)-piperazine (12.2.13), only differs from prazosin in that the furyl radical is replaced with a tetrahydrofuryl radical. It is synthesized in exactly the same manner except using 1-(2-tetrahydrofuroyl)piperazine instead of 1-(2-furoyl)piperazine [48–51].



12.2.13

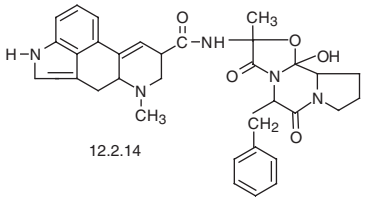
Terazosin is used for the same indications as is prazosin; however, it has the advantage of being able to be used once a day. Synonyms of this drug are heitrin and vasocard.

12.2.4 Ergot alkaloids (alkaloids of ergot)

Ergotamine, ergonovine, and a number of other alkaloids are isolated from ergot, a product of a fungal infection of grain, rye in particular. In the early history of civilization and in the middle ages, consumption of grain of contaminated ergot resulted in gangrene in the extremities, miscarriages, and seizures.

Ergot alkaloids were the first adrenoblockers to be studied. Despite the fact that the majority of ergot alkaloids exhibit α-adrenoblocking activity, their pharmacology is often different. In terms of chemistry, ergotamine and ergonovine are derivatives of lysergic acid.

Ergotamine: Ergotamine, 3′,6′,18′-trione,12′-hydroxy-2′-methyl-5′-benzyl-(5′α)-ergotamine (12.2.14), is obtained via microbiological synthesis [52].

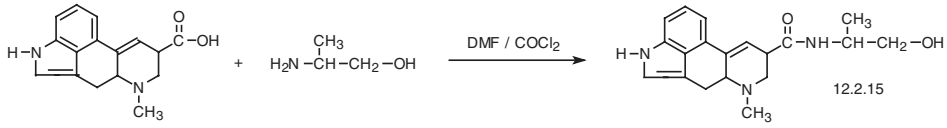


12.2.14

As an α-adrenoblocker, ergotamine exhibits a direct vasoconstricting effect for which it is used in medicine, particularly for alleviation of severe migraine attacks. It is categorically

counterproductive in chronic diseases because of the possibility of side effects such as triggering gangrene. Synonyms of this drug are synergan, secotamine, and others.

Ergonovine: Ergonovine, 1-hydroxymethylethylamide lysergic acid (12.2.15), is synthesized by esterification of D-lysergic acid using 2-aminopropanol in dimethylformamide and direct treatment of the reaction mixture with phosgene [53–59].

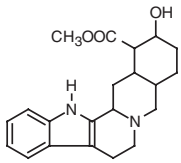


12.2.15

Ergonovine does not exhibit significant α-adrenoblocking activity. However, like ergotamine, it is used in gynecological–obstetrical practice for stopping postnatal bleeding. The most likely mechanism of action is the direct spasmogenic effect on the uterus. Synonyms of ergonovine are ergometrine and ergotren.

12.2.5 Selective α_2-adrenoblockers

Yohimbine: Yohimbine is methyl ether (±)-2α-hydroxyyohimban-1α-carboxylic acid (12.2.16). It is isolated from the plants *Corynanthe johimbe* and *Rauwolfia serpentina* [60,61]. It is also synthesized [62–66].



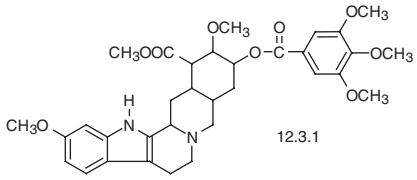
12.2.16

Yohimbine is a selective α_2-adrenergic antagonist. It is chemically similar to the alkaloid reserpine. Being a derivative of indolylalkylamine, it selectively blocks α_2-adrenergic receptors. It weakens the negative feedback mechanism of norepinephrine release in nerve endings. It has a sympathomimetic effect, and can also cause sympathomimetic action. Additional research is evidently needed to conclusively delineate its pharmacological action. Currently there are no indications for use. Synonyms of this drug are corimbin, valimbin, and others.

12.3 ADRENERGIC NEURON BLOCKERS

Adrenergic neuron blockers cause degradation of biogenic amines in neuron endings. These drugs can interfere with the synthesis, storage and release of norepinephrine, dopamine, and serotonin.

Reserpine: Reserpine is methyl ester 2α,11-dimethoxy-3-(3,4,5-trimethoxybenzoyloxy)-yohimban-1-carboxylic acid (12.3.1). Reserpine is one of the alkaloids isolated from a perennial shrub of the *Rauwolfia* family [67–72]. It can also be synthesized [73–76].

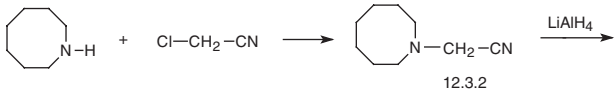


12.3.1

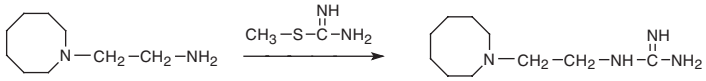
Reserpine causes a breakdown of norepinephrine, dopamine, and serotonin in neuron endings. It weakens intracellular uptake of biogenic amines and reduces the ability if storing them in vesicles. It is possible that reserpine acts on membrane vesicles, irreversibly inhibiting ATP-Mg^{2+} (adenosinetriphosphate) requiring process that is responsible for the uptake of biogenic amines in interneuronal vesicles. Breakdown of catecholamines is expressed by a decreased number of intraneuronal serotonin and dopamine.

Reserpine is used for treating hypertension; however, it is not the drug of choice because of a number of side effects. A number of drugs combined with other hypertensive agents—diuretics in particular—are based on reserpine. Reserpine is prescribed under a number of names, including serpasil, brinerdin, diupres, and others.

Guanethidine: Guanethidine, β-(1-azacyclooctyl)ethylguanidine (12.3.4), is synthesized in the following straightforward manner. Azocine is alkylated by chloracetonitrile, which forms 1-azocinylacetonitrile (12.3.2), which is reduced by lithium aluminum hydride into 1-(2-aminoethyl)azocine (12.3.3). Reacting this with *S*-methylthiourea gives guanethidine (12.3.4) [77–79].



12.3.2



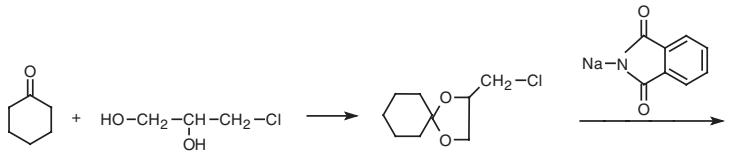
12.3.3 12.3.4

Unlike adrenoblockers, guanethidine does not act on effector cells. It acts on branched ends of sympathetic peripheral nerve fibers and permeates into the neuron by the same mechanism of reverse uptake that returns norepinephrine from the synaptic cleft to neuron endings. Inside the neuron, guanethidine accumulates and competes with norepinephrine for storage space as granules. With an increase in guanethidine concentration, norepinephrine is replaced and thus the quantity of neurotransmitters capable of being released is reduced. In response to stimulation, the nerve may release guanethidine, which, however, is not an adrenergic receptor stimulant. In addition to this disturbance and the presence of stores of catecholamines in adrenergic nerve endings, guanethidine also acts on the stores of catecholamines in organs such as the heart, spleen, and aorta.

Since it does not pass through the blood–brain barrier, it does not act on the central sympathetic neurons.

Guanethidine is used for severe hypertension, where use of more universally accepted drugs is not successful. It is a very powerful and long-lasting drug, and its effects last for 2–3 days after using it. Synonyms of this drug are octadin, ismelin, sanotensin, and others.

Guanadrel: Guanadrel, (1,4-dioxaspiro[4,5]dec-2-ylmethyl)guanidine (12.3.8), is synthesized when cyclohexanone undergoes ketalization by 3-chloro-1,2-proandiol, forming 2-chloromethyl-1,4-dioxyspiro[4,5]decane (12.3.5), which is further akylated by sodium phthalimide. After alkyline hydrazinolysis, the resulting phthalimide derivative (12.3.6) is transformed into 2-aminomethyl-1,4-dioxyspiro[4,5]decane (12.3.7), which is reacted with *S*-methylthiourea, giving the desired guanadrel (12.3.8) [80–82].

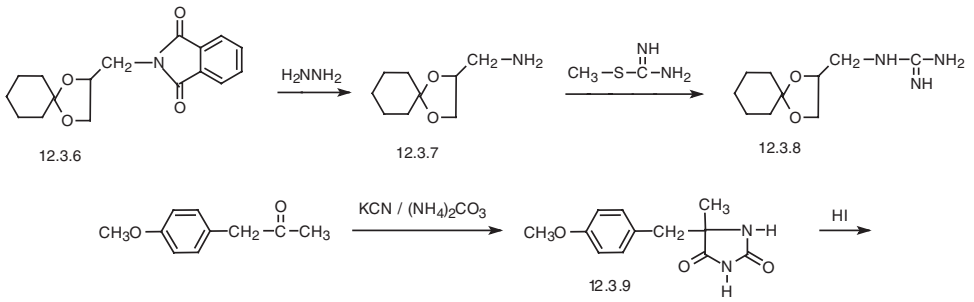


12.3.5

Guanadrel is an adrenergic neuron blocker used for essential hypertension. The mechanism of action and side effects are similar to guanethidine.

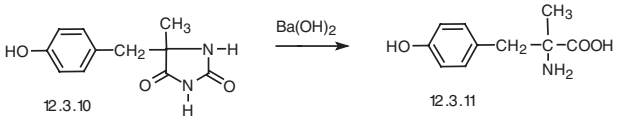
It is used for treating hypertension in patients who do not respond to thiazide diuretics. It can be used as an adjuvant drug in thiazide treatment for reaching an optimal level of blood pressure. A synonym of this drug is hylorel.

Metyrosine: Metyrosine, (–)α-methyltyrosine (12.3.11), is synthesized in a few different ways, the simplest of which is the synthesis from 4-methoxybenzylacetone, which is reacted with potassium cyanide in the presence of ammonium carbonate to give the hydantoin (12.3.9). Treating this with hydrogen iodide removes the methyl-protecting group on the phenyl hydroxyl group and the product (12.3.10) is hydrolyzed by barium hydroxide into a racemic mixture of α-methyl-D,L-tyrosine, from which the desired L-isomer is isolated (12.3.11) [83–86].



12.3.6 12.3.7 12.3.8

12.3.9



Metyrosine is the α-methyl derivative of tyrosine. It competitively inhibits tyrosine hydroxylase action, thus reducing the formation of epinephrine and norepinephrine.

It is used for treating patients with pheochromocytoma, in cases where a rise in the level of catecholamines is observed. A synonym of this drug is demser.

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– 13 –

Cholinomimetics

Cholinomimetics or cholinergic drugs are those drugs that cause effects similar to those resulting from introduction of acetylcholine, or simulation of ganglions of the parasympathetic nervous system. These drugs imitate action of endogenously released acetylcholine. It is known that the effect of acetylcholine in certain organs can be reproduced by the alkaloid muscarine, and in other organs by the alkaloid nicotine. The division of cholinoreceptors into so-called mucarinic (M-cholinoreceptors) and nicotinic (N-cholinoreceptors) is based on this observation. Cholinoreceptors in certain locations have different sensitivities to different drugs.

There are more than 10 billion neurons that make up the human nervous system, and they interact with one another through neurotransmitters. Acetylcholine, a number of biogenic amines (norepinephrine, dopamine, serotonin, and in all likelihood, histamine and norepinephrine), certain amino acids and peptides, and adenosine are neurotransmitters in the central nervous system. Amino acid neurotransmitters are glutamic and aspartic acids that excite postsynaptic membrane receptors of several neurons as well as γ-aminobutyric acid (GABA) and glycine, which are inhibitory neurotransmitters. Endorphins, enkephalins, and substance P are considered peptidergic transmitters. There are many compounds that imitate the action of these neurotransmitters.

Acetylcholine is the primary neurotransmitter in the parasympathetic division of the autonomic nervous system, which mainly innervates the gastrointestinal tract, eyes, heart, respiratory tract, and secretory glands. Although its receptors are crucial for maintaining all normal functions of the body, an extremely small number of illnesses can be explained by the dysfunction of cholinergic regions of the peripheral autonomic system.

Although acetylcholine itself is a substance without which normal body function would not be possible, two properties make it extremely undesirable for use as medicinal agents. First, its action is very brief because of the rapid breakdown by cholinesterases, and second—and more importantly—the diversity of action, which makes it practically impossible to make its action specific in accomplishing certain tasks. However, a number of acetylcholine derivatives are more resistant to cholinesterase action and can have more selective action. Thus, cholinomimetics are those drugs that imitate action of endogenously released acetylcholine. Cholinergic receptors are coupled to G proteins (intramembrane transducers that regulate second messengers). Classifications of these drugs are based on the mechanism of their action, which is exhibited either by direct stimulation of

cholinergic receptors by choline esters or cholinomimetic alkaloids, or in an indirect manner of inhibiting acetylcholinesterases, which are enzymes responsible for the chemical decomposition of acetylcholine. These, in turn, are subdivided into reversible cholinesterase inhibitors and irreversible cholinesterase inhibitors.

So, parasympathetic nerves use acetylcholine as a neurotransmitter and cholinomimetic drugs mimic the action of acetylcholine at its receptors. Muscarinic receptor subtypes are found on neuroeffector junctions. Nicotinic receptor subtypes are found on ganglionic synapses. Cholinomimetics can be classified as:

1. Direct-acting (receptor agonists), acting on muscarinic and nicotinic receptors.
2. Indirect-acting (cholinesterase inhibitors), which, in turn, can be reversible or irreversible.

Muscarinic receptor agonists are drugs that mimic acetylcholine at neuroeffector junctions of PNS and in general act on smooth muscles of eye to constrict the pupil (miosis), contracts ciliary and muscles consequently used mainly in ophthalmology for cataract surgery (causes rapid miosis), decreases intraocular pressure by opening drainage angle of anterior chamber of eye, used to treat glaucoma. At the same time they selectively stimulate urinary and gastrointestinal tracts, facilitating emptying of neurogenic bladder in patients after surgery or parturition or with spinal cord injury. Nicotinic receptor agonists mimic the effects of acetylcholine at nicotinic receptors on autonomic ganglionic synapses and skeletal neuromuscular junctions. They have no therapeutic action but important for their toxicity. The single case of medical usefulness is their use as a transdermal patch or as chewing gum for cessation of smoking.

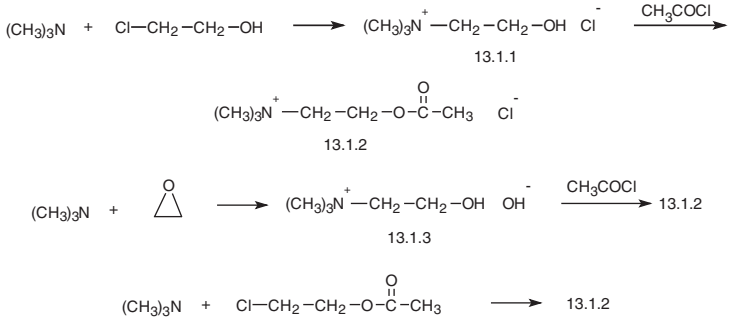
13.1 DIRECT-ACTING CHOLINOMIMETICS

Direct-acting cholinomimetics are drugs that act directly by stimulating cholinergic receptors. These drugs are divided into drugs that stimulate muscarinic (M-cholinoreceptors) or nicotinic (N-cholinoreceptors) receptors. Drugs whose efficacy is primarily connected to stimulation of muscarinic receptors, including choline esters, i.e. acetylcholine and its structural analogues, which are methacholine, carbacholine, betanechol, and natural alkaloids muscarine and pilocarpine. Drugs whose action is based on stimulation of nicotinic receptors include the alkaloids nicotine and lobeline.

13.1.1 Choline esters

Drugs of this class include acetylcholine and its structural analogues: methacholine, betanechol, and carbacholine. Despite the fact that these drugs are able to directly stimulate all cholinergic receptors, their therapeutic efficacy is mediated by reaction with muscarinic receptors (subtypes M_1 and M_2). The only difference between these drugs is their duration of action, and to some extent selectivity for receptors. Acetylcholine is the prototype of all groups. Selective M_1 and M_2 agonists are currently not used for therapeutic use.

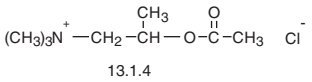
Acetylcholine: Acetylcholine, 2-acetoxy-*N*,*N*,*N*-trimethylethyl ammonium chloride (13.1.2), is easily synthesized in a number of different ways. For example, 2-chloroethanol is reacted with trimethylamine, and the resulting *N*,*N*,*N*-trimethylethyl-2-ethanolamine hydrochloride (13.1.1), also called choline, is acetylated by acetic acid anhydride or acetylchloride, giving acetylcholine (13.1.2). A second method consists of reacting trimethylamine with ethylene oxide, giving *N*,*N*,*N*-trimethylethyl-2-ethanolamine hydroxide (13.1.3), which upon reaction with hydrogen chloride changes into the hydrochloride (13.1.1), which is further acetylated in the manner described above. Finally, acetylcholine is also formed by reacting 2-chloroethanol acetate with trimethylamine [1–7].



Acetylcholine is a choline molecule that has been acetylated at the oxygen atom. Because of the presence of a highly polar, charged ammonium group, acetylcholine does not penetrate lipid membranes. Because of this, when the drug is introduced externally, it remains in the extracellular space and does not pass through the blood–brain barrier.

Acetylcholine does not have therapeutic value as a drug for intravenous administration because of its multi-faceted action and rapid inactivation by cholinesterase. Likewise, it is possible for a collaptoid state to develop, and arterial pressure can rapidly fall and the heart can stop. However, it is used in the form of eye drops to cause miosis during cataract surgery, which makes it advantageous because it facilitates quick post-operational recovery. A synonym of this drug is miochol.

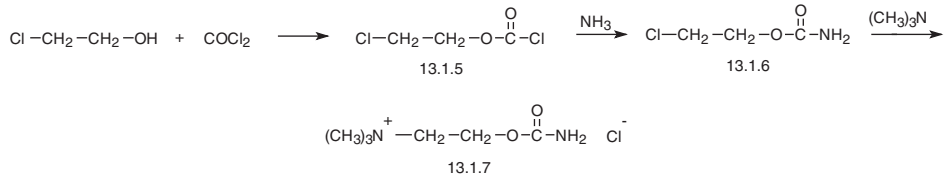
Methacholine: Methacholine, 1-acetoxy-2-(*N*,*N*,*N*-trimethyl)propyl ammonium chloride (13.1.4) or acetyl-β-methylcholine can be synthesized by any of the methods described above [8].



A minor structural change is the presence of a methyl group at the β-carbon atom of choline, which results in two main changes in the pharmacological profile of the molecule. Unlike acetylcholine, methacholine is hydrolyzed only by acetylcholinesterase, and the rate of hydrolysis is significantly less than with acetylcholine. Thus, the action of methacholine is significantly longer lasting than acetylcholine. Moreover, the presence of a methyl group at the β-carbon of choline provides the compound with a greater selectivity of action. Methacholine directly acts on muscarinic receptors of smooth muscle, glands,

and the heart, and it has a very weak effect on nicotinic receptors of the autonomic ganglions of skeletal muscle. These two unique qualities—the duration of action and the increased selectivity—are main differences in the pharmacological action of methacholine and acetylcholine. It is used only for bronchial hyperreactivity diagnostics. A synonym of this drug is provocholine.

Carbachol: Carbachol, 2-carbamoyloxy-*N*,*N*,*N*-trimethylethyl ammonium chloride (13.1.7), is made by reacting 2-chloroethanol with phosgene, which forms 2-chloroethyl chloroformate (13.1.5). Upon reaction with ammonia, it turns into the corresponding amide (13.1.6), which is further reacted with an equimolar quantity of trimethylamine, giving carbachol (13.1.7) [9–13].

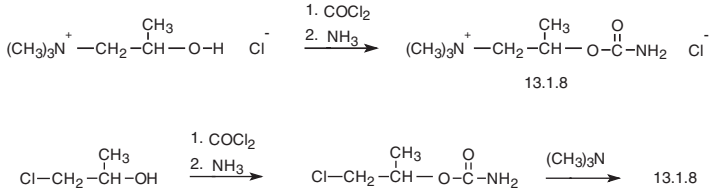


13.1.5 13.1.6 13.1.7

Unlike acetylcholine and methacholine, carbachol contains a carbamino functional group instead of an acetyl group, which is not responsive to hydrolysis by cholinesterase. *In vitro* studies have shown that the rate of hydrolysis is at least twice as slow as that of acetylcholine.

Carbachol is a powerful cholinic ester that stimulates both muscarinic and nicotinic receptors, as well as exhibits all of the pharmacological properties of acetylcholine while in addition resulting in vasodilation, a decrease in heart rate, an increase in tone and contractability of smooth muscle, stimulation of salivary, ocular, and sweat glands as well as autonomic ganglia and skeletal muscle. For this reason, use of carbachol, like acetylcholine, is limited. The exception is that it is used in ophthalmological practice and postoperational intestines and bladder atony. Upon administration in the eye, the pupil constricts and the intraocular pressure is reduced. It is used for severe chronic glaucoma. Synonyms of this drug are doryl and miostat.

Betanechol: Betanechol, 2-carbamoyloxy-1-(*N*,*N*,*N*-trimethyl)propyl ammonium chloride (13.1.8), is made by either the subsequent reaction of 1-(*N*,*N*,*N*-trimethylammonium) propan-2-ol with phosgene, followed by ammonia, or by a completely analogous synthesis of carbachol by the reaction of 1-chloro-2-propanol with phosgene followed by consequent reactions with ammonia, and then with trimethylamine, giving betanechol (13.1.8) [14,15].

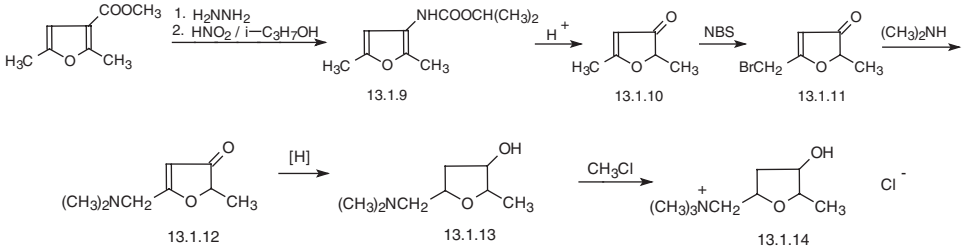


Bentanechol is a drug, which has structurally unique qualities of both methacholine and carbachol, i.e. it contains both β-methyl and carbamate functional groups, and quite logically exhibits pharmacological properties of both the drugs. It is resistant to hydrolysis by cholinesterases and has a very minor effect on nicotinic receptors of the autonomic ganglia and neuromuscular junctions. Betanechol has more of a selective action on muscarinic receptors of the gastrointestinal tract and the bladder than do other cholinic esters.

Therapeutic action of this drug is based on this action, and it is used for treating postoperational non-obstructive retention of urine and neurogenic bladder atony. Earlier, it was used for treating gastrointestinal illnesses and Alzheimer's disease. Synonyms of this drug are duvoid, miotonin, and urecholine.

13.1.2 Natural muscarinic alkaloids

Muscarine: Muscarine, 2-methyl-3-hydroxy-5-(*N*,*N*,*N*-trimethylammonium) methylentetrahydrofuran chloride (13.1.14), was first isolated from the poisonous mushrooms *Amanita muscaria*. It can be synthesized in various ways from completely different substances [16–24], particularly from 2,5-dimethyl-3-carboxymethylflurane, which undergoes a Curtius reaction, i.e. successive reactions with hydrazine and further with nitrous acid in isopropyl alcohol, which forms the urethane (13.1.9), the acidic hydrolysis of which gives 2,5-dimethyl-2*H*-furane-3 (13.1.10). Allylic bromination of this gives 2-methyl-5-bromomethyl-2*H*-furanone-3 (13.1.11), which is reacted with dimethylamine, forming 2-methyl-5-dimethylaminomethyl-2*H*-fluranone-3 (13.1.12). Reducing this compound leads to formation of 2-methyl-3-hydroxy-5-dimethylaminomethyltetrahydroflurane (13.1.13), the reaction of which with methyl chloride gives muscarine (13.1.14) as a mixture of stereoisomers.

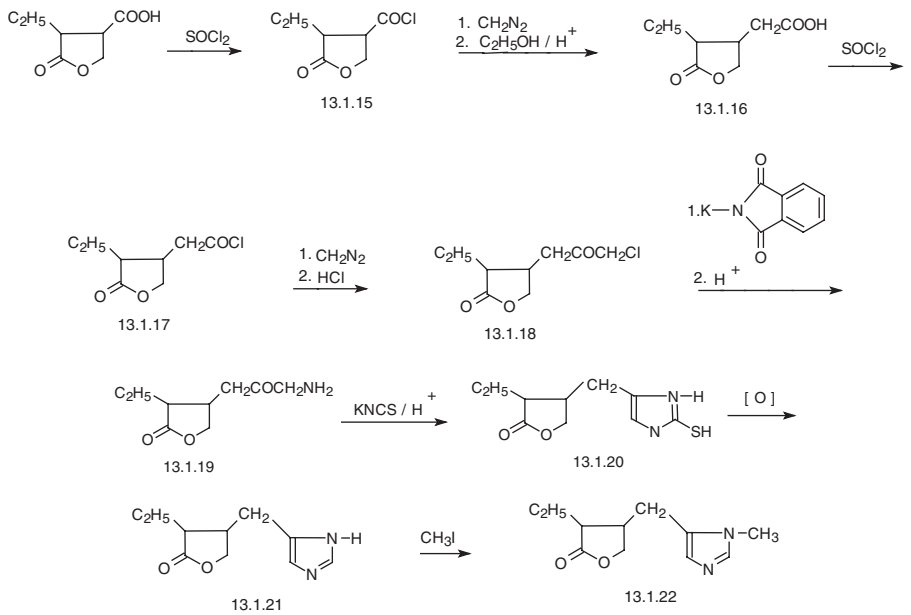


Muscarine is a natural alkaloid that is found in a number of wild mushrooms. Despite the fact that muscarine does not have any therapeutic value, it is of interest because of its expressed toxic properties, which made it one of the first systematically studied cholinomimetic substances. This compound was an underlying classification of cholinergic muscarinic receptors. The action of muscarine is similar to that of acetylcholine on peripheral autonomic effector organs, and atropine is an antagonist to it. Unlike acetylcholine, muscarine does not act on nicotinic receptors.

Mushroom poisoning requires serious medical intervention because muscarine absorbs well in the gastrointestinal tract, and therefore it can lead to death. Muscarine is considerably more powerful than acetylcholine, possibly because of its high stability. Because it is

not an ester, it does not undergo hydrolysis by cholinesterase. It does not have any therapeutic use. Mushroom poisoning is treated with atropine sulfate.

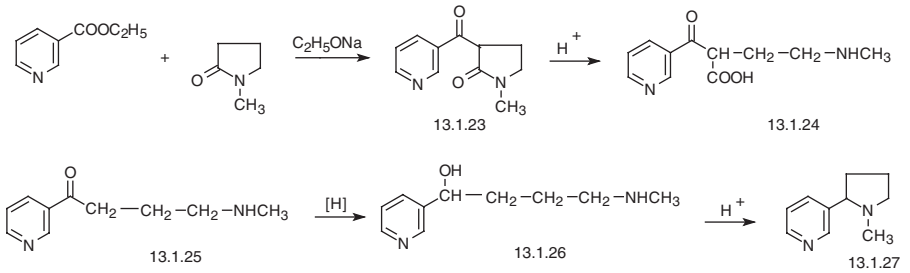
Pilocarpine: Pilocarpine, 3-ethyl-4-(1-methyl-5-imidazolymethyl)tetrahydrofuran-2-one (13.1.22), is an alkaloid that is made from leaves of the tropic plant *Pilocarpus jaborandi*. It is synthesized in a few different ways [25–32], the most relevant of which seems to be from 2-ethyl-3-carboxy-2-butyrolactone [25–27], which with the help of thionyl chloride is turned into the acid chloride (13.1.15) and further reacted with diazomethane and ethanol, to give the corresponding ethyl ester (Arndt–Eistert reaction), which is hydrolyzed into the acid (13.1.16). The resulting acid (13.1.16) is again changed into the acid chloride (13.1.17) by thionyl chloride. The obtained acid chloride is treated with diazomethane. But in this case the intermediate forming ketene is treated with hydrogen chloride to give the chloroketone (13.1.18). Reacting this with potassium phthalimide and subsequent removal of the phthalimide protecting group by acid hydrolysis gives the aminoketone (13.1.19), which is reacted with an acidic solution of potassium thiocyanate, forming 3-ethyl-4-(2-mercapto-5-imidazolylmethyl)tetrahydrofuran-2-one (13.1.20). Mild oxidation of this product allows to remove the mercapto- group from the product (13.1.20), giving 3-ethyl-4-(5-imidazolylmethyl)tetrahydrofuran-2-one (13.1.21). Alkylation of the resulting product with methyl iodide leads to the formation of pilocarpine (13.1.22).



Pilocarpine acts by stimulating muscarinic receptors, therefore making it similar in action to acetylcholine when systematically introduced. This compound differs from acetylcholine in that it does not react with any nicotinic receptors, but by stimulating the CNS. Its effects are blocked by atropine. It has found therapeutic use in ophthalmology as a myotic agent. Synonyms are pilopine, isopto carpine, and atmocaprine.

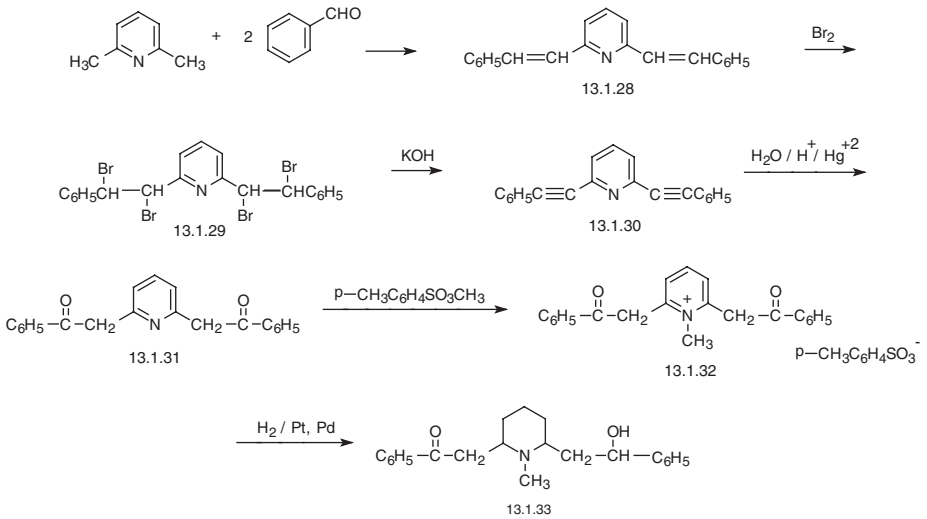
13.1.3 Natural nicotinic alkaloids

Nicotine: Nicotine, 1-methyl-2-(3-piridyl)pirrolidine (13.1.27), is an alkaloid that is isolated from the plant *Nicotiana* (*Nicotiana tabacum, Nicotiana rustica*, and others) and can be synthesized in various ways [33–36]. In particular, it is proposed to proceed from nicotinic acid ethyl ester, which is condensed with *N*-methylpyrrolidone, giving 1-methyl-2-nicotinoyl pyrrolidone-2 (13.1.23). Acidic hydrolysis of this compound leads to an opening of the pyrrolidine ring giving the intermediate (13.1.24), which under the reaction conditions is decarboxylated to the γ-aminoketone (13.1.25). The carbonyl group is reduced to an alcohol and the resulting product (13.1.26) undergoes dehydration to nicotine (13.1.27).



Nicotine has been intensively studied for a number of reasons. It has been used in pharmacology in experiments for characteristics of cholinergic nicotinic receptors and for stimulating and blocking autonomic ganglia. Today, nicotine is an object of attention because of its abundant presence in tobacco, which is a risk factor for a number of illnesses. Nicotine acts by reacting with peripheral cholinergic nicotinic receptors in the postsynaptic membrane in autonomic ganglia and neuromuscular junctions as well as with nicotinic receptors in the CNS. In small doses (such as in smoking a cigarette), nicotine stimulates receptors, thus causing depolarization of the membrane and a flow of sodium and calcium ions. In large doses, stimulation is accompanied by prolonged blockage of repolarization. This causes a lack of response of receptors to subsequent stimulation by acetylcholine, which is released from preganglionic cholinergic tissue, which results in a blockage of nerve transmission. This occurrence is characterized as a depolarized ganglionic blockage. The only therapeutic use of nicotine is as an ingredient of chewing gum as a temporary drug when trying to quit smoking. A synonym of this drug in salicylate form is endernol.

Lobeline: Lobeline, 1-methyl-2-(β-hydroxy-β-phenylethyl)-6-phenacylpiperidine (13.1.33), is the primary alkaloid of leaves from *Lobelia inflata*. It is synthesized by condensation of 2,6-dimethylpyridine with two moles of benzaldehyde, giving α,α'-distyrylpyridine (13.1.28) [37–39]. Exhaustive bromination of this product and subsequent dehydrobromination of the resulting tetrabromo derivative (13.1.29) leads to the formation of α,α'-diphenylethinylpyridine (13.1.30). Hydration of the triple bonds of the product (13.1.30) gives α,α'-diphenacylpyridine (13.1.31). Reacting this with methyl *p*-toluenesulfonate gives α,α'-diphenacylpyridinium *N*-methyl-*p*-toluenesulfonate (13.1.32), which is carefully reduced by hydrogen into the desired lobeline (13.1.33) using simultaneously palladium and platinum catalysts. The product is a racemic mixture from which the levorotatory isomer can be isolated if necessary.



The action of lobeline is in many respects similar to nicotine; however, it is 50–100 times weaker than nicotine. It is also first, a stimulant, and second, a depressant of sympathetic ganglia, parasympathetic ganglia, adrenal glands, and others. It can be used as a drug to assist with quitting smoking. Synonyms of this drug are lobron, ventaron, unilobin, lobeton, and others.

13.2 INDIRECT-ACTING CHOLINOMIMETICS

Cholinesterase inhibitors are a very important class of compounds related to cholinomimetics. Besides their therapeutic importance, a few of them are used as pesticides in agriculture, and the most toxic are used as chemical poisoning agents. Use of these substances is based on changes that take place after inactivation of cholinesterase or pseudocholinesterase (a less specific enzyme), i.e. effects observed as a result of acetylcholine buildup in neuro-effector compounds. Cholinesterase inhibitors are classified both by their chemical structure as well as by the type of their chemical reaction with the enzyme, which determines their temporary action.

There are three main classes of cholinesterase inhibitors. They are carbamates, physostigmine, neostigmine, pyridostigmine, and a number of insecticides, such as carbaryl quaternary amines, such as endorphonium, ambenonium, and demecarium, organophosphates, such as isofurophate, echothiophate, insecticides like malathione and parathione, and also militant poisoning substances like zoman. Cholinesterases can be classified as reversible or irreversible inhibitors based on the difference in duration of their inhibitory effects. Reversible inhibitors are carbamates and quaternary amines. Indirect-acting cholinomimetic drugs, such as anticholinesterase drugs are inhibitors of acetylcholine metabolism and have similar effects to direct-acting cholinomimetics.

Clinical use of reversible inhibitors is directed to eye, skeletal muscle, neuromuscular junctions, gastrointestinal tract, urinary tract, respiratory tract, and heart and used in treatment of glaucoma (an ocular disease caused by increased intraocular pressure due to inadequate drainage of aqueous humor at filtration angle), myasthenia gravis (an autoimmune disease

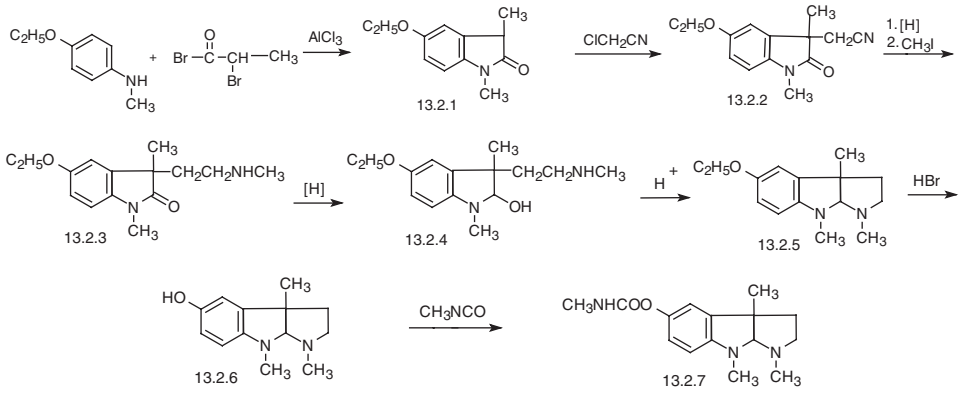
resulting in destruction of nicotinic receptors), stimulation of gastrointestinal and urinary tract motility, reversal of neuromuscular blockade, and atropine poisoning. Irreversible cholinesterase inhibitors are organophosphates.

13.2.1 Reversible cholinesterase inhibitors

Reversible cholinesterase inhibitors form a transition state complex with the enzyme, just as acetylcholine does. These compounds are in competition with acetylcholine in binding with the active sites of the enzyme. The chemical structure of classic, reversible inhibitors physostigmine and neostigmine shows their similarity to acetylcholine. Edrophonium is also a reversible inhibitor. These compounds have a high affinity with the enzyme, and their inhibitory action is reversible. These inhibitors differ from acetylcholine in that they are not easily broken down by enzymes. Enzymes are reactivated much slower than it takes for subsequent hydrolysis of acetylcholine to happen. Therefore, the pharmacological effect caused by these compounds is reversible.

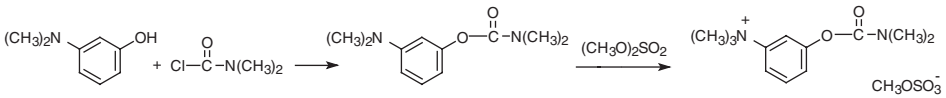
13.2.2 Carbamates

Physostigmine: Physostigmine, 1,3a,8-trimethyl-2,3,3a,8a-tetrahydropyrrolo[2,3-b]-indol-5-yl-*N*-methylcarbamate (13.2.7), is an alkaloid isolated from the so-called grand beans—seeds of the poisonous African plant of the familia *Physostigma venenosum*. Physostigmine is made synthetically in various ways [40–42], one of which being from *p*-ethoxymethylaniline, which is reacted with α-bromopropionyl bromide in the presence of aluminum chloride, giving 1,3-dimethyl-5-ethoxyindolin-2-one (13.2.1). Reacting this with chloracetonitrile in the presence of sodium ethoxide gives 1,3-dimethyl-5-ethoxy-3-cyanomethylindolin-2-one (13.2.2). The nitrile group is reduced to an amine group, which is further methoxided, giving 1,3-dimethyl-5-ethoxy-3-(β methylaminoethyl) indolin-2-one (13.2.3). The carbonyl group of this compound is reduced, forming an aminoalcohol (13.2.4), the dehydration of which leads to formation of 1,3a,8-trimethyl-2,3,3a,8a-tetrahydropyrrolo[2,3b]-5-ethoxyindol (13.2.5). The ethoxy-protecting group is removed by hydrogen bromide, giving a compound with a phenol hydroxyl group (13.2.6), which is reacted with methylisocyanate, giving the desired physostigmine (13.2.7).



Physostigmine is easily absorbed from the gastrointestinal tract and other mucous membranes. Upon entering the bloodstream, it easily permeates the blood–brain barrier. It is inactivated by cholinesterase of the plasma. Physostigmine has a minimal direct effect on cholinesterase receptors. Because of its ability to diffuse into the CNS, it is used as an antidote for toxic concentrations in the organism of drugs with anticholinergic properties such as atropine, antihistamines, phenothiazines, and tricyclic antidepressants. Its action on the organism is basically similar to that of acetylcholine, and it is used for the same indications in ophthalmology for constricting the pupil and lowering ocular pressure in glaucoma. Synonyms of this drug are eserine and mezithinonone.

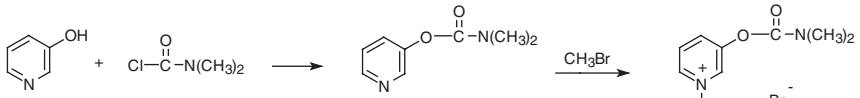
Neostigmine: Neostigmine, *N*,*N*,*N*-trimethyl-*meta*-(dimethylcarbomoyloxy)-phenylammonium methylsulfonate (13.2.9), which can be viewed as a simplified analog of physostigmine, is made by reacting 3-dimethylaminophenol with *N*-dimethylcarbamoyl chloride, which forms the dimethylcarbamate (13.2.8), and its subsequent alkylation using dimethylsulfate forming the desired compound (13.2.9) [43].



13.2.8 13.2.9

Neostigmine is a cholinesterase inhibitor that contains a quaternary nitrogen atom, and as a result it does not easily pass through the blood–brain barrier, thus having minimal toxicity on cholinesterase inhibition in the brain. The presence of a quaternary nitrogen atom in the molecule leads to other significant differences between physostigmine and neostigmine, the main difference being that neostigmine, besides cholinesterase inhibition, has a direct stimulatory effect on cholinergic receptors. However, with the exception of these serious differences, the general action of neostigmine is analogous to the action of physostigmine. Like other reversible cholinesterase inhibitors, neostigmine exhibits powerful antimuscle relaxant action. This property of neostigmine is used in anesthesiology for overcoming paralysis of skeletal muscle caused by muscle relaxants. Neostigmine is primarily used in myasthenia, motor damage after brain trauma, paralysis, for atrophy of the optic nerve, and for treating atony of the bowels and urinary bladder. Synonyms of this drug are prozerin, prostigmin, stigmosan, and others.

Pyridostigmine: Pyridostigmine, 3-[(dimethylaminocarbonyl)oxy]-1-methyl pyridinium bromide (13.2.11), is synthesized from 3-hydroxypiridine, which is reacted with dimethylaminocarbamoyl chloride, which gives 3-(dimethylaminocarbamoyl)piridine (13.2.10). The last is reacted with methylbromide, giving pyridostigmine (13.2.11) [44].

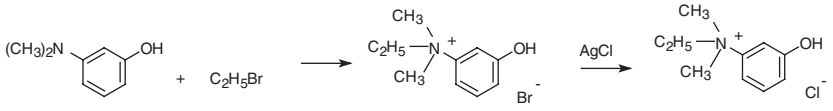


13.2.10 13.2.11

Qualitatively, the pharmacological properties of pyridostigmine are analogous to neostigmine. A synonym of this drug is mestinon.

13.2.3 Quaternary amines

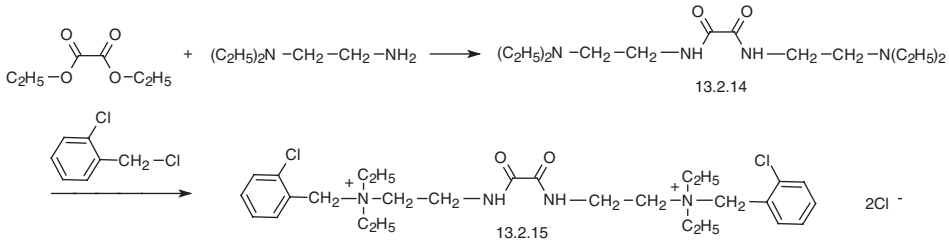
Edrophonium: Edrophonium, ethyl-(3-hydroxyphenyl)dimethylammonium chloride (13.2.13), is made by reacting 3-dimethylaminophenol with ethylbromide, which forms ethyl(3-hydroxyphenyl)dimethylammonium bromide (13.2.12), the bromine atom of which is replaced with a chlorine atom by reacting it with silver chloride, giving edrophonium (13.2.13) [45].



13.2.12 13.2.13

Pharmacologically, edrophonium is also similar to neostigmine; however, it begins to act quicker and is shorter lasting. A synonym of this drug is tensilon.

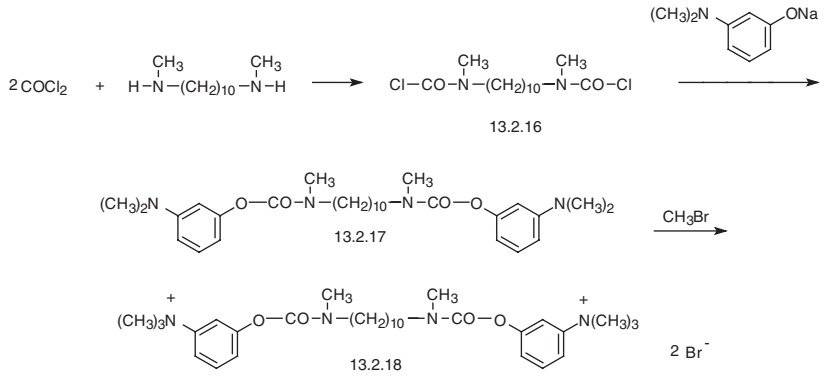
Ambenonium: Ambenonium, [oxalyl-*bis*-(iminoethylen)]-*bis*-[*ortho*-(chlorobenzyl) diethylammonium] chloride (13.2.15), is made by reacting diethyloxalate with two moles of *N*,*N*-diethylethylendiamine, forming oxalyl-*bis*-(iminoethylen)-*bis*-*N*,*N*-diethylamine (13.2.14), which is alkylated by two moles of 2-chlorobenzylchloride, giving ambenonium (13.2.15) [46–48].



13.2.14 13.2.15

The pharmacological properties of ambenonium are similar to neostigmine and pyridostigmine, and it works by reversible inactivation of cholinesterase. A synonym of this drug is ambenonium.

Demecarium: Demecarium, *N*,*N*′-decamethylene-bis-[*meta*-(*N*-methylcarbamoyloxy)-phenyl-trimethylammonium] hydroxide (13.2.18), is made by reacting two moles of phosgene with 1,10-*bis*-(methylamino)-decano(*N*,*N*′-dimethyldecamethylen-1,10-diamine, giving the *bis*-carbamoylchloride (13.2.16), which is transformed into *bis*-carbamoylester (13.2.17) by reaction with two moles of the 3-dimethylaminophenol sodium salt. Reacting this with methylbromide gives demecarium (13.2.18) [49].



Demecarium is a disymmetrical compound that contains two ammonium and two carbamate groups. It is a reversible cholinesterase inhibitor that is longer lasting than the others. It is used to constrict pupils, elevate intraocular pressure in treating glaucoma, and also for alleviating atropine mydriasis. Synonyms of this drug are tosmilen and humorosl.

13.2.4 Irreversible cholinesterase inhibitors

Organophosphates: The second class of cholinesterase inhibitors is made up of organophosphorous compounds with the general formula:



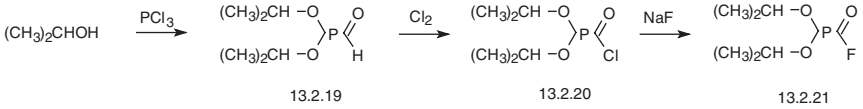
Organophosphorous compounds act by forming a complex with the hydroxyl group of serine of the cholinesterase enzyme, thus forming a covalent bond with the phosphorous atom.

Unlike the rapid hydrolysis of the acetylcholine complex with the enzyme and the somewhat slower hydrolysis of the carbamate complexes, organophosphorous enzymes react very slowly with water, which generally leads to irreversible inhibition of the enzyme. Upon using most organophosphoric substances in the organism, new synthesis of enzyme must take place in order to restore cholinesterase activity of the tissue. Despite the fact that such activity is called irreversible, some chemical compounds, such as oximes, can restore the vital functions of the enzyme. However, phosphorylated enzymes also can undergo a process such as deterioration, during which organophosphate loses an alkyl group and makes a stronger, irreversible bond with the enzyme, which makes the enzyme unable to be restored by oximes.

Signs of toxicity are the following: on mild exposure—pupillary constriction, tightness of the chest, watery discharge from the nose, and wheezing; on severe exposure— more intensified symptoms, visual disturbances, muscle fasciculation, bronchoconstriction and pulmonary edema, pronounced muscle weakness, shallow respiration, vomiting and diarrhea, CNS effects, anxiety, headache, tremor, seizures, depression, and death. Signs and symptoms of severe toxicity caused by introduction of organophosphorous anticholinesterase compounds can be easily predicted and explained by the hyperactivity of the parasympathetic nervous system, neuromuscular junctions, autonomic ganglia, and

cholinergic nerves of the CNS. Death results from respiratory depression caused by CNS depression, and paralysis of the diaphragm and intercostals because of the accumulation of excess acetylcholine. A few organophosphates are useful as medical drugs, and others as insecticides and potential chemical weapons because of their high toxicity.

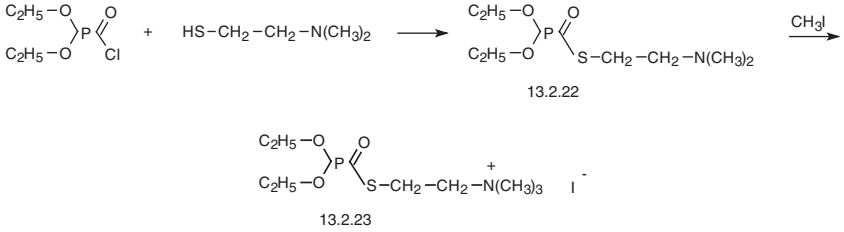
Isoflurophate: Isoflurophate, the di-*iso*-propyl ester of fluorophosphoric acid (13.2.21), is made by reacting *iso*-propyl alcohol with phosphorous trichloride, forming di-*iso*-propylphosphite (13.2.19), which is chlorinated to (13.2.20), and further reacted with sodium fluoride to replace the chlorine atom with fluorine, thus giving isofluorophate (13.2.21) [50].



13.2.19 13.2.20 13.2.21

The initial difference between isofluorophate and agents such as physostigmine is the constancy (sluggishness) of its action. According to the possible mechanism described above, isofluorophate causes irreversible inactivation of cholinesterases. It also inactivates acetylcholinesterase and 'nonspecific' cholinesterases of the plasma. However, isofluorophate has a higher affinity with the latter. Isofluorophate is used for treating certain types of glaucoma in which short-lasting myotics are unsuitable. Synonyms of this drug are floropryil, fluostigmine, and diflupyl.

Echothiophate: Echothiophate, *S*-(2-trimethylaminoethyl)-*O*,*O*-diethylthiophosphate (13.2.23), is made by reacting diethylchlorophosphoric acid with 2-dimethylaminoethylmercaptane, giving *S*-(2-dimethylaminoethyl)-*O*,*O*-diethylthiophosphate (13.2.22), which is alkylated by methyliodide, forming echothiophate (13.2.23) [51].



13.2.22 13.2.23

Echothiophate is a phosphorylthiocholine with pharmacological action analogous to that of isofluorophate; however, spontaneous reduction of phosphorylated enzyme occurs faster after using isofluorophate. It is used in various forms of glaucoma. Synonyms of this drug are echodide and phospholine iodide.

13.2.5 Other organophosphorous cholinesterase inhibitors

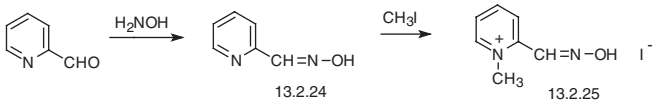
Currently, there are a number of organophosphorous compounds used in everyday life and agriculture as insecticides. Many of them are lipid-soluble compounds that are quickly and completely absorbed in practically every way, including skin as well as respiratory and

gastrointestinal tracts. Most organophosphorous compounds undergo biotransformation through hydrolysis of the ester groups and are excreted with urine. Malthion is widely used in the home and garden and is not very toxic to humans because it is easily hydrolyzed. However, its use is based on the fact that it is hydrolyzed much slower in insects.

Organophosphorous compounds such a zarin, zoman, and tabun are some of the most toxic chemical compounds known that are used as poisonous substances in weapons. They cause rapid deterioration of enzymes and cannot undergo reactivation. Therefore, there is no appropriate therapy for the treatment of such poisons.

Treatment of intoxication of organophosphorous compounds includes artificial respiration, administration of atropine—an antagonist of muscarinic receptors, and administration of pralidoxime, which is a cholinesterase reactivator.

Pralidoxime: Pralidoxime, 2-pyridinaldoxime methylchloride (13.2.25), is synthesized by reacting piridine-2-aldehyde with hydroxylamine, giving piridine-2-aldoxime (13.2.24), which is further reacted with methyliodide, giving the desired pralidoxime (13.2.25) [52–55].



13.2.24 13.2.25

Before aging occurs, patients can be treated with pralidoxime, which breaks the phosphorus–enzyme complex and regenerates the enzyme. Pralidoxime is a strong nucleophile. It reactivates phosphorylated enzymes in a two-staged reaction. First, a complex is formed between the oximate ion and the phosphorylated enzyme. Second, enzyme activity is restored and phosphorylated oxime is formed. The high reactivating ability of pralidoxime is attributed to its ability to combine with a negatively charged group on the surface of an enzyme and a high level of molecular correlation between oxime and phosphorylated cholinesterase. It is possible that oximes may react directly with the inhibitor, turning it into a harmless compound as well as reactivating the inhibitory enzyme both in blood and in tissue. It is used for treating organophosphate poisonings, paralysis of skeletal muscle, and in general for cholinesterase crisis. Synonyms of this drug are contrathione and protopam.

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– 14 –

Anticholinergic Drugs

Anticholinergic drugs are those compounds that exhibit competitive blocking action on cholinergic receptors. This vast group of drugs can be broken down into three subgroups based on their respective specificity to various types of cholinoreceptors. The first group of "classic" anticholinergic agents is represented by the antimuscarinic compounds (atropine, propantheline), which block acetylcholine action, or cholinomimetic drugs introduced to muscarinic M-receptive regions of the CNS and glandular system, myocardium, and smooth muscle. The second group of anticholinergic drugs is represented by ganglioblockers (mecamylamine, trimethaphan), which inhibit cholinergic transmission in the autonomic parasympathetic and sympathetic ganglia by blocking (nicotinic) N-receptors. The third group of anticholinergic drugs is represented by neuromuscular junction blockers (tubocurarine, pancuronium), which block nicotinic N-receptors of skeletal muscle, and they will be examined in Chapter 15, "Muscle relaxants."

14.1 ANTIMUSCARINIC DRUGS

M-cholinoblockers are competitive antagonists of acetylcholine as well as other M-cholinoblockers in terms of postsynaptic M-cholinoreceptors. Parasympathetic cholinergic receptors are localized in smooth muscle of vessels, bronchi, gastrointestinal tract, urinary bladder, heart, ocular muscles, most of the exocrine glands, and in the CNS. M-cholinoblockers exhibit a wide spectrum of pharmacological effects and are used for a number of different indications. They can be used for causing mydriasis or cycloplegia in ophthalmologic research. They are used in pre-operational situations for reducing salivation and preventing bradychardia. These drugs are used for reducing secretion of the gastrointestinal tract in cases of ulcers, spasms, and other gastrointestinal illnesses. They are used for reducing nasopharyngeal and bronchial secretions during respiratory and allergic illnesses, for preventing and relieving motor abnormalities, for treating childhood enuresis and reducing frequency of urination, and for relieving a few symptoms of Parkinsonism. As an antidote, they are used for overdoses of cholinergic drugs, and for anticholinesterase and organophosphorous insecticide and pesticide drug poisoning.

Antimuscarinic drugs are classified in the following manner: alkaloids (atropine, hyocyamine, scopolamine); anticholinergic of the quaternary amine series (anisotropin,

clidinium, glycopyrrolate, hexacyclium, isopropamid, mepenzolat, methanteline, methscopolamine, propantheline); antiparkinsonian drugs of the tertiary amine series (dicyclomine, oxybutynin, oxyphencyclimine); and mydriatics of the tertiary amine series (cyclopentolate, tropicamide).

14.1.1 Alkaloids

The oldest drugs of this group are different galena drugs isolated from belladonna (*Atropa belladonna*), henbane (*Hyoscyamus niger*), and stramonium (*Datura stramonium*). They are all obtained from plants that contain the L-hiocyamine and a somewhat lesser quantity of L-scopolamine. As a muscarinic receptor blocker, L-hioscyamine is much more active that D-hioscyamine on both the periphery as well as on the CNS; however, a racemic mixture of D,L-hioscyamine—known better as atropine—is preferred in the majority of medical cases because it is readily available.

Atropine and its analog scopolamine are two of the most important antimuscarinic drugs. These alkaloids and the compounds derived from them are used in ophthalmology and anesthesiology, in cardiac and gastrointestinal illnesses, and in Parkinsonism. It also is very important as an antidote during anticholinesterase intoxication.

Atropine and scopolamine are esters of tropoyl acid—tropine and scopine, respectively. Scopine differs from tropine only in that it has an expoxide bridge between carbon atoms C_6 and C_7 of tropine.

The subgroups of muscarinic receptors (M_1 and M_2) are activated or blocked by various substances; however, both types of muscarinic receptors are activated by an endogenic neurotransmitter—acetylcholine—and are blocked by atropine or scopolamine. Despite the fact that atropine and scopolamine are reversible cholinoblocking agents, the constants of their dissociation with M-receptors are several times less than acetylcholine. Accordingly, their action is more prolonged (for a few days).

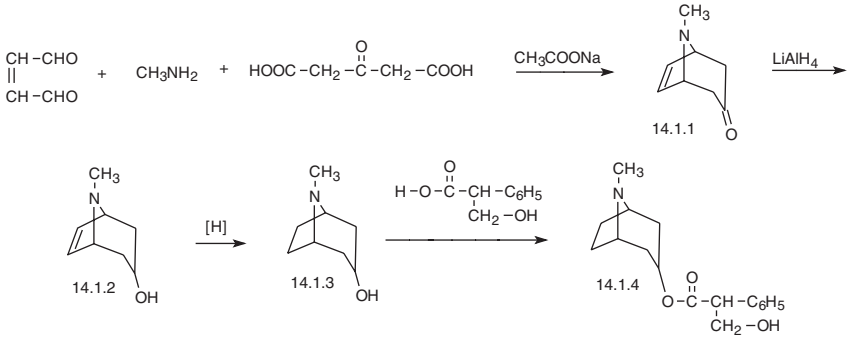
It has been repeatedly observed that atropine is more effective in blocking effects of exogenously introduced acetylcholine and other parasympathomimetics than in blocking effects resulting from stimulation of fibers of the parasympathetic and cholinergic nerves. There are two factors that could be the reason for this:

(a) Acetylcholine is released after nerve impulses in the region very close to M-receptors of effector cells, and consequently it acts more effectively than acetylcholine coming from circulation than parasympathetic substances coming in the same manner.
(b) In certain organs such as the urinary bladder, other neurotransmitters in addition to acetylcholine such as adenosine triphosphate can be released into postganglionic parasympathetic fibers, the action of which is not blocked by atropine.

Belladonna alkaloids have an extremely broad pharmacological spectrum. In addition to their ability to block M-receptors, atropine and scopolamine also act on other receptors, thus showing corresponding effects. They can only block nicotinic cholinergic receptors, however, in significantly larger doses than those used in clinics. Atropine also exhibits properties of local anesthetics and histamine (H_1) receptor blockers. Atropine and

scopolamine are almost completely absorbed from the intestinal track and from the conjunctiva. Scopolamine can be absorbed through the skin.

Atropine: Atropine, the D,L-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester of α-hydroxymethyl phenylacetic acid (14.1.4), can be synthesized by a standard scheme of synthesizing of tropane alkaloids. Condensation of maleyl aldehyde with methylamine and acetonedicarboxylic acid gives tropenone (14.1.1), which is the main starting material for the synthesis of both atropine and scopolamine. The carbonyl group of tropenone is reduced, thus forming tropenol (14.1.2), after which the double bond between C_6 and C_7 of the tropane ring is hydrogenated, giving tropine (14.1.3). Esterification of the tropenol gives the desired atropine (14.1.4) [1–6].



Atropine is used for stomach ulcers, pylorospasms, cholesystis, kidney stones, spasms of the bowels and urinary tract, and bronchial asthma.

Atropine is frequently used during anesthesia in surgery. The main goal is to minimize secretion in the bronchi and nasopharynx, which can impede respiration. In cases where additional sedative action is needed, scopolamine is preferred.

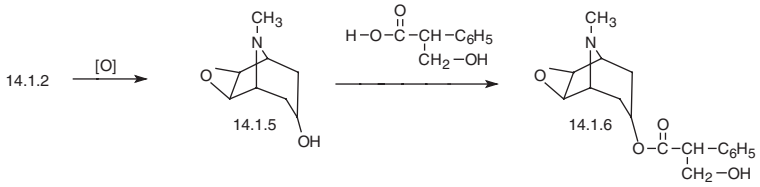
In ophthalmological practice, atropine is used for diagnostic purposes, dilating pupils, for severe inflammatory illnesses, and for eye trauma.

Atropine is often used for colds for temporarily draining the nasopharynx. Atropine is also used in combination with other drugs as an antidote for poisonous anticholinesterase agents such as organophosphorous insecticides and neuroparalytic gases. In such situations, atropine removes or balances toxicities that are a result of a high concentration of acetylcholine.

Atropine was the first effective drug used for symptomatic treatment of Parkinsonism. It has been shown that, unlike gastrointestinal antispasmodics, various synthetic substances such as trihexiphenydil, ethopropazine, benztropine, procyclidine, orphendrine, and biperidene, which pass through the blood–brain barrier are also effective for symptomatic treatment of Parkinsonism. The universally recognized drug levodopa is used for treating Parkinsonism, however, current research has identified certain limitations to its use. Synonyms of this drug are atroptol, atropisol, D,L-hioscyamine, and others.

Scopolamine: Scopolamine, the L-9-methyl-3-oxa-9-azatricyclo[3.2.1.0.^{2,4}]non-7-yl ester of α-hydroxymethylphenylacetic acid (14.1.6), can be synthesized from tropenol (14.1.2) by oxidizing the double bond between carbon atoms C_6 and C_7 of the tropine ring, giving

an epoxide derivative, scopine (14.1.5). Esterification of this product using tropic acid gives scopolamine (14.1.6) [7,8].



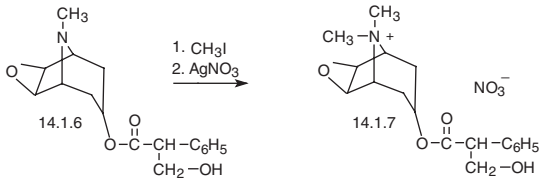
Scopolamine is used for practically the same indications as atropine, but it should be noted that it has a sedative effect on motor activity, and it is recommended for the treatment of Parkinsonian symptoms. Synonyms of this drug are joscyn, oscine, and others.

14.1.2 Anticholinergics of the quaternary amine series

Over the course of the past few decades, a number of synthetic atropine-like substances with more spasmolytic and less anticholinergic action and causing fewer side effects have been used clinically in treating stomach ulcers, pylorospasms, and hyperperistaltics.

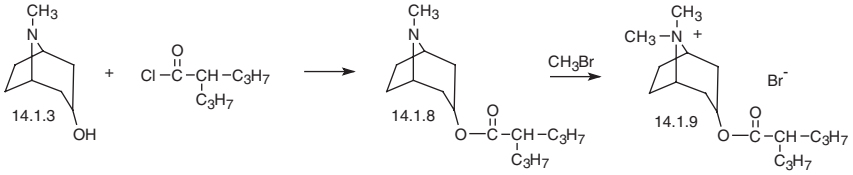
Most of these drugs act using one of three mechanisms: muscarinic blockage, direct suppression of smooth muscle activity, and blockage of parasympathetic ganglia, none of which are devoid of the side effects associated with atropine. The list of these drugs includes a number of quaternary ammonium salts (propantheline, methscopolamine, anisotropin, mepenzolat, isopropamid, glycopyrrolate, clidinium, and hexocyclium).

Methscopolamine: Methscopolamine, 7-(3-hydroxy-1-oxo-2-phenylpropoxy)-9, 9-dimethyl-3-oxa-9-azoniticyclo[3.2.1.0.^{2,4}]nonane nitrate (14.1.7), is synthesized by reacting scopolamine (14.1.6) with methylbromide and sometimes with a subsequent replacement of the bromide ion with a nitrate ion by using silver nitrate [9,10].



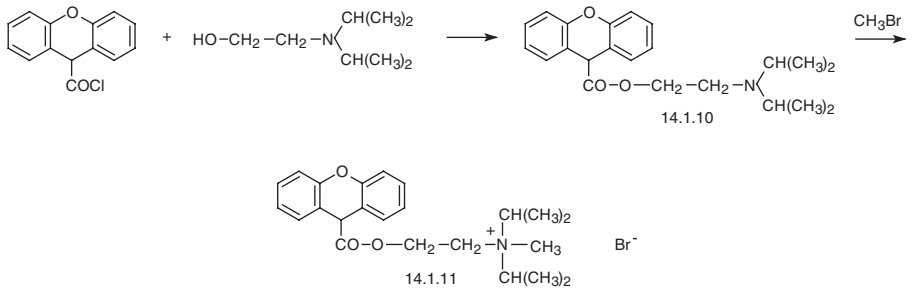
Methscopolamine inhibits the muscarinic action of acetylcholine on postganlionic para sympathetic effector regions. It is used for treating stomach ulcers. Synonyms of this drug are pamine and scoline.

Anisotropine: Anisotropine, the methylbromide of 2-propylpentanoyltropine (14.1.9), is synthesized by the acidifying tropine (14.1.3) with 2-propylvalerianic acid, giving the ester (14.1.8), and subsequent reaction with methylbromide to give anisotropine (14.1.9) [11].



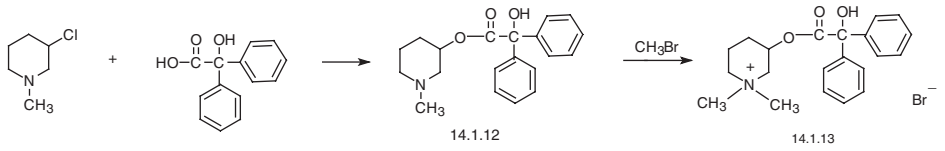
Anisotropine inhibits secretion of digestive juices and restores normal stomach function. It is used for treating stomach ulcers. A synonym of this drug is valpin.

Propantheline: Propanetheline, *N*-methyl-*N*-(1-methylethyl)-*N*-[2-[(9*H*-xanthen-9-ylcarbonyl) oxy]ethyl]-2-propanaminium bromide (14.1.11), is synthesized by reacting xanthen-9-carboxylic acid chloride with 2-di-*iso*-propylaminoethanol, giving the ester (14.1.10), which upon reaction with methylbromide turns into the quaternary salt, propantheline (14.1.11) [12,13].



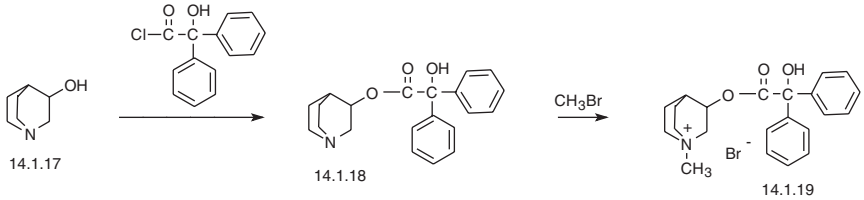
The pharmacological action of propantheline is qualitatively similar to atropine. It has a weaker effect on the CNS than atropine. Unlike atropine, it exhibits greater ganglioblocking action than antimuscarinic action. Moreover, upon overdose it causes neuromuscular curare-like blockage. It is used for treating stomach ulcers. Synonyms of this drug are norpant, propanthel, and robantalin.

Mepenzolate: Mepenzolate, 3-[(hydroxydiphenylacetyl)oxy]-1,1-dimethyl piperidinium bromide (14.1.13), is synthesized by esterification of benzilic acid with 1-methyl-3-chloropiperidine and subsequent reaction of the resulting ester (14.1.12) with methyl bromide [14,15].

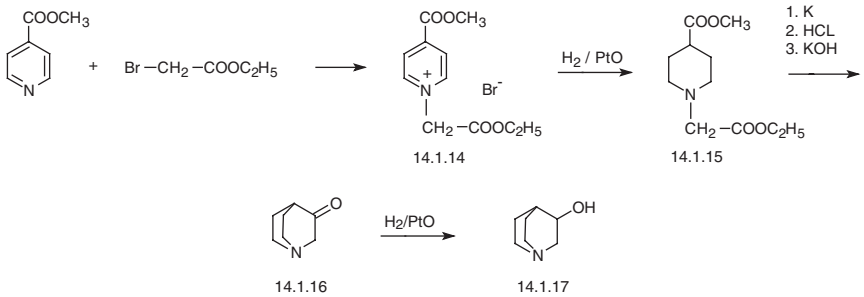


Mepenzolate inhibits muscarinic action of acetylcholine on postganglionic parasympathetic effector regions. It is used in place of other drugs for treating stomach ulcers and inflammation of the intestine. Synonyms of this drug are cantil and eftoron.

Clidinium: Clidinium, 3-benzyloyloxy-1-methylcynuclidinium bromide (14.1.19), is synthesized by reacting 3-hydroxycynuclidine (14.1.17) with the of benzilic acid chloride producing the ester (14.1.18), which if further alkylated at the nitrogen atom by methylbromide, giving clidinium (14.1.19) [16].

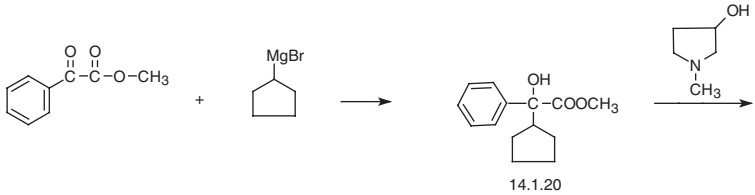


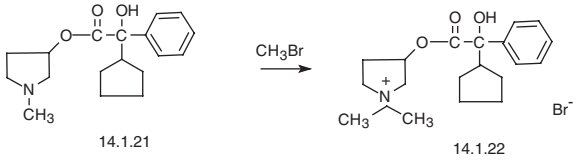
3-Hydroxycynuclidine (14.1.17) is synthesized from the methyl ester of *iso*-nicotinic acid, which is reacted with the ethyl ester of bromoacetic acid to give the piridinium salt (14.1.14). This is reduced by hydrogen using a platinum catalyst, giving 1-carbethoxymethyl-4-carbomethoxypiperidine (14.1.15), from which quinuclidin-3-one (14.1.16) is formed by a Dieckman cyclization using potassium or potassium ethoxide as a base. The carbonyl group of this compound is reduced to an alcohol by hydrogen over platinum oxide, giving 3-hydroxyquinuclidine (14.1.17).



Clidinium inhibits muscarinic action of acetylcholine on postganglionic parasympathetic effector regions. It is used for treating stomach ulcers. A synonym of this drug is quarzan.

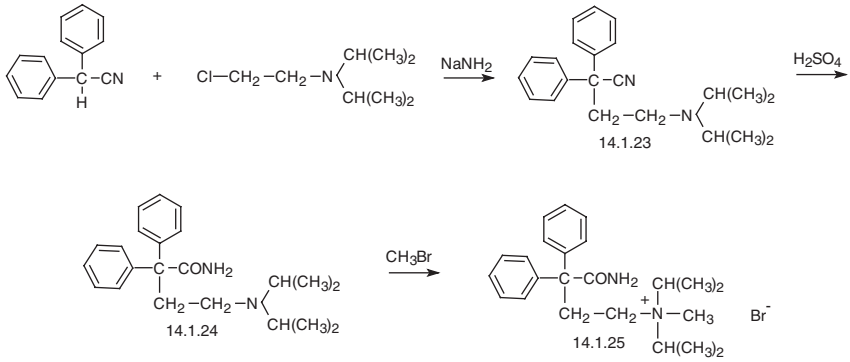
Glycopyrrolate: Glycopyrrolate, 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide (14.1.22), is synthesized from the methyl ester of α-cyclopentylmandelic acid (14.1.20) by transesterification using 3-hydroxy-1-methylpyrrolidine as an alcohol component, which forms the ester (14.1.21), which is further transformed into a quaternary salt upon reaction with methylbromide, giving glycopyrrolate (14.1.22). The starting methyl ester of α-cyclopentylmandelic acid (14.1.20) is synthesized by reacting cyclopentylmagnesiumbromide with the methyl ester of phenylglyoxylic acid [17,18].





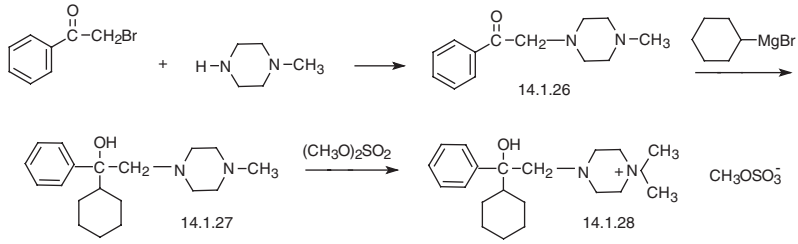
Glycopyrrolate inhibits secretion of digestive juices and restores normal stomach function. It is used for treating stomach ulcers, inflamed intestine, and also as a pre-operational drug for inhibiting excess stomach secretion. A synonym of this drug is robinul.

Isopropamide: Isopropamide, (3-carbamoyl-3,3-diphenylpropyl)di-*iso*-propylmethyl ammonium iodide (14.1.25), is synthesized by alkylating diphenylacetonitrile with di-*iso*-propylaminoethylchloride in the presence of sodium amide, and the subsequent hydrolysis of the nitrile group of the resulting compound (14.1.23) to an amide group (14.1.24). Alkylation of this compound with methyliodide gives isopropamide (14.1.25) [19–22].



Isopropamide inhibits muscarinic action of acetylcholine on postganglionic parasympathetic effector regions. It is used for treating stomach ulcers and inflamed intestine. Synonyms of this drug are darbid and mobadid.

Hexocyclium: Hexocyclium, 4-(β-cyclohexyl-β-hydroxyphenethyl)-1,1-piperazinium methylsulfate (14.1.28), is synthesized by alkylating 1-methylpiperazine with α-bromacetophenone, which forms 4-methyl-1-phenacylpiperazine (14.1.26). Reacting this with cyclohexylmagnesiumbromide gives 4-(β-cyclohexyl-β-hydroxyphenethyl)-1,1-piperazine (14.1.27), the alkylation of which using dimethylsulfate gives hexocyclium [23].

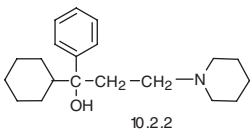


Hexocyclium inhibits muscarinic action of acetylcholine on postganglionic parasympathetic effector regions. It is used for treating stomach ulcers. A synonym of this drug is tral.

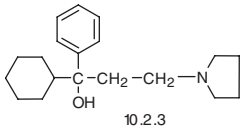
14.1.3 Antiparkinsonian drugs of the quaternary amine series

Drugs that exhibit central anticholinergic properties are used in treating Parkinsonism. It is believed that they do not affect the synthesis, release, or hydrolysis of acetylcholine. Their medicinal efficacy is manifest by the reduction or removal of motor disturbances caused by damage to the extrapyramidal system. They reduce rigidity, and to a somewhat lesser degree, akinesia, and they have little effect on tremors.

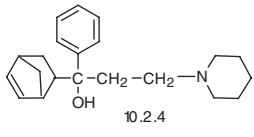
The therapeutic value of these drugs is relatively small, and they are used either in combination with levodopa, or in cases of minor Parkinsonism. Drugs described in Chapter 10—trihexyphenidyl (10.2.2), procyclidine (10.2.3), biperiden (10.2.4), benztropine (10.2.6), ethopropazine (10.2.7), and others belong to this group of drugs.



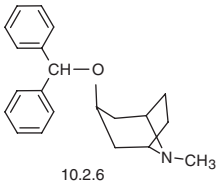
10.2.2



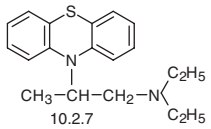
10.2.3



10.2.4



10.2.6



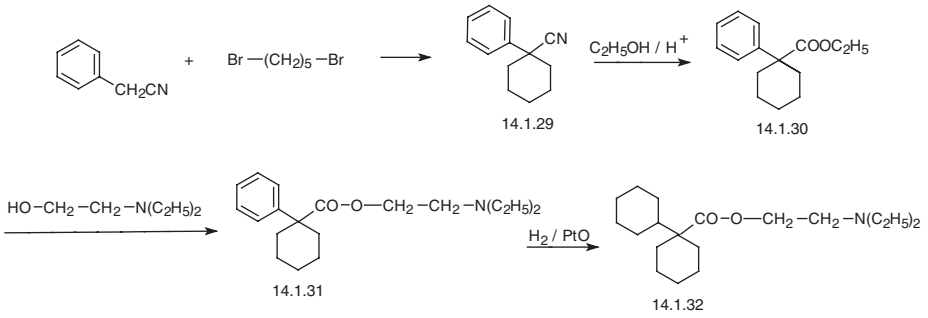
10.2.7

14.1.4 Antispasmodics of the tertiary series

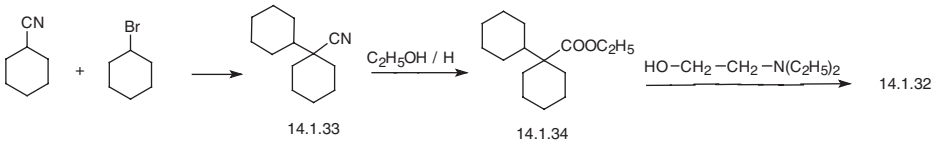
Synthetic antispasmodics of the tertiary series (dicyclomine, oxybutynin, oxyphencyclimine) exhibit direct antispastic action on smooth muscle and inhibit muscaric-like action of acetylcholine on smooth muscle.

These drugs have weaker anticholinergic activity than atropine; however, they have a significantly more expressed antispastic action. They are used for treating so-called irritable bowel syndrome and diarrhea.

Dicyclomine: Dicyclomine, diethylaminoethyl ester of 1-cyclohexylcyclohexanecarboxylic acid (14.1.32), is synthesized in two different ways. According to the first, benzyl cyanide undergoes alkylation by 1,5-dibromopentane, which forms 1-cyano-1-phenyl-cyclohexane (14.1.29). This undergoes alcoholysis, which gives the ethyl ester of 1-phenyl-1-cyclohexanecarboxylic acid (14.1.30), which undergoes transesterification using 2-diethylaminoethanol in the presence of sodium as an alcoholic component, giving the 2-diethylaminoethyl ester of 1-phenylcyclohexanecarboxylic acid (14.1.31), the phenyl group of which is reduced to a cyclohexyl group using hydrogen over platinum oxide [24,25].

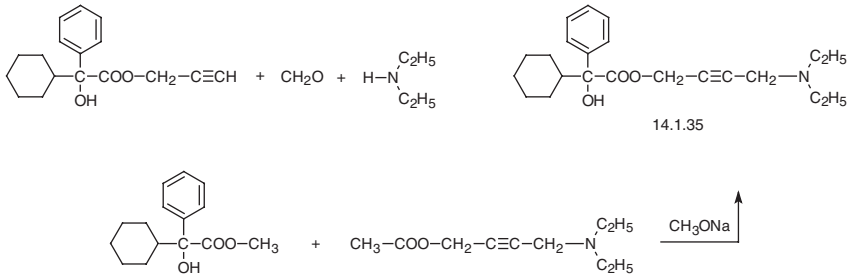


The second method for the synthesis of dicyclomine is started from cyanocyclohexane, which undergoes alkylation by cyclohexylbromide, forming 1-cyanobicyclohexane (14.1.33). This undergoes alcoholysis, forming the ethyl ester of 1-bicyclohexanecarboxylic acid (14.1.34), which undergoes transesterification by 2-diethylaminoethanol in the presence of sodium [25].



Dicyclomine inhibits muscarinic action of acethylcholine on postganglionic parasympathetic effector regions. It is used in combination with other drugs for treating stomach ulcers, colic in children, and for treating irritable bowel syndrome. Synonyms of this drug are anaspaz, bentyl, dibent, and formulex.

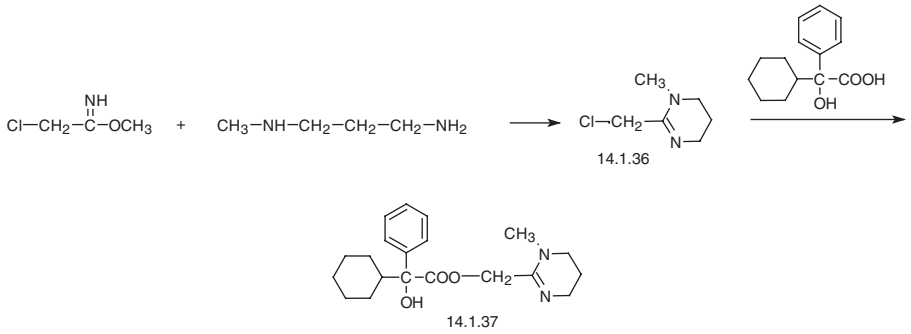
Oxybutynin: Oxybutynin, 4-diethylamino-2-butynylic ester α-phenylclohexaneglycolic acid (14.1.35), is synthesized either by a Mannich reaction using propargyl ester of α-phenyl-α-cyclohexaneglycolic acid, paraform and diethylamine, or transesterification of the methyl ester of α-phenyl-α-cyclohexaneglycolic acid using 1-acetoxy-4-diethylamino-2-butene in the presence of sodium methoxide [26].



Oxybutynin is intended for relieving unpleasant symptoms associated with emptying the intestine or urinary bladder. A synonym of this drug is ditropan.

Oxyphencyclimine: Oxyphencylimine, the 1,4,5,6-tetrahydro-1-methyl-2-pyrimidinylmethanolic ester of α-phenylcyclohexaneglycolic acid (14.1.37), is synthesized by the

esterification of α-phenyl-α-cyclohexaneglycolic acid with 2-chloromethyl-1-methyl-1,4,5,6-tetrahydropyrimidine (14.1.36) in the presence of potassium iodide. The initial 2-chloromethyl-1-methyl-1,4,5,6-tetrahydropyrimidine (14.1.36), is synthesized in turn by reacting methyl ester of iminochloracetic acid with 3-methylaminopropylamine [27–29].



14.1.36

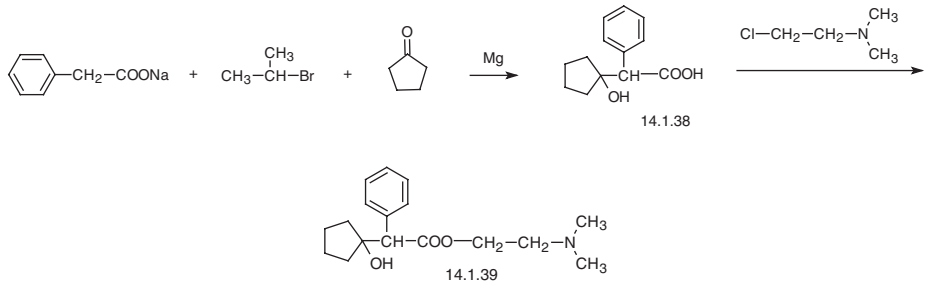
14.1.37

Oxyphencyclimine is widely used for the same indications as dicyclomine and oxybutynin. Synonyms of this drug are orbigastil, gastriced, gastrix, daricon, and others.

14.1.5. Mydriatics of the tertiary amine series

Anticholinergic drugs of the tertiary amine series (cyclopentolate, tropicamide) also are used locally as mydriatics for causing cycloplegia and mydriasis. They are primarily used as adjuvant drugs for eye examinations and other diagnostic procedures before, during, and after opthalmological interventions.

Cyclopentolate: Cyclopentolate, 2-(dimethylamino)ethylic ester of 1-hydroxycyclopentane-α-phenylacetic acid (14.1.39), is synthesized by the esterification of α-(1- droxycylopentyl) phenylacetic acid (14.1.38) using 2-dimethylaminoethylchloride, α-(1- Hydroxycyclopentyl) phenylacetic acid (14.1.38) is synthesized by reacting the sodium salt of phenylacetic acid with cyclopentanone in the presence of isopropylmagnesium bromide [30].

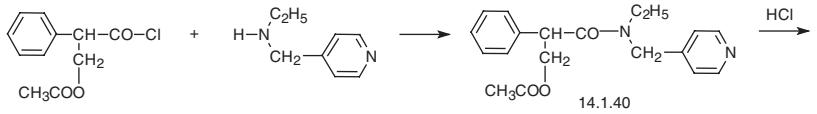


14.1.38

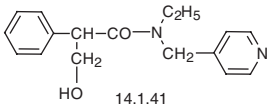
14.1.39

Cyclopentolate is an effective mydriatic and cycloplegic that begins to act very quickly and has a relatively short duration. It is used also in ophthalmoscopy for causing pre-operational mydriasis. Synonyms of this drug are mydrilate, cyclogyl, cyclomydril, pentolair, and others.

Tropicamide: Tropicamide, *N*-(4-piridinylmethyl)-*N*-ethyl-β-hydroxy-α-phenylpropionamide (14.1.41), is synthesized by reacting *O*-acetyltropyl chloride with ethyl (4-piridinylmethyl)amine and the subsequent acidic hydrolysis of the acetyl group in the resulting amide (14.1.40) [31].



14.1.40



14.1.41

Tropicamide, like cyclopentolate, is used in ophthalmoscopy for reaching pre-operational mydraises and for testing narrow-angle glaucoma. Synonyms of this drug are mydrin, mydriacyl, mydriafair, tropicacyl, tripatar, and others.

14.2 GANGLIOBLOCKING SUBSTANCES

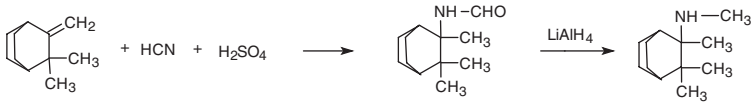
Ganglioblockers are those compounds that selectively act on nerve transmission in the autonomic ganglia. (Theoretically, ganglioblockers can stop all autonomic activity in the organism). These drugs are classified as depolarizing and antidepolarizing ganglioblockers. Depolarizing ganglioblockers such as nicotine initially stimulate postganglionic receptors, and then they block subsequent activation of the receptor, thus preventing repolarization of the postsynaptic membrane. The pharmacological effects of nicotine are very diverse and largely depend on the dose, exposition, and physiological condition of the individual.

Antidepolarizing ganglioblockers such as the clinically effective drugs mecamylamine and trimethaphan act as competitive antagonists to acetylcholine on postganglionic receptive regions. Their main action consists of reducing vessel tonicity, expressed dilation of vessels, and reducing peripheral resistivity. Venous dilation causes congestion of blood, and therefore a reduction in the quantity of returnable blood to the heart and a reduction in cardiac output. Both of these effects are expressed as hypertension. At the same time, ganglioblockers cause orthostatic hypotension, which is an extremely undesirable side effect. They are drugs for lowering blood pressure; however, they are rarely used because of a large number of side effects such as tachycardia, mydriases, reduced gastrointestinal tract activity, urine retention, dry mouth, and others.

Because their actions are so broad, including blocking of sympathetic and parasympathetic systems, their therapeutic use has been largely supplanted by more specific drugs. They may still be used in the control of blood pressure in patients with acute dissecting aortic aneurysm and for the induction of hypotension in surgery.

During the 1950s and 1960s, ganglioblockers were practically the only substances used for treating general hypertension. Currently they have been practically replaced by more effective drugs, and clinically speaking their use is quite obsolete.

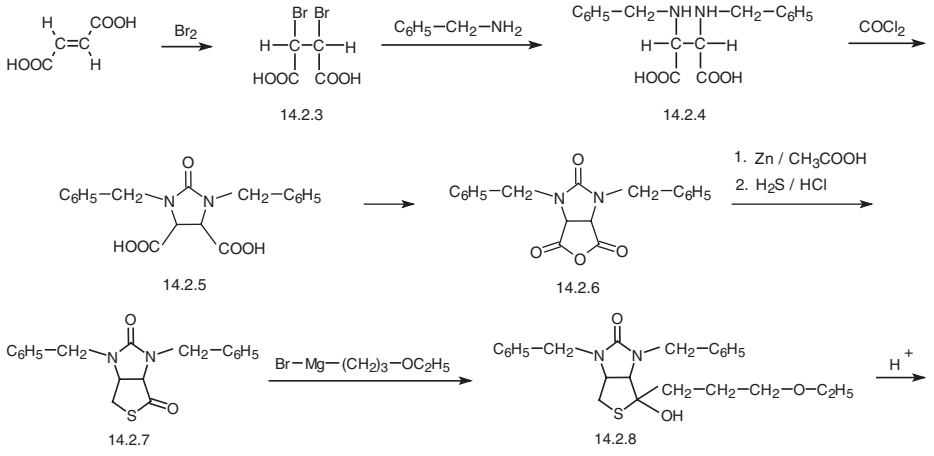
Mecamylamine: Mecamylamine, *N*,2,3,3-tetramethylnorbornan-2-ylamine (14.2.2), is synthesized from 2,3,3-trimethylnorbornen-2, which is reacted in a Ritter reaction conditions with hydrogen cyanide in concentrated sulfuric acid, giving 2,3,3-trimethylnorbornan-2-ylformylamine (14.2.1), the reduction of which by lithium aluminum hydride leads to mecamylamine (14.2.2) [32,33].



14.2.1 14.2.2

Currently, mecamylamine is the only ganglioblocker used for general hypertension; however, the need has declined because of the possibility of addiction and the introduction of many other antihypertensive drugs into medical practice. Synonyms of this drug are mevasine, inversine, and others.

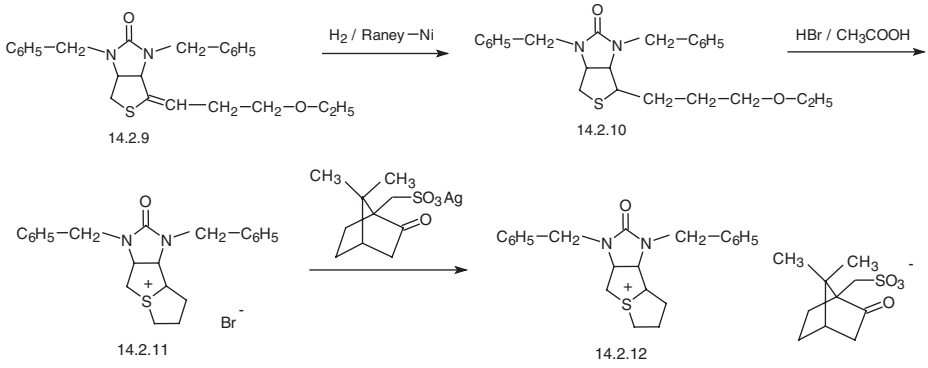
Trimethaphan: Trimethaphan, D-3,4-(1,3-dibenzyl-2-oxoimidazolidino)-1,2-trimethylenthiophanium D-camphorsulfonate (14.2.12), is an intermediate product of biotin (vitamin H) synthesis. It is synthesized from fumaric acid, the bromination of which leads to *meso*-dibromosuccinic acid (14.2.3). Reacting this with benzylamine gives 2,3-*bis*-(benzylamino)succinic acid (14.2.4), which when treated with phosgene gives 1,3-dibenzyl-2-oxoimidazolidin-4,5-dicarboxylic acid (14.2.5). Dehydration of this product produces the corresponding imidazoline derivative of succinic acid (14.2.6). Reduction of this using zinc in acetic acid and subsequent treatment with hydrogen sulfide gives 1,3-dibenzyl-2,5-dioxotetrahydrothieno[3,4]imidazoline (14.2.7), which is reacted with 3-ethoxypropylmagnesiumbromide. The resulting carbinol (14.2.8) undergoes acidic dehydration to (14.2.9) and is further reduced (having formed a double bond) by hydrogen using Raney nickel as a catalyst. Cleavage of the ester bond in the resulting product (14.2.10) with the help of hydrogen bromide in acetic acid gives 3,4-(1,3-dibenzyl-2-oxoimidazolidino)-1,2-trimethylenthiophanium bromide (14.2.11), the treatment of which with silver D-camphorsulfonate gives trimethaphan (14.2.12) [34-38].



14.2.3 14.2.4

14.2.5 14.2.6

14.2.7 14.2.8



Trimethaphan is used for the controlled reduction in blood pressure during surgical interventions, for quick regulation during sharp increases in blood pressure, immediate interventions during pulmonary edema, ischemic illnesses of the heart, and in cases where other drugs cannot be used. Synonyms of this drug are arfonad and others.

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– 15 –

Muscle Relaxants

Muscle relaxants (myorelaxants) are a large group of chemical compounds that have the ability to relax skeletal muscle. They are a separate class of drugs used during intubations and surgery to reduce the need for anesthesia and facilitate intubation.

Skeletal muscle relaxants may be used for relief of spasticity in neuromuscular diseases, such as multiple sclerosis, as well as for spinal cord injury and stroke. They may also be used for pain relief in minor strain injuries and control of the muscle symptoms of tetanus. Dantrolene (Dantrium) has been used to prevent or treat malignant hyperthermia in surgery.

A quite large, diverse group of substances can affect skeletal muscle by acting both at the level of neuromuscular junctions as well as at various levels of the spinal cord and brain stem. A few of them influence transmission of nerve impulses at neuromuscular contacts and are capable of paralyzing skeletal muscle. They are used mainly as adjuvant substances in anesthesia during minor surgical interventions.

On the other hand, there are myorelaxants that have an effect on transmission of nerve impulses in neuromuscular synapses, or that have a direct effect on the contractile mechanism of skeletal muscle as well as on the transmission of impulses at the level of the spinal cord, which causes various degrees of muscular relaxation right up to complete blockage of skeletal muscle. They are used for relieving muscle spasms, hyperreflexia, and hyperkinesias associated with inflammation, stress, and a number of neurological illnesses. Depending on the localization and mechanism of action, myorelaxants can be classified as peripherally acting myorelaxants, direct-acting muscle relaxants, and centrally acting muscle relaxants.

The activity of peripherally acting myorelaxants is exhibited in the area of neuromuscular contacts, which results in a weakened transmission from motor neuron endings to the membranes of skeletal muscle cells. These drugs, in turn, can be subdivided into neuromuscular transmission blockers, which include antidepolarizing drugs (tubocurarine, atracurium, gallamine), and depolarizing drugs (succinylcholine).

Direct-acting muscle relaxants directly block the process of contraction of the muscle fibers themselves. Of all the direct-acting myotropic drugs, only dantrolene is used in medical practice.

Centrally acting muscle relaxants are also widely used (baclofen, cyclobenzaprin, carisoprodol, methocarbamol, chlorphenesin, chlorzoxazone, orphenadrine, and

diazepam), which suppress motor impulse transmission in interneuronal synapses of the CNS.

15.1 NEUROMUSCULAR JUNCTION BLOCKING AGENTS

These compounds block impulses from motor neuron endings to skeletal muscle.

There are two suggested mechanisms of blocking nerve impulse transmission. One group of drugs, the typical representative and progenitor of which is tubocurarine, are called antidepolarizing drugs. By competitively binding with corresponding H-cholinoreceptor regions, they counteract action of acetylcholine on the postsynaptic membranes, thus preventing its depolarizing action and excluding the possibility of exciting muscle fibers. It should be noted that because of minor differences in dosage causing necessary muscle relaxation and facilitating the development of paralysis of skeletal muscle, a slight overdose of muscle relaxant compounds can lead to serious damage of respiratory function and a sharp decline in blood pressure. Overdose is reversed by introducing anticholinesterase agents, which block acetylcholinesterase and elevate the concentration of acetylcholine in the synaptic chain, using artificial respiration with oxygen, and when necessary, using drugs that elevate arterial blood pressure (levarterenol).

Drugs of the other group, which is represented by succinylcholine, are referred to as depolarizing drugs. Compounds of this group cause initial activation (depolarization) of the receptor and subsequent prolonged, stable blockage, which leads to a delay in repolarization and the inability to subsequently stimulate receptors, and in short, it disturbs the development of excitation from the nerve to the muscle. Unlike nondepolarizing agents, these drugs are not competitive antagonists, but on the contrary—they are more stable agonists than acetylcholine itself. Suitable antagonists of depolarizing agents are currently not available.

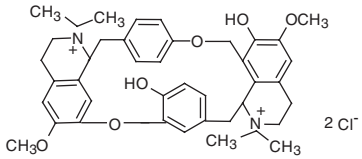
15.1.1 Antidepolarizing neuromuscular junction blockers

Initially, neuromuscular junction blockers were isolated from curare, the extract of which is produced from South American plants *Strychnos* and *Chondodendron*. Today, synthetic compounds as well as tubocurarine, an alkaloid isolated from curare, are used as antidepolarizing or curare-like drugs, which are called antidepolarizing or competitive blockers.

Tubocurarine and the majority of synthetic curare-like compounds contain two or more quaternary nitrogen atoms located approximately 1.0 ± 0.1 nm from each other, which is a necessary condition for this drug to bind with nicotinic cholinoreceptors.

These drugs are used in operations in which relaxation of skeletal muscle is required, in traumatology for repositioning broken bones, for resetting dislocations, and for tetanus. Interestingly, curare-like drugs relax muscles in a specific sequence. First, muscles of the face and neck relax, followed by the extremities and torso. Respiratory muscles and the diaphragm are last to relax, which leads to a discontinuation of respiration. Compounds of this group include tubocurarine, metocurine, gallamine, pancuronium, vecuronium, and atracurium.

Tubocurarine: Tubocurarine, 7′,12′-dihydroxy-6,6′-dimethoxy-2,2,2′,2′-tetramethyltubocuraranium dichloride (15.1.1), is synthesized from an aqueous extract of the *Chondodendron* plant [1–6].

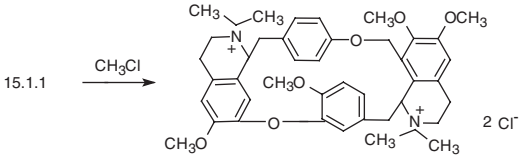


15.1.1

Methods of synthesis of tubocurarine have been proposed [7,8].

Tubocurarine is used mainly in anesthesiology as a myorelaxant, causing prolonged muscle relaxation during an operation. Small doses are successful at causing temporary relaxation of skeletal muscle without any vital change of primary body functions. It is used particularly in endotracheal intubation or orthopedic surgery for repositioning fractures, resetting compound dislocations, and so on. The main synonyms are tubarine and curarine.

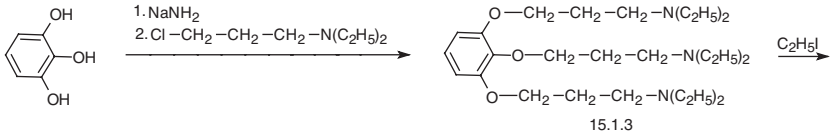
Metocurine: Metocurine, 6,6′,7′,12′-tetramethoxy-2,2,2′,2′-tetramethyltubocuraranium dichloride (15.1.2), is synthesized by methylating two hydroxyl groups of tubocurarine with methylchloride [9].



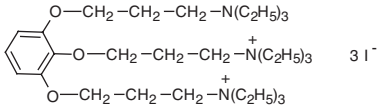
15.1.2

Metocurine is used for the same indications as tubocurarine. A synonym of this drug is metubine.

Gallamine: Gallamine, 1,2,3-*tris*-(2-triethylaminoethoxy)benzene triiodide (15.1.4), is synthesized from pyrogallol, the hydroxyl groups of which are esterified by 2-diethylaminoethylchloride in the presence of sodium amide. The resulting 1,2,3-*tris*-(2-triethylaminoethoxy)benzene (15.1.3) is further alkylated at all three nitrogen atoms by ethyliodide, giving gallamine (15.1.4) [10,11].



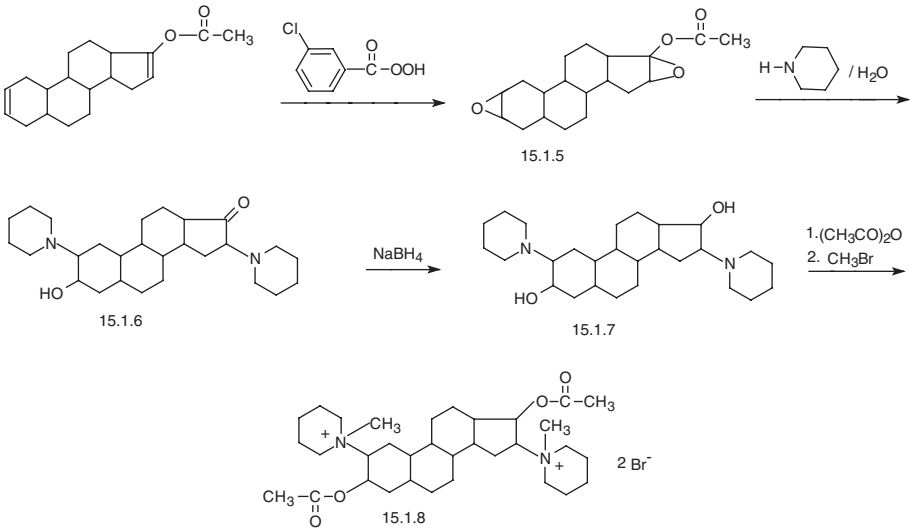
15.1.3



15.1.4

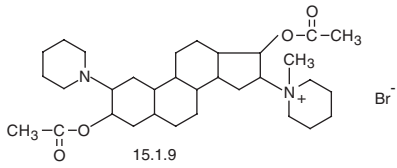
Gallamine is used for the same indications as tubocurarine. A synonym of this drug is flaxedil.

Pancuronium: Pancuronium, 1,1′-(3α,17β-diacetoxy-5α-androstan-2β,16β-ylene)-*bis*-(1-methylpiperidinium) dibromide (15.1.8), is synthesized from 3,17-*bis*-(acetoxy)-2,16-5α-androstane. Oxidation with 3-chloroperbenzoic acid gives the *bis*-epoxy compound (15.1.5), the reaction of which with piperidine and subsequent hydrolysis gives an aminoketone (15.1.6). The keto group of the resulting compound (15.1.6) is reduced by sodium borohydride to hydroxyl group, giving the *bis*-aminoalcohol (15.1.7), subsequent acetylation of which by acetic anhydride and alkylation of both nitrogen atoms by methylbromide give the desired pancuronium (15.1.8) [12–14].



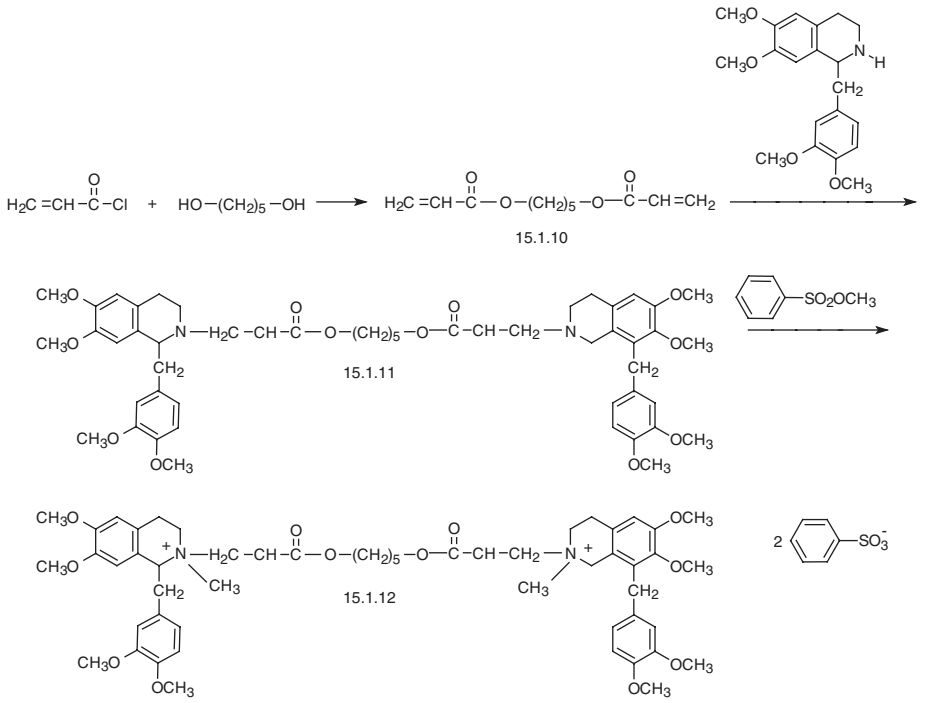
Pancuronium is a steroid compound that does not possess hormonal activity. It is used in anesthesiology as a myorelaxant, causing prolonged muscle relaxation during surgical interventions of the thoracic and abdominal cavities, in proctology, ophthalmology, orthopedic practice, and in heart surgeries. A synonym of this drug is pavulon.

Vecuronium: Vecuronium, 1-[(2β,3α,5α,16β,17β,)-3,17-*bis*(acetyloxy)-2-(1-piperidinyl) androstan-16-yl]-1-methylpiperidinium bromide (15.1.9), differs from panuronium only in the extent of alkylation. Only the piperidine substituent on C_{16} of the steroid skeleton is transformed into a quaternary salt [15,16].



Vecuronium is used for the same indications as pancuronium. A synonym of this drug is norcuron.

Atracurium: Atracurium is 2,2′-[1,5-pentanediyl*bis*[oxy(3-oxo-3,1-propanediyl)]] *bis* [1-[(3,4-dimethoxyphenyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolinium] dibenzene sulfonate (15.1.12). This compound is synthesized from *bis*-acrylic ester of 1,5-pentandiol (15.1.10), which is synthesized from acrylic acid chloride and 1, 5-pentandiol. Two molecules of a secondary amine, tetrahydropapaverine, are joined to the product in a Michael reaction, forming compound (15.1.11). Then both nitrogen atoms are methylated by methylbenzenesulfonate, giving atracurium (15.1.12) [17–19].

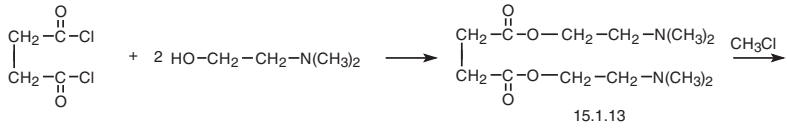


Atracurium is used for the same indications as tubocurarine. A synonym of this drug is tetracurium.

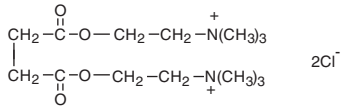
15.1.2 Depolarizing neuromuscular blockers

Unlike nondepolarizing substances, depolarizing neuromuscular junction blockers are not competitive antagonists; conversely, they are more stable agonists than acetylcholine. They differ from acetylcholine only in that they have more prolonged action. These drugs react with the same receptors as acetylcholine. However, since these drugs are inactivated slower than acetylcholine, they act longer in the synapse, causing a more stable depolarization. In this manner, the process of receptor repolarization is blocked and skeletal muscles relax. Succinylcholine has a lot of very practical value in medicine as a neuromuscular blocker.

Succinylcholine: Succinylcholine, 2,2′-[(1,4-dioxo-1,4-butanediyl)*bis*(oxy)]*bis*[*N*,*N*,*N*-trimethylethanaminium(diacetylcholine)] dichloride, which can be viewed as a dimeric molecule of acetylcholine (diacetylcholine), is synthesized by reacting succinic acid dichloride with 2-dimethylaminoethanol and subsequent transformation of the resulting *bis*-(2-dimethylaminoethyl)succinate (15.1.13) into a quaternary salt, succinylcholine (15.1.14) [20–24].



15.1.13



15.1.14

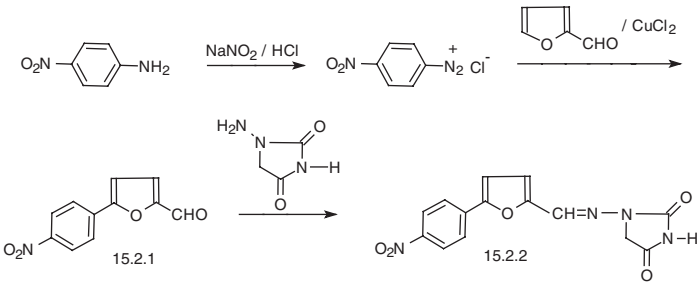
Succinylcholine is the only therapeutically used depolarizing neuromuscular blocker. Unlike nondepolarizing substances, succinylchloride is not a competitive antagonist; conversely, it is a more stable agonist than acetylcholine. In this manner, succinylcholine differs from acetylcholine only in duration—it lasts longer, causing a more stable depolarization. Thus the process of repolarization is blocked and the muscles relax. During this period, muscles that cause fine movement (ocular, facial, neck) are the most sensitive and are blocked first, after which muscles of the extremities are blocked, and finally the most stable respiratory muscles. Restoration occurs upon completion of drug action.

Therapeutic use of succinylcholine consists of preventing involuntary patient movement. It is used for brief operations, intubation of the trachea, and other endoscopic procedures.Synonyms of this drug are listenon, midarine, sucostrin, ditilin, and others.

15.2 DIRECT-ACTING MUSCLE RELAXANTS

The only drug of this type that is widely recognized is dantrolene.

Dantrolene: Dantrolene, 1-[[[5-(4-nitrophenyl)-2-furanyl]methylene]amino]-2,4-imidazolidinedione (15.2.2), is synthesized by reacting 4-nitrophenyldiazonium chloride with furfurol, forming 5-(4-nitrophenyl)-2-furancarboxaldehyde (15.2.1), which is reacted further with 1-aminohydantoin, to give the corresponding hydrazone, dantrolene (15.2.2) [25,26].



15.2.1 15.2.2

Dantrolene is a drug that causes spastic muscle contraction. Unlike other muscle relaxants, it has a direct effect on the contractile mechanism by interfering in the process of calcium ion release from the sarcoplasmic reticulum. This results in a lack of coordination in the mechanism of excitation—contraction of skeletal muscle, which has a greater effect on fast muscle fibers than on slow muscle fibers. Dantrolene is used for controlling the onset of clinical spasticity resulting from serious clinical cases such as wounds, paralysis, cerebral palsy, and disseminated sclerosis. Synonyms of this drug are dantrium and danlen.

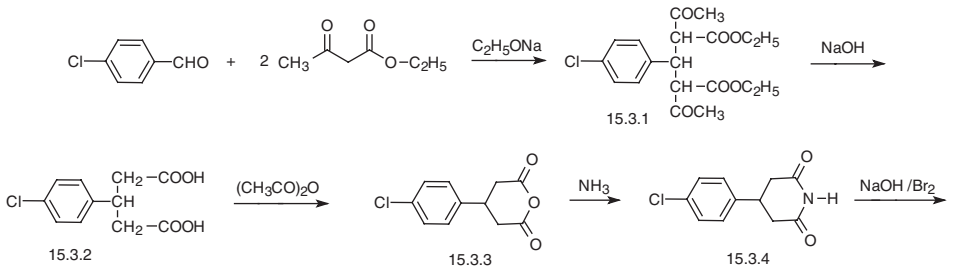
15.3 CENTRALLY ACTING MUSCLE RELAXANTS

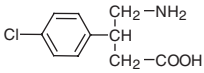
Unfortunately, paralysis of skeletal muscle attained by using curare-like compounds, in the majority of cases, is not useful for general conditions of spasticity accompanied by the CNS involvement, as well as for local injuries or inflammation. Of course, neuromuscular blockage reduces spasms; however, it is accompanied by loss of voluntary movement.

In conditions of muscle spasticity, there need to be drugs capable of relieving painful muscle spasms that do not take away the ability of voluntary muscle contraction and that do not hamper brain function.

Many CNS depressants cause muscle relaxation. Among these it is noteworthy to mention alcohol and barbiturates, which, however, are not used for this purpose because they cause significant sedation and other effects. The search for selective CNS-active substances responsible for achieving muscle relaxation led to the formation of a number of interesting compounds proposed for clinical applications; however, not one of them could completely satisfy the necessary requirements. Moreover, muscle relaxants acting by affecting the CNS are widely used in treating sprains, ruptures, arthritis, and other muscular disturbances. Included is a large heterogenic group of chemical compounds that have an effect on the spinal cord and suppress monosynaptic and polysynaptic reflexes. Among these are baclofen, cyclobenzaprine, carisoprodol, methocarbamol, chlorphenesin, chlorzoxazone, orphenadrine, and diazepam.

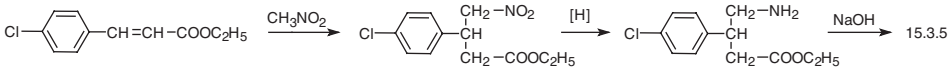
Baclofen: Baclofen, 4-amino-3-(4′-chlorophenyl)butyric acid (15.3.5), is synthesized in two ways. According to the first, 4-chlorobenzaldehyde is condensed with two moles of acetoacetic ester, giving the product (15.3.1), which initially undergoes alkaline hydrolysis and decarboxylation forming 3-(4-chlorphenyl)glutaric acid (15.3.2). Dehydration of this gives 3-(4-chlorophenyl)glutaric acid anhydride (15.3.3), and further treatment with ammonia gives the corresponding glutarimide (15.3.4). Reacting this with an alkaline solution of a halogen (Hofmann rearrangement) gives baclofen (15.3.6) [27,28].





15.3.5

The second way of synthesizing baclofen is started from ethyl ester of 4-chlorocinnamic acid. Adding nitromethane to this in the presence of base gives ethyl ester of β-(4-chlorophenyl)-γ-nitrobutyric acid (15.3.6), the nitro group of which is reduced by hydrogen over Raney nickel to the ethyl ester of β-(4-chlorophenyl)-γ-aminobutyric acid (15.3.7), which is further hydrolyzed into the desired baclofen (15.3.5) [29].

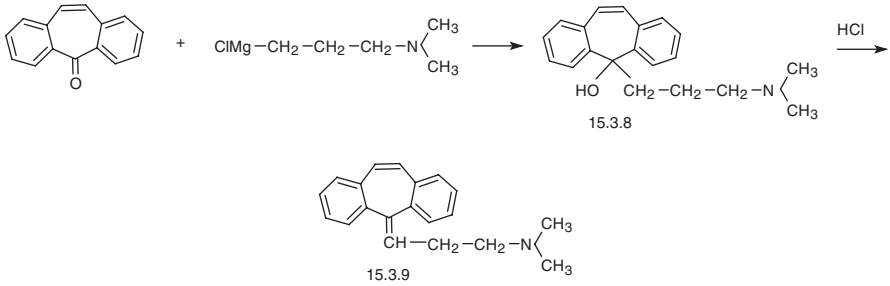


15.3.6 15.3.7

Baclofen is a substituted analog of GABA. It is presumed that its action consists of a reaction with GABA receptors, which leads to an inhibition of stimulatory neurotransmitter release.

Signs of muscle spasticity have been shown in disseminated sclerosis and other spinal disorders. It may be useful to patients with muscle spasms resulting from spinal cord injuries. A synonym of this drug is lioresal.

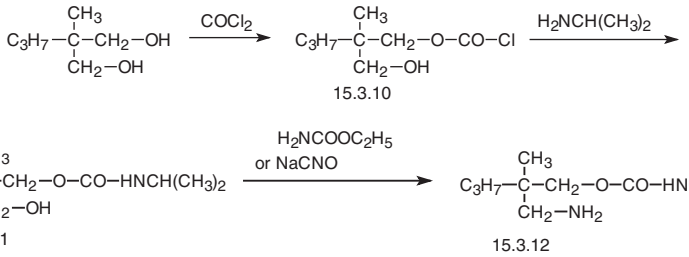
Cyclobenzaprine: Cyclobenzaprine, *N*,*N*-dimethyl-3-(dibenzo[a,d]cyclohepten-5-ylidene) propylamine (15.3.9), is synthesized by reacting 5*H*-dibenzo[a,d]cyclohepten-5-one with 3-dimethylaminopropylmagnesium chloride and subsequent dehydration of the resulting carbinol (15.3.8) in acidic conditions into cyclobenzaprine (15.3.9) [30–32].



15.3.8 15.3.9

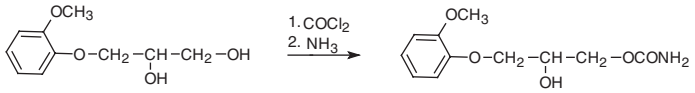
Cyclobenzaprine is structurally similar to tricyclic antidepressants. It acts at the brain stem level. It is used as an adjuvant agent for relieving muscle spasms associated with severe diseased conditions of the muscle. A synonym of this drug is flexeril.

Cariosoprodol: Carisoprodol, *N-iso*-propyl-2-methyl-2-propyl-1,3-propanediol (15.3.12), is synthesized by reacting 2-methyl-2-propylpropanediol-1,3 dicarbamate with 1 mol of phosgene, forming the chloroformate (15.3.10), from which carbamate (15.3.11) is formed by reacting it with isopropylamine. Reacting this with either urethane or sodium cyanate gives carisoprodol (15.3.12) [33].



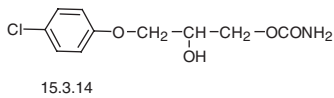
Carisoprodol suppresses interneuronal action of reticular formation of the spinal cord. It is used as an adjuvant drug for loss of flexibility of skeletal muscle as well as for relieving pain caused therein. Synonyms of this drug are rela, soma, carisoma, and sanoma.

Methocarbamol: Methocarbamol, 3-(2-methoxyphenoxy)-1,2-propanediol-1 carbamate (15.3.13), is synthesized by successive reaction with phosgene and then ammonia into 3-(2-methoxyphenoxy)propanediol-1,2 [34,35].



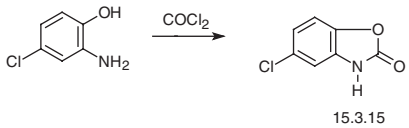
Methocarbamol suppresses multisynaptic pathways in the spinal cord. It is used for relieving spasms and skeletal muscle pain as well as for treating tetanus. Synonyms of this drug are delaxin, forbaxin, robamol, robaxin, and tresortil.

Chlorphenesin: Chlorphenesin, 3-(4-chlorophenoxy)-1,2-propanediol (15.3.14), is synthesized in the same manner as methocarbamol from 3-(4-chlorophenoxy)-1,2-propanediol [36–38].



Chlorphenesin acts by an unexplainable mechanism. It is used for relieving skeletal muscle pain. Synonyms of this drug are maolate and musil.

Chlorzoxazone: Chlorzoxazone, 5-chloro-2-benzoxazolione (15.3.15), is synthesized by a hetercyclization reaction of 2-amino-4-chlorphenol with phosgene [39].



Chlorzoxazone suppresses multisynaptic pathways in the spinal cord. It is used for relieving skeletal muscle pain. Synonyms of this drug are oxyren and paraflex.

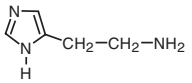
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– 16 –

Antihistamine Drugs

Drugs that competitively block effects of histamine on corresponding receptor regions are called antihistamine drugs. The discovery and synthesis of histamine was a great achievement in pharmacology, medicine, and immunology. This natural, powerful, biogenic amine is widely distributed in practically all tissues of mammals and is involved in various physiological processes. The body's reaction to histamine is characterized by contraction of smooth muscle, signs of inflammation, constriction of vessels, and symptoms characteristic of shock. It is certain that histamine plays a central role in allergic reactions, hypersensitivity reactions, and is part of the body's response mechanism in the inflammatory process.



histamine

Histamine is synthesized in tissues by decarboxylation of amino acid L-histidine, a process catalyzed by the pyridoxalphosphate-dependent enzyme L-histidinedecarboxylase. Histamine can enter the organism with food; it also can be generated by bacteria of the gastrointestinal tract. However, these sources do not create additional reserves of histamine since exogenous histamine is easily catabolized in the organism.

Histamine is dispersed and stored in mast cells in the majority of organs, in which it is preserved in secretory cytoplasmic granules in the form of a heparin-proteasic matrix making up over 10% of their mass. Histamine becomes physiologically active only after being released from granules. Histamine is also found in interstitial fluid such as digestive juices, blood, and urine. Only 2–3% of histamine leaves the body unaltered. It is primarily metabolized by two enzymes by deamination with deaminoxidase and methylating histamine with *N*-methyltransferase.

Upon being secreted from the tissue, histamine can cause a large number of physiological effects. Its role in various pathological processes associated with severe and chronic allergic reactions and hypersensitivity reactions has been uniquely proven. At the same time, functions of endogenous histamine (in development of nerve transmission, secretion of digestive juices, tissue growth and restoration) remain inconclusive.

Despite the fact that a number of various factors can cause the release of endogenous histamine, it is believed that the most important reason is an immunological response of the organism. Accepted knowledge states that during anaphylaxis and allergies, a specific

reaction of immunoglobulin E with an antigen takes place on the surface of the mast cell and basophiles, which results in a cascade of biochemical events that lead to degranulation and a release of histamine.

Besides such antigen–antibody reactions, which play a critical role in the pathogenesis of many allergic, anaphylactic, and hypersensitivity reactions, histamine also can be released from tissue stores in response to physical stimuli, effects of the so-called histamine liberators, a number of chemical substances, various drugs, and toxins.

There is a large class of compounds that are capable of releasing histamine. They can be enzymes, toxins, morphine, d-tubocurarine, and polymers such as dextran. Moreover, tissue damage such as trauma, bites, and stress can also cause a release of histamine, and in all probability as a result, an endogenous polypeptide bradykinin is released. Action of all of these listed substances as well as a number of others can facilitate formation of anaphylactic reactions in the organism.

Release of histamine is blocked by various enzyme inhibitors and other substances (nicotinamide).

The main physiological effect of histamine is exhibited in the cardiovascular system, nonvascular smooth musculature, and exocrine and adrenal glands.

Its most important pharmacological effects are dilation of veins and capillaries, increased permeability of capillaries, increased heart rate, contraction of nonvascular smooth musculature (constriction of bronchi, gastrointestinal tract peristalsis), stimulation of gastric juice secretion, and release of catecholamines from adrenal glands.

Two membrane-receptive binding sites called H_1 and H_2 receptors mediate the pharmacological effect of histamine. H_1 receptors are located in smooth muscle of vessels, and bronchial and gastrointestinal tract, while H_2 receptors are found in the walls of the stomach, myocardium, and certain vessels.

Therefore, it is very likely that contraction of nonvascular smooth muscle is an effect of activation of H_1 receptors, while secretion of digestive juice and increased heart rate are connected to activation of H_2 receptors; and dilation of vessels and increased permeability of capillaries is a result of combined activation of both types of receptors.

There are also specific differences in the location of receptors in various tissues and in various animals. If mice and rats are sufficiently stable to effects of histamine, then guinea pigs and humans will be very sensitive.

Antihistamine drugs are classified as antagonists of H_1 and H_2 receptors, and quantitatively speaking H_1 antagonists dominate. Moreover, the term antihistamine drug is associated more with H_1 antagonists. H_2 blockers exhibit a specific effect on histamine receptive sites located in walls of the stomach and they significantly increase secretion of hydrochloric acid.

Allergic illnesses are a complex collection of disturbances with chronic and severe effects ranging from slight reddening, rashes, and runny nose to severe and even fatal anaphylaxis. It has been shown that around 10% of the population may be prone to some form of allergy. Therapy directed toward removing the source of allergen is not always successful. In a number of cases, the allergen itself is never found. Therefore, symptomatic treatment using H_1 antihistamines is carried out.

H_1 antihistamines are clinically used in the treatment of histamine-mediated allergic conditions. Specifically, these indications may include allergic rhinitis, allergic conjunctivitis, allergic dermatological conditions (contact dermatitis), pruritus (atopic dermatitis, insect

bites), anaphylactic or anaphylactoid reactions—adjunct only nausea and vomiting, as well as sedation (first-generation H_1 antihistamines).

Antihistamines can be administered topically (through the skin, nose, or eyes) or systemically, based on the nature of the allergic condition.

First-generation H_1 antihistamines are the oldest antihistaminergic drugs and are relatively inexpensive and widely available. Representatives of first-generation H_1 antihistamines are:

Ethanolamines—(diphenhydramine was the prototypical agent in this group).
Ethylenediamines, which were the first group of clinically effective H_1 antihistamines developed. (pyrilamine).
Alkylamines—pheniramine chlorphenamine, chlorpheniramine, dexchlorphenamine, brompheniramine.
Piperazines—compounds are structurally related to the ethylenediamines and to the ethanolamines: hydroxyzine, meclizine.
Tricyclics—compounds which differ from the phenothiazine antipsychotics in the ring-substitution and chain characteristics—promethazine, trimeprazine, cyproheptadine, azatadine.

Second-generation H_1-receptor antagonists are newer drugs that are much more selective for peripheral H_1 receptors in preference to the central nervous system (CNS) histaminergic and cholinergic receptors. This selectivity significantly reduces the occurrence of adverse drug reactions compared with first-generation agents, while still providing effective relief improved of allergic conditions The samples of second-generation H_1-receptor antagonists are astemizole, fexofenadine, loratadine, mizolastine, terfenadine.

H_2-receptor antagonists are drugs used to block the action of histamine on parietal cells in the stomach, decreasing acid production by these cells. These drugs are used in the treatment of dyspepsia; however, their use has waned since the advent of the more effective proton pump inhibitors.

H_2 antagonists are clinically used in the treatment of acid-related gastrointestinal conditions. Specifically, these indications may include peptic ulcer disease, gastroesophageal reflux disease, and dyspepsia.

Cimetidine was the prototypical member of the H_2 antagonists. Further developments, using quantitative structure–activity relationships led to the development of further agents with tolerability-profiles—cimetidine ranitidine, famotidine, nizatidine.

Currently, histamine itself does not have any therapeutic value and is not used in clinics, although there was an attempt to use it as a drug for treating achlorhydria (lack of hydrochloric acid in the stomach). It can be used in small doses for diagnostic purposes such as stimulating gastric glands for testing their ability to generate hydrochloric acid, and sometimes for pheochromocytoma diagnostics.

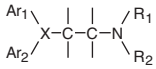
16.1 H_1 ANTIHISTAMINE DRUGS

Antihistamine drugs were discovered at the end of the 1930s. By 1950, highly effective histamine antagonists tripelennamine and diphenhydramine were synthesized, which triggered broad research in the area of synthesis of such drugs.

All of these compounds are reversible, competitive histamine H_1 antagonists that do not exhibit substantial activity with respect to H_2 receptors. H_1-receptor antagonists bock effects of histamine in different degrees in various organs or systems, and can protect the organism from allergic and anaphylactic reactions. By themselves they do not have significant independent activity, and therefore they are only used therapeutically for blocking effects caused by histamine release. In other words, their effects are noticeable only with elevated histamine activity. Moreover, these antihistamine drugs only reduce the release or metabolism of histamine, but in no way affect its synthesis.

Despite the fact that there are minute differences in relative activity of these drugs, they have comparable pharmacodynamic properties and therapeutic use when viewed as a single group of drugs.

The most common H_1 antihistamine drugs are structurally similar to histamine with a substituted ethylamine side chain; however, they have two aromatic rings and can be formally represented by the general formula:



where Ar_1 and Ar_2 are carbocyclic or heterocyclic aromatic rings, one or both of which can be separated from the X atom of carbon, and where X is oxygen, carbon, or nitrogen. R_1 and R_2 represent alkyl substituents, usually methyl groups.

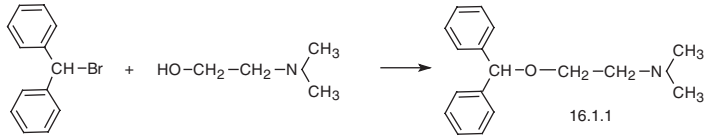
H_1 histamine receptor blockers can be grouped according to their chemical structures: ethanolamine derivatives (diphenhydramine, clemastine); ethylenediamine derivatives (tripelennamine, pyrilamine); alkylamines (chloropheniramine, dexchlorpheniramine, brompheniramine); piperazines (cyclizine, meclizine, hydroxizine); phenothiazines (promethazine, trimeprazine); piperidines (cyproheptadine, diphenylpyraline); and others that do not belong to a specific chemical classification (terfenadine, astemizole).

Their clinical efficacy and side effects differ significantly from group to group and from patient to patient. These drugs prevent action of both endogenic and exogenic histamine; however, they are considerably more effective in relation to the first.

They all act by competitively binding with H_1 receptors. They are used for relieving symptoms of allergic diseases (allergic rhinitis and other allergic reactions), for treating anaphylactic reactions, for temporary relief of insomnia, as an adjuvant therapy for treating parkinsonism and extrapyramidal disorders caused by antipsychotics, relieving coughs due to colds, allergies, or other conditions, preventing and controlling nausea and vomiting, as an adjuvant drug for analgesia of post-operational pain, and for pre-operational sedation.

16.1.1 Aminoalkyl esters

Diphenhydramine: Diphenhydramine, *N*,*N*-dimethyl-(diphenylmethoxy)ethylamine (16.1.1), is synthesized by a simple reaction of benzhydrylbromide and 2-dimethylaminoethanol [1–3].

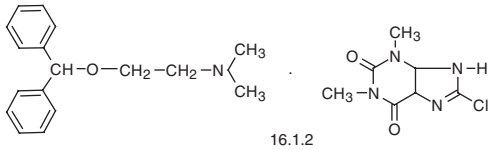


16.1.1

Diphenhydramine is one of the main representatives of antihistamine drugs that block H_1 receptors. Besides antihistamine activity, diphenhydramine exhibits a local anesthetic effect, relaxes smooth muscle, and has sedative and soporific action.

Diphenhydramine is used for symptoms of allergies, for treating hives, hay fever, serum sickness, and other allergic illnesses, and also as a sedative and soporific drug as an independent as well as in combination with other drugs. Synonyms of this drug are dimedrol, benadryl, allergina, valdren, and many others.

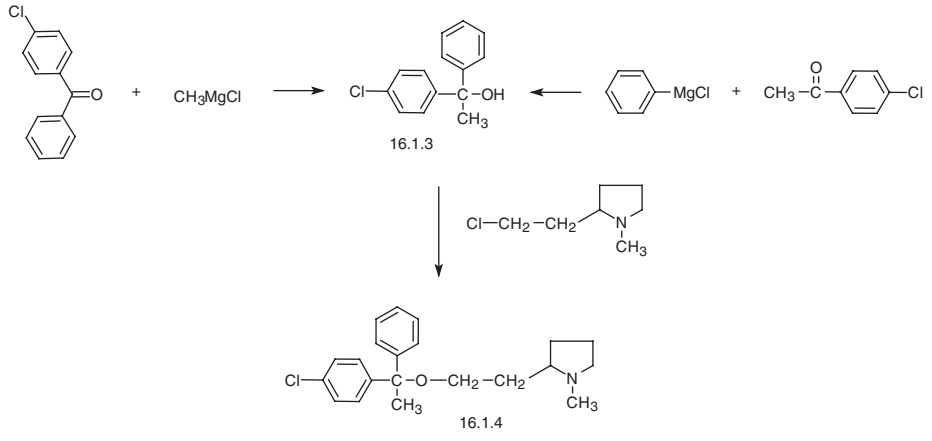
Dimenhydrinate: Dimenhydrinate (16.1.2) is a complex compound of *N*, *N*-dimethyl (2-diphenylmethoxy)ethylamine—diphenhydramine with 8-chlorotheophylline. While blocking the H_1 receptor, dimenhydrinate simultaneously acts on the vomiting center [4,5].



16.1.2

Dimenhydrinate is used for preventing and stopping sea or airsickness, and for nausea and vomiting. Synonyms of this drug are dramamine, dadalon, emedyl, travelin, and others.

Clemastine: Clemastine, 2-[2-[1-(4-chlorophenyl)-1-phenylethoxy]ethyl]-1-methylpyrrolidine (16.1.4), is synthesized by reacting 1-(4-chlorophenyl)-1-phenylethanol (16.1.3) with 2-(2-chlorethyl)-2-methylpyrrolidine using sodium amide as a base. The starting 1-(4-chlorophenyl)-1-phenylethanol (16.1.3) is synthesized either by reacting 4-chlorobenzophenone with methylmagnesium chloride, or by reacting 4-chloroacetophenone with phenylmagnesium bromide [6–8].



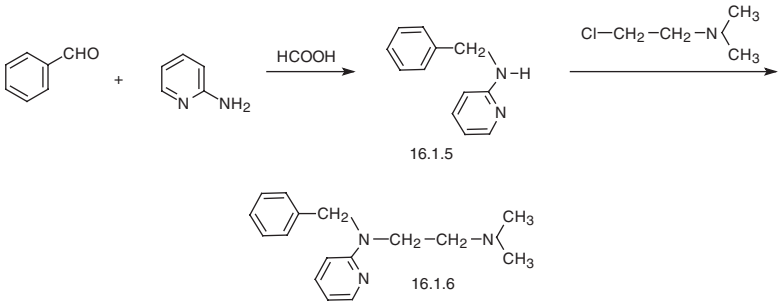
16.1.3

16.1.4

Clemastine is used for allergy symptoms, rhinites, Quinke's edema, anaphylactic shock, hay fever, allergic dermatitis and dermatosis, and chronic eczema. Synonyms of this drug are tavegil and meclastine.

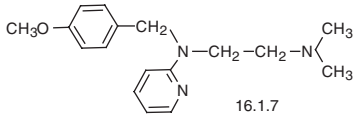
16.1.2 Ethylenediamines

Tripelennamine: Tripelennamine, *N*-benzyl-*N*′,*N*′-dimethyl-*N*-2-pyridylethylenediamine (16.1.6), is synthesized by reacting 2-benzylaminopyrridine (16.1.5) with 2-dimethylaminoethylchloride in the presence of sodium amide. 2-Benzylaminopyrridine, in turn, can be easily synthesized by reduction of a Schiff base, synthesized by condensation of 2-aminopyrridine with benzaldehyde [9–11].



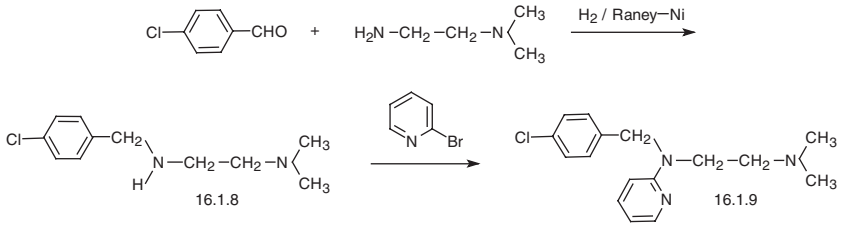
This drug lessens the allergic response of the organism caused by histamine. Tripelennamine is used for allergic symptoms, rhinitis, conjunctivitis, and for allergic and anaphylactic reactions. Synonyms of this drug are pelanin and pyribenzamine.

Pyrilamine: Pyrilamine, *N*-(4-methoxybenzyl)-*N*′,*N*′-dimethyl-*N*-2-pyridilethylenediamine (16.1.7), is synthesized in the same manner, except using 2-(4-methoxybenzylamino)pyridine [10–12].



Pyrilamine is also used for allergy symptoms and rhinitis. Synonyms of this drug are vistosan, anthisan, and triaminic.

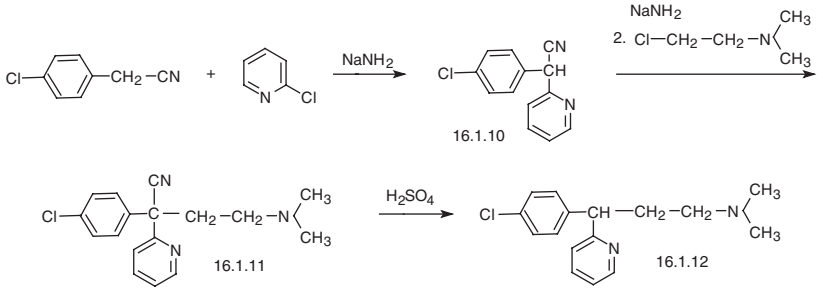
Chloropyramine: Chloropyramine, *N*-(4-chlorobenzyl)-*N*′,*N*′-dimethyl-*N*-2-pyridylethylenediamine (16.1.9), is synthesized in a somewhat different manner, which is by reacting 2-brompyridine with *N*-(4-chlorobenzyl)-*N*′,*N*′-dimethylethylenediamine (16.1.8). *N*-(4-Chlorobenzyl)-*N*′,*N*′-dimethylethylenediamine (16.1.8), in turn, is synthesized by condensation of 4-chlorobenzaldehyde c *N*,*N*-dimethylethylenediamine with subsequent reduction of the imine group [13–19].



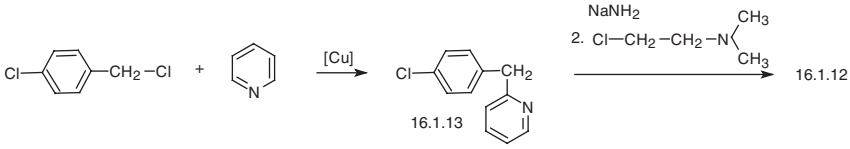
Chloropyramine is used for allergic dermatosis, allergic rhinitis and conjunctivitis, for drug-induced allergies, in the beginning stages of bronchial asthma, eczema, neurodermatitis, contact dermatitis, and toxicodermia. It also exhibits a sedative effect. Synonyms of this drug are suprastin, chlortripelenamine, and synopen.

16.1.3 Alkylamines

Chlorpheniramine: Chlorpheniramine, 3-(*p*-chlorophenyl)-3-(2-pyridyl)propyldimethylamine (16.1.12), is synthesized in two ways. The first is from 4-chlorbenzylcyanide, which is reacted with 2-chlorpyridine in the presence of sodium amide to form 4-chlorphenyl (2-pyridyl)acetonitrile (16.1.10). Alkylating this with 2-dimethylaminoethylchloride in the presence of sodium amide gives γ-(4-chlorphenyl)-γ-cyano-*N*,*N*-dimethyl-2-pyridinepropanamine (16.1.11), the hydrolysis and decarboxylation of which lead to chlorpheniramine (16.1.12) [20].



The second way is from pyridine, which undergoes alkylation by 4-chlorobenzylchloride, giving 2-(4-chlorobenzyl)pyridine (16.1.13). Alkylating this with 2-dimethylaminoethylchloride in the presence of sodium amide gives chlorpheniramine (16.1.12) [21].



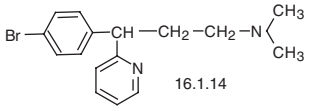
Chlorpheniramine reduces the allergic response of the organism caused by histamine. It is used for allergy symptoms, rhinitis, and also as an ingredient in numerous compositions with ephedrine and pseudoephedrine, which are recommended for colds, upper respiratory

tract infections, and allergic rhinitis. Synonyms of this drug are chlortrimeton, histaspan, tripolon, and teldrin.

Dexchlorpheniramine: Dexchlorpheniramine, D(+)-3-(*p*-chlorophenyl)-3-(2-pyridyl) propyldimethylamine, is synthesized by separating the racemate obtained from the synthesis of chlorpheniramine (16.1.12) using D-phenylsuccinic acid [22–24].

Activity of this drug is approximately twice that of chlorpheniramine. Dexchlorpheniramine is also used for allergy symptoms, rhinitis, and dermatitis. A synonym of this drug is polaramin.

Brompheniramine: Brompheniramine, 3-(*p*-bromophenyl)-3-(2-pyridyl)propyldimethylamine (16.1.14), is an analog of chlorpheniramine. The only difference is that the chlorine atom in the benzene ring is replaced with a bromine atom. It is also synthesized in an analogous manner [22,23].

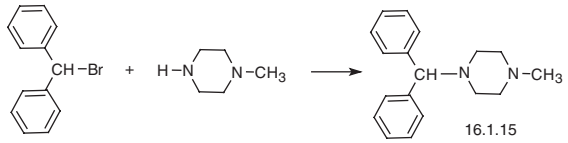


16.1.14

Brompheniramine is also used for allergy symptoms, rhinitis, and dermatitis. Its activity is approximately the same as that of chlorpheniramine. Synonyms of this drug are dimetane, brombey, spentan, veltane, and others.

16.1.4 Piperazines

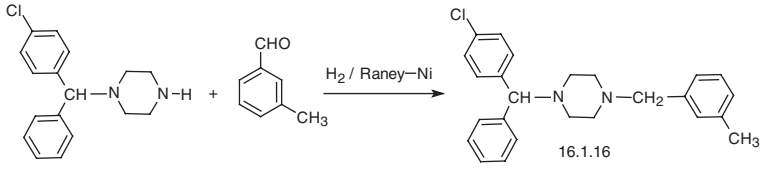
Cyclizine: Cyclizine, 1-(diphenylmethyl)-4-methylpiperazine (16.1.15), is synthesized by alkylating 1-methylpiperazine with benzhydrylbromide [25,26].



16.1.15

Cyclizine exhibits antihistamine and anticholinergic action and is used for vomiting and diarrhea. The exact mechanism of action is not known. Synonyms of this drug are marezine and migril.

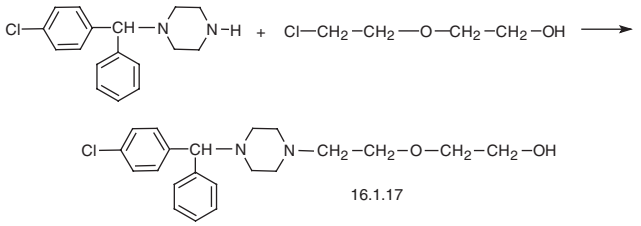
Meclizine: Meclizine, 1-[(4-chlorphenyl)methyl]-4-[(3-methylphenyl)phenyl]piperazine (16.1.16), is synthesized by reductive amination of a mixture of 3-methylbenzaldehyde with 1-(4-chlorbenzhydryl)piperazine using hydrogen over Raney nickel [27–29].



16.1.16

Meclizine actively affects the vomiting center and is used for vomiting and diarrhea. Synonyms of this drug are antivert, bonine, lamin, roclizin, and vertol.

Hydroxyzine: Hydroxyzine, 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]ethanol (16.1.17), is synthesized by alkylating 1-(4-chlorbenzhydryl)piperazine with 2-(2-hydroxyethoxy)ethylchloride [30–35].

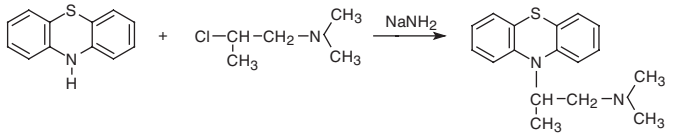


16.1.17

Hydroxyzine is an antihistamine drug with M-cholinoblocking properties and expressed action on the CNS. It suppresses subcortical regions of the CNS including the limbic system and reticular formation. It potentiates the effect of narcotic analgesics and exhibits sedative effects. It is used as a sympthomatic drug for atopic dermatitis as a sedative drug before and after operational interventions, for preventing vomiting and diarrhea, and for relieving agitation and emotional disorders. Synonyms of this drug are atarax, durrax, and vistaril.

16.1.5 Phenothiazines

Promethazine: Promethazine, 10-(2-dimethylaminopropyl)phenothiazine (16.1.18), is synthesized by alkylating phenothiazine with 1-dimethylamino-2-propylchloride [36,37].

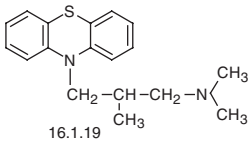


16.1.18

As a derivative of phenothiazine, promethazine is structurally and pharmacologically similar to chlorpromazine. It exhibits strong antihistamine activity as well as expressed action on the CNS. It potentiates action of sedative and analgesic drugs.

Promethazine is used for treating allergic illnesses such as hives, serum disease, hay fever, dermatosis, and also for rheumatism with expressed allergic components, for allergic complications caused by antibiotics and other medicinal drugs, and for enhancing action of analgesics and local anesthetics. Synonyms of this drug are allergen, phenergan, pipolphen, prothazine, and others.

Trimeprazine: Trimeprazine, 10-(3-dimethylamino-2-methylpropyl) phenothiazine (16.1.19), is synthesized by alkylating phenothiazine with 1-dimethylamino-2-metylpropylchloride [38].

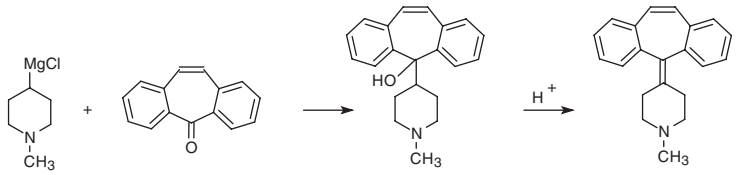


16.1.19

Trimeprazine is used for treating itching during dermatitis of both allergic and nonallergic origin. A synonym of this drug is temaril.

16.1.6 Piperidines

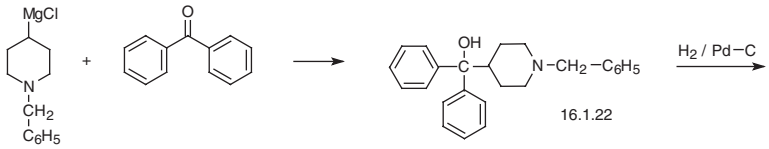
Cyproheptadine: Cyproheptadine, 4-(dibenzo[a,d]cyclohepten-5-ylidene)-1-methylpiperidine (16.1.21), is synthesized by reacting 1-methyl-4-magnesiumchloropiperidine with 5*H*-dibeno[a,d]cycloheptene-5-one, which forms carbinol (16.1.20), the dehydration of which in an acidic medium leads to the formation of cyproheptadine (16.1.21) [39,40].



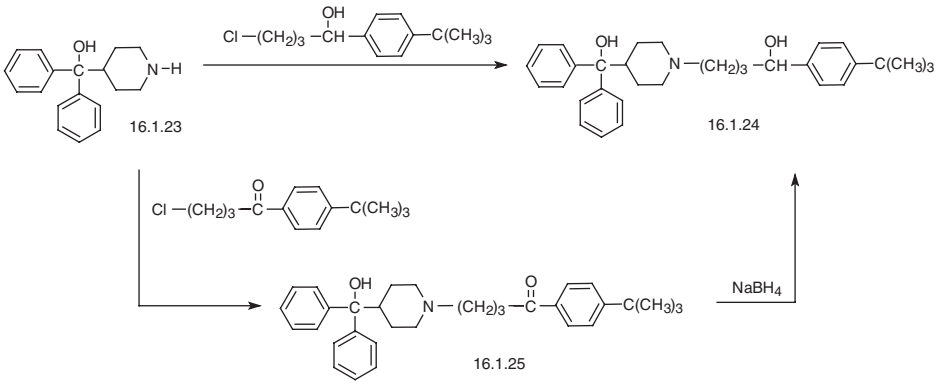
16.1.20 16.1.21

Cyproheptadine has antianaphylactic activity that is associated with its ability to slow down the release of histamine and other mediators from fat cells. It is mainly used for treating bronchial asthma attacks, allergic bronchitis, rhinitis, and allergic skin reactions as well as in adjuvant therapy for anaphylactic reactions. Synonyms of this drug are periactin and vimicon.

Terfenadine: Terfenadine, α-(4-*tert*-butylphenyl) -4-hydroxydiphenylmethyl)-1-piperidinebutanol (16.1.24), is synthesized in two ways. According to the first, benzyl-4-magnesiumchloropiperidine is reacted with benzophenone, giving (1-benzyl-4-piperidyl) diphenylcarbinol (16.2.22), which undergoes further debenzylation by reduction with hydrogen using a palladium over carbon catalyst, giving (4-piperidyl)diphenylcarbinol (16.2.22). This product is alkylated by either 1-(4-*tert*-butylphenyl)-4-chlorobutanol, which forms terfenadine (16.1.24), or by alkylating with (4-*tert*-butylphenyl-3-chloropropiophenone, which forms the product (16.1.25), the carbonyl group of which is reduced to an alcohol group, thus giving the desired terfenadine (16.1.24) [41–46].

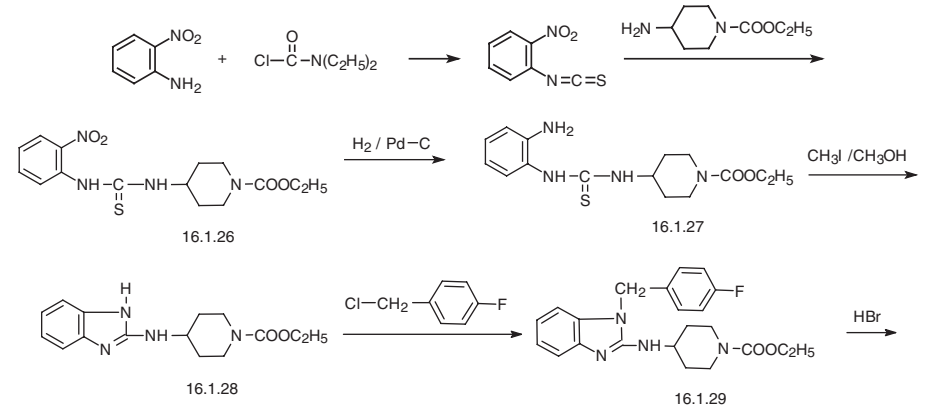


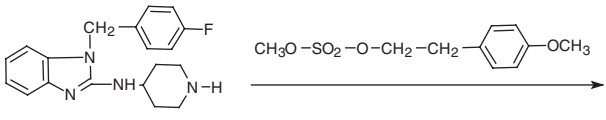
16.1.22



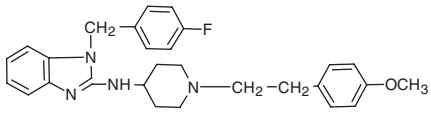
Terfenadine not only differs from the other antihistamine drugs in its chemical structure, but also in that its action begins within 1–2 h and last approximately 12 h, reaching its peak of action in 3–4 h. It is used for relieving symptoms associated with seasonal allergic rhinitis and conjunctivitis, for angioneurotic edema and allergic skin reaction, and also as an ingredient of complex therapy for bronchial asthma. Synonyms of this drug are seldane, hystadin, trexil, and others.

Astemizole: Astemizole, 1-[(4-fluorophenyl)methyl]-*N*-[1-[2-(4-methoxyphenyl) ethyl]-4-piperidinyl]-benzimidazol-2-amine (16.1.31), is synthesized in a multi-stage synthesis from 1-carbethoxy-4-aminopiperidine and 2-nitroisothiocyanobenzol, from which a derivative of thiourea (16.1.26) is synthesized upon their reaction. The nitro group of the product is reduced and the further *S*-methoxided. In reaction conditions intermolecular cyclization into a derivative of benimidazol, *N*-[1-[2-(4-carethoxy)]-4-piperidinyl]benzimidazol-2-amine (16.1.28) occurs. The obtained aminobenzimidazole derivative is alkylated with 4-fluorobenzylchoride into 1-[(flurophenyl)methyl]-*N*-[1-[2-(4-carethoxy)]-4-piperidinyl] benzimidazol-2-amine (16.1.29). The carbethoxyl group of the resulting compound (16.1.29) is hydrolyzed by hydrobromic acid, forming a non-substituted on the nitrogen atom derivative of piperidine (16.1.30), the alkylation of which with 2-(4-methoxyphenyl)ethylmetanesulfonate leads to the formation of astemizole (16.1.31) [47,48].





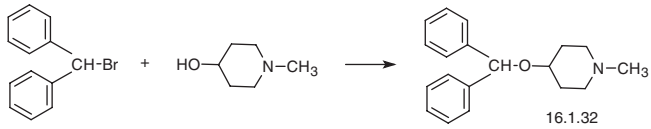
16.1.30



16.1.31

Astemizole is used for preventing and treating severe seasonal and chronic allergic rhinitis, allergic conjunctivitis, hives, Quinke's edema, other allergic conditions and dermatitis. Synonyms of this drug are hismanal, histazol, and others.

Diphenylpyraline: Diphenylpyraline, 4-diphenylmethoxy-1-methylpiperidine (16.1.32), is synthesized by alkylating 4-hydroxy-1-methylpiperidine with benzhydrylbromide [49,50].



16.1.32

Diphenylpyraline is an antihistamine drug with anticholinergic and sedative action.

It is intended for symptomatic treatment of seasonal allergies and allergic reactions as well as an adjuvant drug in anaphylactic reaction therapy. Synonyms of this drug are arbid, timpil, histryl, hispril, and others.

16.2 H_2 RECEPTOR ANTAGONISTS

H_2-receptor antagonists almost completely block secretion of hydrochloric acid in the stomach in response to most stimuli. These drugs play a major role in treating stomach ulcers associated with hypersecretion, because they have the ability to reduce both the volume of stomach secretion and overall acidity as well as pepsin activity.

Drugs of this kind are used for treating stomach and duodenum ulcers and hypersecretive conditions.

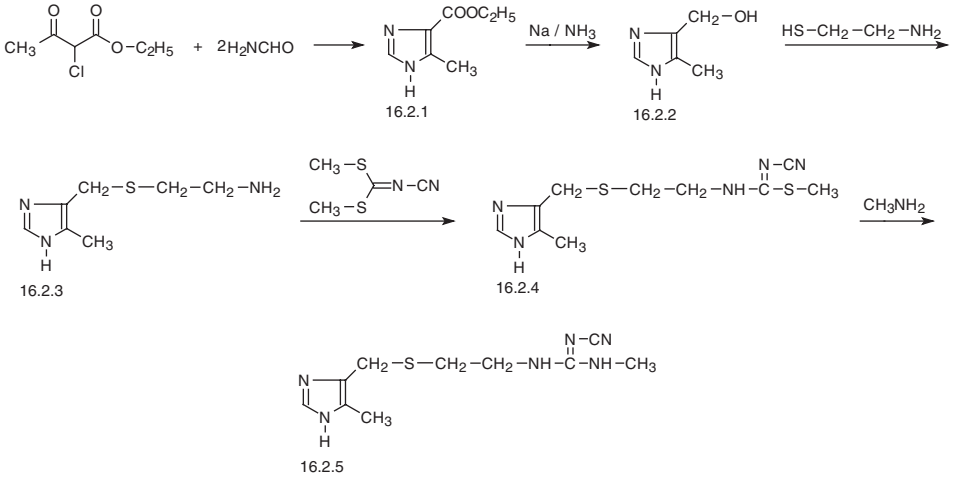
Traditional or H_1 antihistamine drugs block many effects caused by histamine; however, it turns out that they are not able to withstand events mediated by H_2 receptors, in particular excess gastric juice secretion. In 1977 an H_2-receptor antagonist, cimetidine, was proposed, which revolutionized stomach ulcer treatment. Later on, ranitidine was proposed, followed by drugs with minor structural and pharmacological differences such as famotidine and nizatidine.

H_2-receptor antagonists reversibly and competitively inhibit histamine action on H_2 receptors. They are pure antagonists since they do not affect H_1 receptors, β-adrenoreceptors, or muscarinic receptors.

Moreover, they do not have a significant effect on the synthesis, release, and biotransformation of histamine.

The structure of cimitidine is synthesized up of a methylimidazol ring with a sulfur-containing side chain with a cyanoguanidine group. It seemed that the presence of an imidazol ring in cimetidine contained in the structure of histamine should be the determining factor in the exhibition of H_2 blocking activity; however, the formation of ranitidine, famotidine, and nizatidine, which contain furane and thiazol rings in place of an imidazole ring showed the incorrectness of this suggestion.

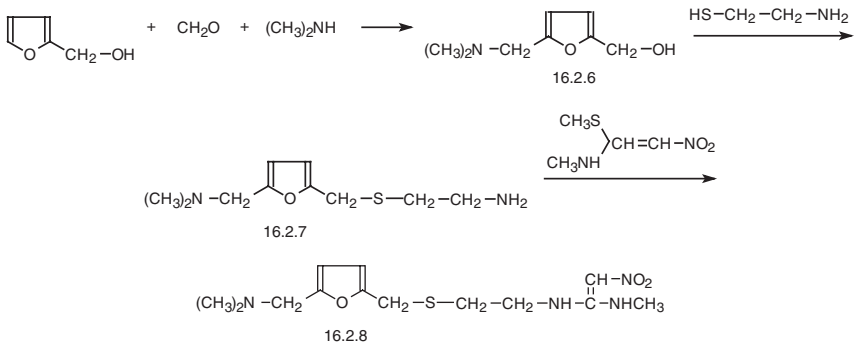
Cimetidine: Cimetidine, 1-cyano-2-methyl-3-[2-[[5-[[methylimidazol-4-yl)methyl]thio] ethyl] guanidine (16.2.5), is synthesized in the following manner. Reacting 2-chloroacetoacetic ether with two moles of formamide gives 4-carbethoxy-5-methylimidazol (16.2.1). Reduction of the carbethoxy group of this produced with sodium in liquid ammonia gives 4-hydroxymethyl-5-methylimidazol (16.2.2). The hydrochloride of the resulting alcohol is reacted with 2-mercaptoethylamine hydrochloride to produce 4-(2-aminomethyl)-thiomethyl-5-methylimidazol dihydrochloride (16.2.3). This is reacted with *N*-cyanimido-*S*,*S*-dimethyldithiocarbonate to give a thiourea derivative (16.2.4), which upon reaction with methylamine turns into cimetidine (16.2.5) [51–58].



Cimetidine is a representative of first-generation antihistamine drugs that block H_2 receptors. The main pharmacological effect of cimetidine is the suppression of gastric juice secretion associated with H_2 receptors of the stomach walls. It suppresses both basal and stimulated hydrochloric acid produced by food as well as histamine and gastrine, which simultaneously lower pepsin activity.

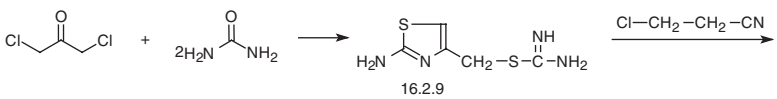
Cimetidine is used for treating ulcer problems of the stomach and duodenum and for other conditions accompanied by an elevation of acidity and excess secretion of gastric juice. It is used for preventing injuries and the blood flow of the upper regions of the gastrointestinal tract. Synonyms of this drug are tagamet, cinamet, and belomet.

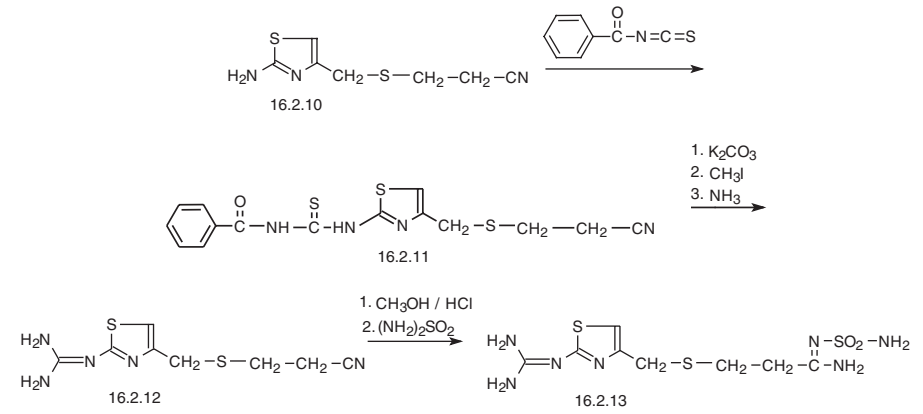
Ranitidine: Ranitidine, *N*[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-*N*′-methyl-2-nitro-1,1-ethendiamine (16.2.8), is synthesized from furfuryl alcohol, which undergoes aminomethylation reaction using dimethylamine and paraform, which form 5-(dimethylaminomethyl)furfuryl alcohol (16.2.6). Further reaction with 2-mercaptoethylamine hydrochloride gives a product of substitution of the hydroxyl group in (16.2.6), 5-dimethylaminomethyl-2-(2′-aminoethyl)thiomethylfurane (16.2.7). Reacting this with *N*-methyl-1-methylthio-2-nitroethenaamine gives ranitidine (16.2.8) [59–64].



Ranitidine is a second-generation H_2-receptor-blocking drug. Like cimetidine, ranitidine suppresses both basal and stimulated hydrochloric acid produced by food, histamine, gastrin, and acetylcholine. It simultaneously reduces pepsin activity and is used for treating stomach and duodenum ulcers as well as other conditions accompanied by elevated acidity of the gastrointestinal tract. Synonyms of this drug are zantac, azantac, raniplex, ranidil, and others.

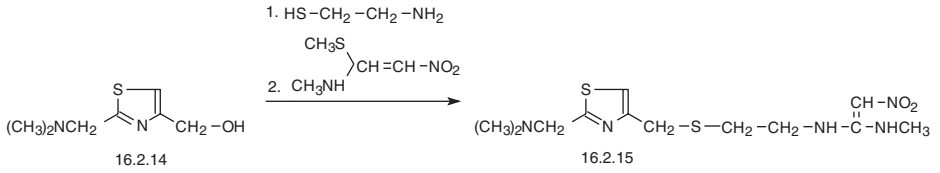
Famotidine: Famotidine, 3-[[[2-[(aminomethyl)amino]-4-thiazolyl] methyl]thio]-*N*-(aminosulfonyl)propanimidamide (16.2.13), is synthesized from *S*-(2-aminothiazol-4-yl-methyl)isothiourea (16.2.9), which is synthesized by reacting 1,3-dichloroacetone with two molecules of thiourea, during which a thiazol ring is formed and the chlorine atom is substituted, giving an intermediate 2-amino-5-chlormethylthiazol. Reacting this with 2-chlorpropionitrile gives *S*-(2-aminothiazol-4-yl-methyl)-2-cyanoethane (16.2.10), which in turn is reacted with benzoylizthiocyanate. The resulting benzoylthiourea derivative (16.2.11) first undergoes S-methylation by methyliodide and further cleaved by ammonia into 3-[[[2-(aminomethyl)amino]-4-thiazolyl]-methyl]thio]ethylcyanide (16.2.12). Successive methanolysis of the nitrile group and subsequent reaction of the resulting iminoether with sulfonamide gives famotidine (16.2.13) [65–70].





Like ranitidine, famotidine belongs to the group of second-generation H_2-receptor-blocking drugs, and also like two other drugs described above, it is used for treating stomach and duodenum ulcers and other conditions accompanied by elevated acidity of the gastrointestinal tract. Synonyms of this drug are famodil, gastridin, pepcid, and others.

Nizatidine: Nizatidine is *N*-[2-[[[2-[(dimethylamino)methyl]-4-thiazolyl]methyl] thio] ethyl]-2-nitro-1,1-ethenediamine (16.2.15). According to its chemical structure, nizatidine is somewhat of a hybrid structure of ranitidine and famotidine, in which a side chain of ranitidine and carrying heterocycle, 2-aminothiazol, are used. Likewise, its synthesis also is a specific combination of pathways used for making both prototype drugs. 2-(Dimethylaminomethyl)-4-hydroxymethylthiazol serves as the initial compound, from which the desired nizatidine (16.2.15) is synthesized by subsequent reaction with 2-mercaptoethylamine hydrochloride and then with *N*-methyl-1-methythio-2-nitroethenamine [71,72].



Like other drugs described above, nizatidine is used for treating stomach and duodenum ulcers and other conditions accompanied by elevated acidity of the gastrointestinal tract. Synonyms of this drug are axid and pulvules.

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– 17 –

Cardiotonic Drugs

Drugs that increase the contractile power of the myocardium and thus enhance its capability and efficacy are called cardiotonic agents. This definition has traditionally referred to a group of drugs called cardiac glycosides (strophanthin, digitoxin, digoxin); however, new cardiotonic drugs (nonglycoside cardiotonic agents that inhibit phosphodiesterases, amrinone, and milrinone) that exhibit similar properties have recently been introduced into medical practice.

Cardiac glycosides are drugs used in the treatment of congestive heart failure or cardiac arrhythmia, by inhibiting the Na^+/K^+ pump. This inhibition increases the amount of Ca^{2+} ions available for contraction and improves cardiac output and reduces distention of the heart. Cardiac glycosides are extracted from plant material.

Cardiotonic agents are sometimes called positive inotropic drugs, i.e. substances that enhance the strength of muscle contractions, and in this case those that enhance the strength of myocardium contraction. Cardiotonic drugs are intended for treating cardiac insufficiency.

Cardiac insufficiency is a very common disease. It can be defined as an inability of the heart to pump a sufficient amount of blood to supply oxygen and nutrients to organs and tissue, which leads to fatigue, shortness of breath, and edema. Cardiac insufficiency is most often caused by arterial hypertension and ischemic heart disease. It can be manifested in severe form, as a sharp decline in cardiac output with symptoms of disrupted blood flow, and in chronic form, which is manifest as heart pain.

In addition to inotropic agents, also used for treating cardiac insufficiency are: diuretics (Chapter 21), which increase sodium ion and water secretion from the organism, lower the volume of circulated blood, increase the workload on the heart, and relieves edema; vasodilating agents (vasodilators), which facilitate reduction of venous and arterial blood pressure, thus reducing vessel tonicity and therefore workload on the heart, and reducing the need for oxygen. Adrenomimetics, epinephrine (adrenaline), norepinephrine (noradrenaline), isoproterenol, terbutaline, and albuterol are sometimes also used because of their ability to enhance strength of cardiac contractions and stimulate an elevation in cardiac output. However, the simultaneous raise in heart rate, have arrythmogenic action, and also increase the myocardial need for oxygen, which is undesirable and can lead to increased ischemia. Dopamine and levodopa are also sometimes used. Levodopa turns

into dopamine in the organism, thus being an oral form of dopamine in the form of a prodrug.

All of the mentioned sympathomimetics are limited to short-term use (24 h or less) for supporting the heart.

Optimal therapy for cardiac insufficiency frequently requires simultaneous use of two or more of the aforementioned groups of drugs.

17.1 CARDIAC GLYCOSIDES

Glycosides isolated from leaves of various types of foxglove *Digitalis lanta*, *Digitalis purpurea*, and strophanthus *Strophantus kombe*, and also a number of other plants (lilies, periploca, oleander, hellebore, erysimum, jute, Irish ballon), which exhibit a direct effect on the myocardium and which strengthen its contractions.

The main property of cardiac glycosides is their selective action on the heart, the main effect of which is the strengthening of systole, which creates a more economic condition for heart work: strong systolic contractions change into periods of "rest" (diastole), which facilitate restoration of energetic resources of the myocardium.

The general cardiodynamic effects of cardiac glycosides are quite complex because of the combination of their direct action on the heart and indirect action, which changes the electrophysiological properties of the heart (automatism, conductivity, and excitability).

There is reason to believe that cardiac glycosides, like other inotropic substances, act on the contractibility of the heart by affecting the process of calcium ion transfer through the membrane of myocardiocytes. The effect of cellular membranes in electric conductivity is mediated by transport of sodium, calcium, and potassium ions, which is a result of indirect inhibitor action on the (Na^+–K^+) ATPase of cell membranes.

Cardiac glycosides are used for treating severe, chronic cardiac insufficiency, for certain forms of cardiac arrhythmia, and for cardiac shock. They are examined as a single group since they have similar pharmacological characteristics. They can have the same aglycon, but various sugar residues, and *vice versa*. When choosing a drug of this series, not only its activity should be taken into consideration, but also the speed with which it takes effect, which depends a great deal on the physicochemical properties of this series of drugs, which can be subdivided into polar and nonpolar. Strophanthin, which is used in injectable form and whose effect is already observed within 5–10 min after introduction, is usually grouped with polar (hydrophilic) glycosides. Digitoxin and digoxin, which are generally taken orally or rectally, and whose effects are seen within 2–4 h after introduction are grouped with nonpolar glycosides. The choice of drugs and method of administration also depends on symptoms. Strophanthin or corglucon are intravenously administered for severe cardiovascular insufficiency and sudden decompensation. Digitoxin and digoxin are taken orally for chronic cardiac insufficiency.

That which is usually extracted from both types of *Digitalis* is made up of already partially hydrolyzed glycosides. Purpureaglycoside A and B are natural glycosides contained in *Digitalis purpurea* that are broken down by enzymes into digitoxin and glucose, or

likewise gitoxin and glucose, and it is completely hydrolyzed by acid into digitoxingenin aglycons, or digitoxingenin, and also digitose and glucose deoxysugars.

Digitalis lanta contains glycosides—lanthozides A, B, and C. During alkaline hydrolysis, Lanthozide A liberates an acetyl group and turns into purpureaglycoside A, while lanthozide B turns into purpureaglycoside B. The structure of two of these lanthozides, lanthozide B and lanthozide C differs only in that lanthozide B has a hydroxyl group at C_{16} of its genin (ditoxigenin), while in the genin of lanthozide C (digoxigenin) there is an additional hydroxyl group at C_{12} of genin.

The product usually extracted from both types of *Digitalis* is made up of already partially hydrolyzed glycosides, namely digitoxin and digoxin.

Digoxin is isolated only from *Digitalis lanta.*

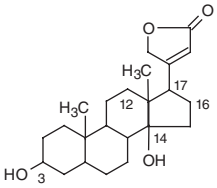
A mixture of cardiac glycosides isolated from *Strophantus kombe* mainly contains K-strophanthin-β and K-strophanthozide.

K-Strophanthin-β consists of the aglycon of strophanthidin and a sugar residue made up of cymarose-β-D-glucose. K-strophantozide has a sugar residue of three units: cymarose-β-D-glucoso-α-D-glucose. Use of the term *strophanthin* generally refers to all glucosides of this series.

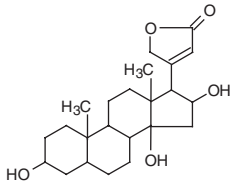
The carbohydrate part of various cardiac glycosides can be mono-, di-, tri-, and tetrasaccharide, and the aglycon (genin) is a steroid with certain unique structural characteristics. The main purpose of sugar residues is evidently to facilitate solubility of genins.

The following unique structural features are characteristic of glycons of cardiac glycosides: a coupling of rings A and B—*cis*, rings B and C—*trans*, rings C and D—*cis*, and a butenolide region is located at position 17β. Most of the compounds belong to the 5β series. With one exception, the hydroxyl group at C_3 also has β-configuration. Physiologically active compounds must contain a hydroxyl group at 14β. OH and CO groups at positions 11, 12, 16, and 19 evidently have less of an effect on activity.

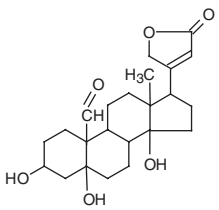
The main purpose of sugar residues, which esterify hydroxyl groups at C_3, evidently lies in facilitating the solubility of genins. The most simple cardiac genins, digitoxigenin, gitoxigenin, and strophanthidin are aglycons of the most important glycosides *Digitalis lanta*, *Digitalis purpurea*, *and Strophantus kombe.*



digitoxigenin

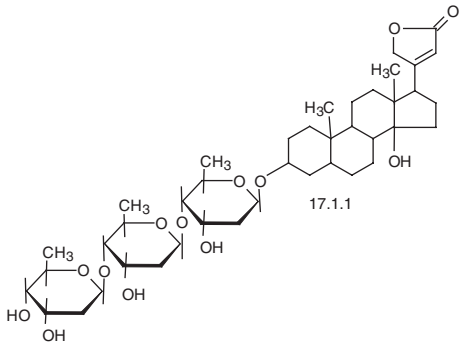


gitoxigenin



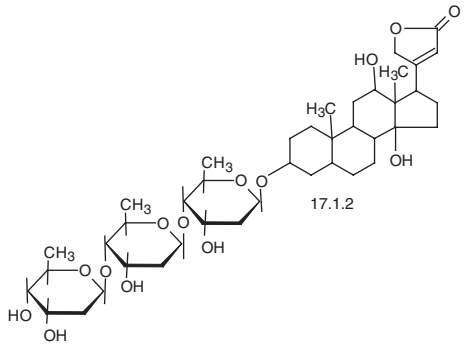
strophanthidin

Digitoxin: Digitoxin, 3b,14b-dihydroxy-5b-card-20(22)enolide-3-tridigitoxide (17.1.1), is a glycoside isolated from leaves of various types of foxgloves. About 6 g of digitoxin are isolated from 10 kg of leaves [1–9].



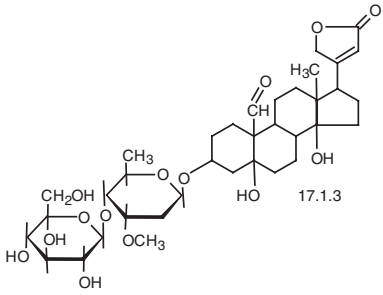
Digitoxin is used for chronic cardiac insufficiency, tachyarrhythmia form of atrial fibrillation, paroxysmal ciliary arrhythmia, and paroxysmal supraventricular tachycaria. Synonyms of this drug are cardigin, cordalin, crystodigin, purodigin, and others.

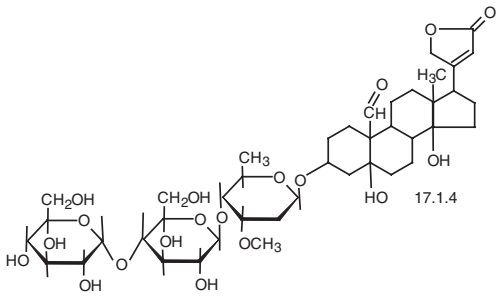
Digoxin: Digoxin, 3β,14β-dihydroxy-5β-card-20(22)-enolide-3-rigitoxide (17.1.2), is also a glycoside isolated from various types of foxgloves. It differs from digitoxin in that it has an additional hydroxyl group at C_{16} of the steroid skeleton. It is extracted form the leaves of *Digitalis lanta*, *Digitalis orientalis*, or *Scrophulariaceae* [10–16].



Digoxin exhibits strong systolic action and slows heart rate. It is removed from the organism faster than digitoxin. It is used from chronic cardiac insufficiency in decompensated valvular disease of the heart, myocardium overload in arterial hypertension, tachycardia, ventricular fibrillation, and other analogous situations. Synonyms of this drug are cedoxin, lanacordin, lanoxin, and others.

Strophanthin: Strophanthin is made up of a mixture of glycosides, mainly K-strophanthin-β, 3β,5,14-trihydroxy-10-oxo-5β-card-20(22)-enolide-3-D-cymaro-β-D-glycoside (17.1.3), and K-strophanthoside, 3β,5,14-trihydroxy-10-oxo-5β-card-20(22)-enolide-3-D-cymaro-β-D-gluco-α-D-glycozide (17.1.4). It is isolated primarily from the family *Strophantus kombe* [17, 18].





Strophanthin is used in severe cardiovascular insufficiency, in particular after myocardial infarction, for chronic cardiac insufficiency, cardiac decompensation, supraventricular tachycardia, and ventricular arrhythmia. Synonyms of this drug are combetin, strofopan, and others.

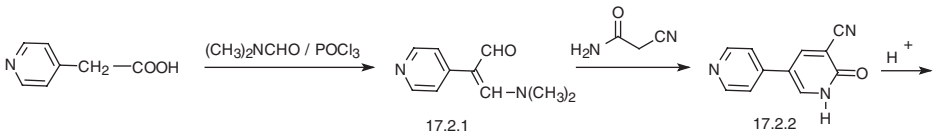
17.2 OTHER POSITIVE INOTROPIC DRUGS

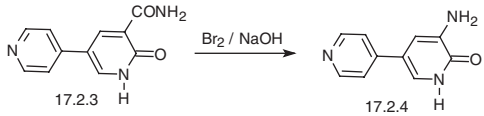
There is no doubt that the aforementioned glycosides are the most satisfactory inotropic compounds. However, digitalis drugs can be counter productive in some patients for a number of reasons. Theophylline has been intensively studied as an inotropic agent; however, it turned out to be unfit for long-term use.

Derivatives of the bipiridine series, such as amrinone and minrinone, have recently been found useful as inotropic agents.

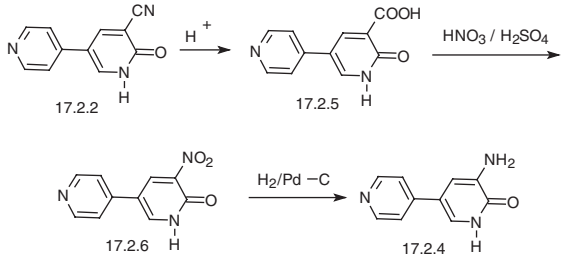
The mechanism of action of these drugs is not completely understood. However, it is very likely that they inhibit cellular phosphodiesterase of the myocardium, which leads to an elevation in the cellular level of cyclic AMP, which in turn facilitates contraction of myocardial cells. It is clear that these drugs are not β-adrenoreceptor antagonists, and that their effect is not mediated by inhibition of (Na^+–K^+) ATPase. They simultaneously increase the flow of calcium ions into the cell. They are used for short-term control of patients that inadequately react to cardiac glycosides, diuretics, and coronary vasodilating agents.

Amrinone: Amrinone, 3-amino-5-(4-piridinyl)-2(1*H*)-pyridinone (17.2.4), can be synthesized from piridine-4-acetic acid, the reaction of which with a mixture of diemthylformamide—phosphorous oxychloride gives 2-(4-piridyl)-3-dimethylaminoacrolein (17.2.1). Reacting this with cyanoacetamide gives 3-cyano-5-(4-piridyl)-2(1*H*)-pyidinone (17.2.2). Hydrolysis of the cyano group of this product gives 3-carbamyl-5-(4-piridyl)-2(1*H*)-pyidinone (17.2.3). A Hofmann rearrangement of this product (using bromine in sodium hydroxide) gives amrinone (17.2.4).

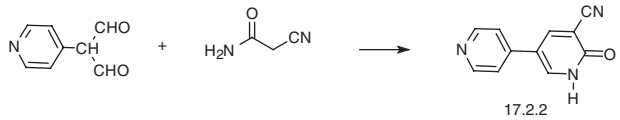




An alternative method for the synthesis of amrinone from 3-cyano-5-(4-piridyl)-2(1*H*)-pyridinone (17.2.2) is based on it's acidic hydrolysis to the corresponding acid, 3-carboxy-5-(4-piridyl)-2(1*H*)-pyridinone (17.2.5), nitration of which with nitrous acid in the presence of sulfuric acid forms 3-nitro-5-(4-piridyl)-2(1*H*)-pyridinone (17.2.6). Reducing the nitro group of this product with hydrogen gives the desired amrinone (17.2.4) [19, 20].

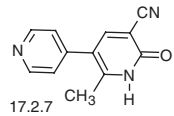


3-Cyano-5-(4-piridyl)-2(1*H*)-pyridinone (17.2.2) is also synthesized by condensing 2-(4-piridyl)malonaldehyde with cyanoacetamide [21].



Amrinone is a derivative of bipiridine and has found a very beneficial niche in the arsenal of inotropic agents for short-term use, and in situations where the organism inadequately responds to glycoside drugs and coronary dilating agents. It is unique in that it causes dilation of vessels and does not cause arrhythmia or signs of myocardial arrhythmia. Amrinone is used for short-term treatment of cardiac insufficiency that does not respond to treatment of other drugs. Synonyms of this drug are inocor and vinocarm.

Milrinone: Milrinone, 1,6-dihydro-2-methyl-6-oxo-(3,4′-bipiridin)-5-carbonitrile (17.2.7), is a methylated analogue of the intermediate product of amrinone synthesis (17.2.2).



Milrinone possesses the same properties as amrinone, is better tolerated when used orally, and is a more powerful drug; however, it is not recommended for use in the USA for a number of reasons. A synonym of this drug is primacor.

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– 18 –

Antiarrhythmic Drugs

Drugs used for preventing and treating irregular heart rate and heartbeat are called antiarrhythmic drugs. Arrhythmia results from disruptions in the formation of electric impulses and their conduction to the heart, or when both of these happen simultaneously. Heart rate is regulated by acetylcholine and norepinephrine (noradrenaline). Heart rate normally depends on the activity of pacemaker cells of the synoatrial ganglia. When their function is disrupted, heart rate is disturbed, thus resulting in various clinical symptomology. Arrhythmia may also be associated with ectopic centers, which generate impulses more frequently than normal pacemakers.

The rhythm of heart contractions depends on many parameters: condition of pacemaker cells and the conduction system, myocardial blood flow, and other factors; consequently, arrhythmia can originate for different reasons that are caused by disruptions in electrical impulse generation or conduction. They can be caused by heart disease, myocardial ischemia, electrolytic and acid–base changes, heart innervation problems, intoxication of the organism, and so on.

Drugs used for treating arrhythmia can have an effect on the electrical conduction system of the heart, its excitability, automatism, the size of the effective refractory period, and adrenergic and cholinergic heart innervation. Accordingly, compounds of various chemical classes can restore heart rate disturbances.

As already noted, arrhythmia originates from problems forming electric impulses and propagating them to the heart, or when both of these happen simultaneously, which can be accomplished by transferring Na^+, K^+, and Ca^{2+} ions through cell membranes. Therefore, the mechanism of action of many antiarrhythmic drugs consists of blocking Na^+ and Ca^+ ion channels of the myocardium, which prolongs the time necessary for restoration after being activated by these channels, and which in turn acts on the electrical conduction system of the heart, its excitability, automatism, and so on.

Based on an understanding of the mechanism that causes tachycardia, which requires a good understanding of electrophysiology, and an understanding of the effects of various group of drugs on this mechanism, in most cases a specific drug for a specific patient can almost always be selected.

Classifying antiarrhythmic drugs is based on different principles; for example, the location of the drug action. They can be substances that act directly on the myocardium and the conduction system of the heart itself, or substances that have an effect on the efferent

innervation of the heart. They can be viewed as groups of drugs effective for supraventricular arrhythmia, and those effective for ventricular arrhythmia.

Currently, however, the more or less universally accepted classification of drugs used for treating tachyarrhythmia is based on the characteristics of their effect on electrophysiological or biochemical processes in the myocardium.

Antiarrhythmic drugs can therefore be subdivided into four main groups. The first group is made up of drugs that block Na^+ channels of the myocardium (quinidine, procainamide, disopyramide, lidocaine, tocainide, phenytoin, mexiletine, flecainide, encainide). Drugs that block action of endogenous catecholamines on the heart that have certain significance in the pathogenesis of arrhythmia belong to the second group of antiarrhythmia drugs (β-blockers—propranolol etc.). The third group is made up of drugs, which predominantly block the potassium channels, thereby prolonging repolarization. Since these agents do not affect the sodium channel, conduction velocity is not decreased (amiodarone, bretylium). Finally, the fourth group of antiarrhythmic drugs is represented by antianginal drugs—Ca^{2+} channels blockers (verapamil).

These groups, in particular the first group, are in turn subdivided based on specific characteristics of various substances within that group.

Some researchers adhere to a system of dividing antiarrhythmic drugs into five groups without putting them in subgroups.

18.1 GROUP I DRUGS

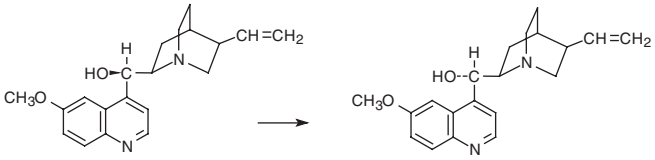
Drugs belonging to this group are, with a few rare exceptions, local anesthetics which form complexes with lipoproteins of cell membranes of the myocardia, thus blocking Na^+ channel conductivity and the flow of Na^+ into the cell, and facilitate the release of K^+ from myocardial cells, which as a result leads to a weak suppression of depolarization of myocardial cells, reduction of repolarization time, and a slowing of the propagation of excitation. This series of drugs prolongs action potentials and increases the effective refractory period of the myocardium. Automatism of ectopic centers is suppressed in the myocardium, primarily in the ventricles.

18.1.1 Subgroup IA

Drugs of this subgroup slow down the speed of transmitting excitation, reduce excitability of Purkinje fibers, suppress automatism of ectopic regions and increase the effective refractory period. They exhibit direct and mediated anticholinergic action. The antiarrhythmic drugs quinidine, procainamide, and disopyramide belong to this subgroup. Drugs of this subgroup are used for treating irregular sinus rhythm, paroxysmal, supraventricular, and ventricular arrythmia, preventing arterial fibrillation, and premature heartbeats.

Quinidine: Quinidine, (5-vinyl-2-quinyclidinyl)-(6-methyoxy-4-quinolyl)-methanol (18.1.1) is the dextro-isomer of the alkaloid quinine and is one of the four most important alkaloids, which are isolated from the bark of the cinchona tree [1–3]. Quinidine is a secondary alcohol,

the radicals in which are a 5-methyoxyquinoline ring and 3-vinylquinuclidine. Quinidine only differs from quinine in the configuration of the carbon atom of the carbinol group, and it can be made by isomerization of quinine (37.1.1.47) [4]. Quinidine is proposed to synthesize by different ways [5–7].

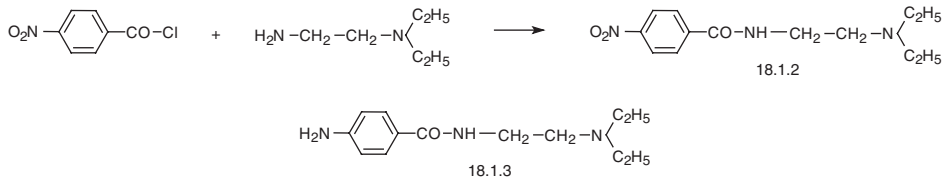


37.1.1.47 18.1.1

Quinidine exhibits all of the pharmacological properties of quinine, including antimalarial, fever-reducing, and other properties. Quinidine is used in various forms of arrhythmia for preventing tachycardia and atrial fibrillation, and particularly for preventing ciliary fibrillation, paroxysmal supraventricular tachycardia, extrasystole, and ventricular tachycardia. However, it is a toxic drug and is used relatively rarely.

It is also prescribed under the name cardioquin, duraquin, quinidex, and others.

Procainamide: Procainamide, 4-amino-N-[2-(diethylamino)ethyl]benzamide (18.1.3), is synthesized by reacting 4-nitrobenzoic acid chloride with N,N-diethylethylendiamine and subsequent reduction of the nitro group of the resulting 4-nitro-N-[2-(diethylamino)ethyl]benzamide (18.1.2) into an amino group [8,9].

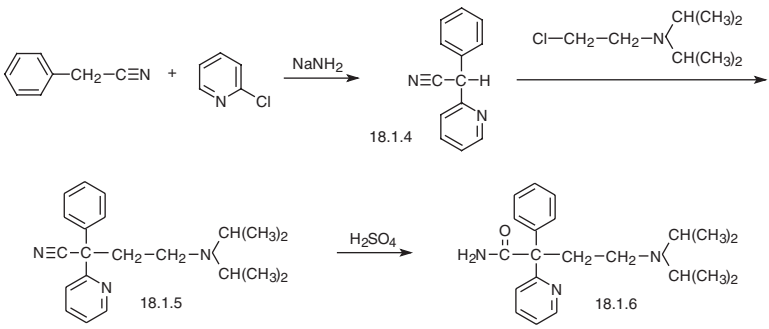


The chemical difference between procainamide and procaine lies in the replacement of the ester group with an amide group. The action of procainamide is qualitatively similar to the action of procaine. Its effect on the heart is identical to that of quinidine. As an antiarrhythmic, procainamide is preferred over procaine because unlike procaine, it is better absorbed when taken orally and it is more difficult for the esterases of the plasma to hydrolyze it, which results in long-lasting action.

Procainamide is intended for treating paroxysmal atrial tachycardia, atrial fibrillation, premature ventricular contraction, and ventricular tachycardia. For quickly reaching therapeutic concentrations, parenternal introduction of procainamide is preferred over cynidine. Synonyms of this drug are amidoprocaine, cardiorythmine, novocainamide, pronestyl, and others.

Disopyramide: Disopyramide, α-(2-diisopropylaminoethyl)-α-phenyl-2-pyridineacetamide (18.1.6), is synthesized by arylating benzylcyanide with 2-chloropiridine in the presence of sodium amide and subsequent alkylation of the resulting α-phenyl-α-(2-pyridyl) acetonitrile

(18.1.4) with 2-diisopropylaminoethylchloride using sodium amide. Sulfuric acid hydrolysis of the resulting nitrile (18.1.5) leads to the formation of α-(2-diisopropylaminoethyl)-α-phenyl-2-pyridineacetamide, disopyramide [10–12].



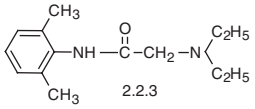
Structurally, disopyramide does not belong to any of the known classes of antiarrhythmics; however, being a drug of the class IA sodium channel blockers, it exhibits membrane-stabilizing action and increases the effective refractory period and duration of an action potential in the atrium and ventricles. It causes a decrease in contractability and excitability of the myocardium, slowing of conductivity, and suppression of sinoatride automatism. Disopyramide is used for preventing and restoring atrial and ventricular extrasystole and tachycardia in order to prevent atrial flutter and arrhythmia.

This drug is also prescribed under the name dicorantil, dimodan, napamid, norpace, rhythmilen, rhythmodan, and others.

18.1.2 Subgroup IB

Drugs of subgroup IB increase the electrical threshold of ventricular excitation during diastole, suppress automatism and diastolic depolarization, reduce the duration of the refractive period, and differ from drugs of subgroup IA in that if they block open Na^+ channels, then drugs of subgroup IB mainly block inactive Na^+ channels. This means that they have little effect on healthy regions of the myocardium because they are quickly eliminated from normal, open Na^+ channels. In terms of myocardial ischemia, hypoxia causes cellular membranes to depolarize and arrhythmogenic centers to emerge. During this, many Na^+ channels are inactivated and become sensitive to drugs of this class, which increase conductivity and reduce the repolarization time of heart cells. Drugs of subgroup IB have little effect on muscles of the atrium, arterioventricular conductivity, myocardial contraction, cardiac output, and systolic arterial pressure. Drugs of this subgroup—lidocaine, tocainide, and mexiletine are local anesthetics; however, they are used for severe ventricular arrhythmia that can originate during myocardial infarction, surgical intervention, catheterization of the heart, and intoxication by cardiac glycosides. Penytoin, which does not belong to the class of local anesthetics and is an anticonvulsant drug, is used only as an oral agent, thus replacing lidocaine in paroxysmal tachycardia caused by intoxication.

Lidocaine: Lidocaine is 2-diethylamino-2′,6′-dimethylacetanilide (2.2.3). Synthesis of lidocaine is described in Chapter 2.

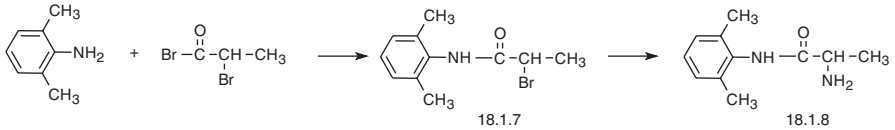


2.2.3

Lidocaine is a prototype of antiarrhythmic drugs of subgroup IB, and is widely used for treating and preventing ventricular ectopic activity during myocardial infarction.

Like procainamide, lidocaine is an amide with local anesthetizing action. Lidocaine is usually administered intravenously for short-term therapy of ventricular extrasystole, tachycardia, especially in the severe phase of myocardial infarction, arrhythmia of natural cause, and for arrhythmia that can originate in the heart during surgical manipulations. Synonyms of this drug are lidopen, xylocaine, xylocard, and others.

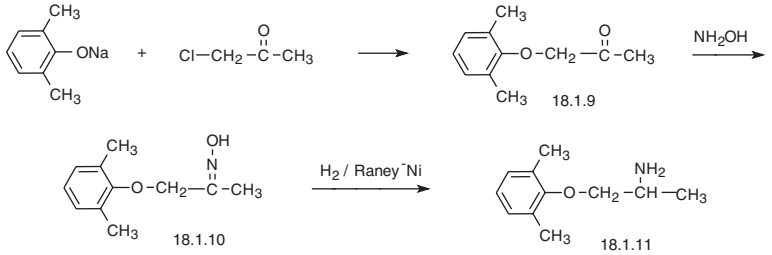
Tocainide: Tocainide, 2-amino-2′,6′-dimethylpropionanilide (18.1.8), is synthesized by reacting 2,6-dimethylaniline with 2-bromopropionic acid bromide and subsequent substitution of the bromine atom in the resulting amide (18.1.7) with an amino group [13–16].



18.1.7 18.1.8

Tocainide is used for suppressing symptoms of ventricular arrhythmia and tachycardia, and for premature cardiac contractions. A synonym of this drug is tonocard.

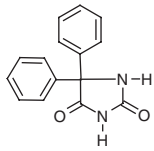
Mexiletine: Mexiletine is 1-methyl-2-(2′,2′-dimethylphenoxy)ethylamine (18.1.11). Mexiletine is synthesized by reacting the sodium salt of 2,6-dimethylphenol with chloroacetone, forming 1-(2,6-dimethylphenoxy)-2-propanone (18.1.9). Reacting this with hydroxylamine gives the corresponding oxime (18.1.10). Reduction of the oximine group using hydrogen over Raney nickel gives mexiletine (18.1.11) [17–20].



18.1.9 18.1.10 18.1.11

Mexiletine is used for ventricular extrasystole and ventricular tachycardia, and ventricular fibrillation (including during the severe period of myocardial infarction). A synonym of this drug is mexitil.

Phenytoin: Synthesis of this anticonvulsant drug phenytoin (9.1.1) is described in Chapter 9.



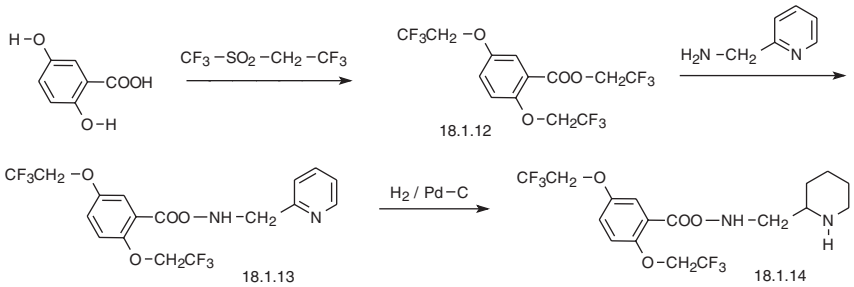
9.1.1

Phenytoin has the same main effects on the heart as lidocaine. Its use is essentially limited, and it is primarily used only as an oral replacement of lidocaine for paroxysmal tachycardia that is caused particularly by intoxication of digitalis drugs. Synonyms of this drug are dilantin and diphenylan.

18.1.3 Subgroup IC

Drugs of this group are also referred to as sodium channel blockers. They substantially suppress depolarization of myocardial cells, while insignificantly reducing the time of their repolarization, and they also suppress automatism of sinoatrial nodes. These drugs differ from those examined above in that they reduce conductivity and increase the refractory period of the ventricles. Flecainide and encainide are included in this group. The indicated drugs are used for preventing and regulating supraventricular tachycardia and atrial fibrillation in patients with normal or close to normal ventricular function as well as for ventricular arrhythmia.

Flecainide: Flecainide, *N*-(2-piperidylmethyl)-2,5-*bis*-(2,2,2-trifluoroethoxy)benzamide (18.1.14), is synthesized from 2,5-dihydroxybenzoic acid. Reacting this with trifluoroethylfluoromethylsulfonate gives 2.2.2-trifluoroethoxylation of all three hydroxyl groups, to produce 2,2,2-trifluoroethyl ester of 2,5-*bis*-(2,2,2-trifluoroethoxy)benzoic acid (18.1.12). Reacting this with 2-aminomethylpiridine gives the corresponding amide (18.1.13), which upon reduction of the pyridine ring with hydrogen gives flecainide (18.1.14) [21–24].



18.1.12

18.1.13

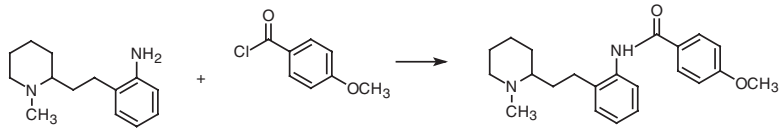
18.1.14

From the chemical point, flecainide is an analog of procainamide, to which a 2.2.2-trifluoroethoxyl group was added at C_2 and C_3 of the benzene ring, and a diaminoethyl side chain is ended in the piperidine ring.

These changes substantially alter the pharmacological properties of procainamide; however, flecainide maintains local anesthetic properties.

Flecainide, as with other local anesthetics, is used for naturally occurring ventricular arrhythmia. A synonym of this drug is tambocor.

Encainide: Encainide, 4-methoxy-N-[2-[2-(1-methyl-2-piperidinyl)ethyl]phenyl]-benzamide (18.1.15), is synthesized by acylating 2-(1-methyl-2-piperidylethyl)aniline with 4-methoxybenzoic acid chloride. The chemical structure of encainide is substantially different than other local anesthetics and antiarrhythmics [25–27].



18.1.15

Clinical use of encainide is primarily associated with the presence of serious ventricular tachycardia; however, like flecainide, it is also sufficiently effective for atrial arrhythmia and is used for natural occurrences. A synonym of this drug is enkaid.

18.2 GROUP II DRUGS

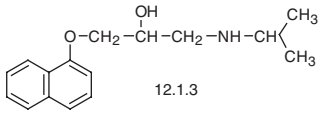
This group consists of β-adrenergic receptor blockers, the antiarrhythmic activity of which is associated with inhibition of adrenergic innervation action of the circulatory adrenaline on the heart. Because all β-adrenoblockers reduce stimulatory sympathetic nerve impulses of catecholamines on the heart, reduce transmembrane sodium ion transport, and reduce the speed of conduction of excitation, sinoatrial node and contractibility of the myocardium is reduced, and automatism of sinus nodes is suppressed and atrial and ventricular tachyarrhythmia is inhibited.

It is possible that β-adrenergic receptor blockers regulate heart rate and calm ischemia as well as reduce the heart's need for oxygen.

They are used for arrhythmias associated with nervous stress, myocardial infarction, and thyrotoxicosis accompanied by elevated adrenergic activity. Moreover, many antiarrhythmic drugs themselves can cause arrhythmia, especially in patients with ischemic heart disease. The examined β-adrenergic receptor blockers are an exception. Having said that, practically all β-adrenergic receptor blockers can be used as antiarrhythmics.

In applied medicine, however, only one drug of this group, propranolol, is represented. Publications on using atenolol as an antiarrhythmic have appeared. There is no contradictory evidence for using β-blockers with other antiarrhythmics.

Propranolol: The synthesis of propranolol, 1-isopropylamino-3-(1-napthyloxy)propan-2-ol (12.1.3) is described in Chapter 12.



12.1.3

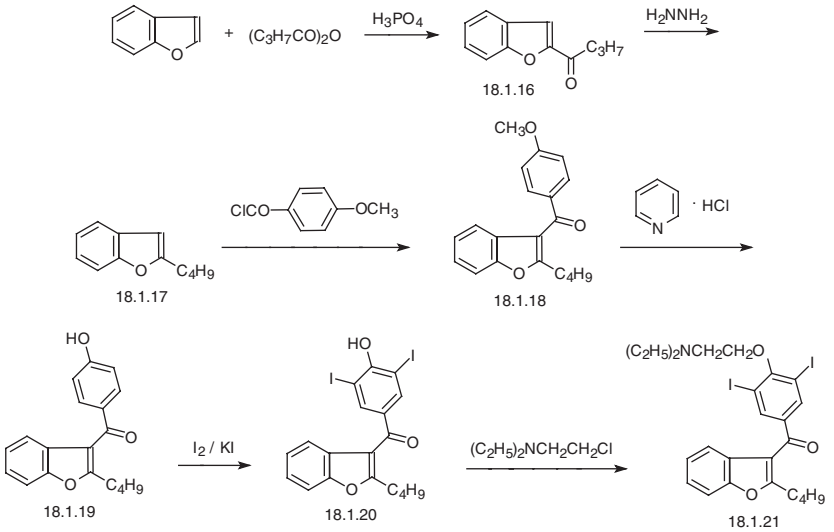
Propranolol has been studied most carefully in experiments and in clinics. It is used for ventricular tachycardia, arrhythmia caused by digitalis drug overdose, or as a result of thyrotoxosis or excess catecholamine activity. Despite the fact that there are a number of β-adrenoblockers, propranolol is considered the first choice of drugs although other blockers of calcium blockers can be just as effective.

Propranolol slows heart rate, increases the effective refractory period of atrioventricular ganglia, suppresses automatism of heart cells, and reduces excitability and contractibility of the myocardium. It is used for supraventricular and ventricular arrhythmias. Synonyms of this drug are anaprilin, detensiel, inderal, novapranol, and others.

18.3 GROUP III DRUGS

Drugs of this group exhibit antiarrhythmic action, slow repolarization, and increase conductivity of potential action and effective refractory period in all parts of the heart. Amiodarone, a drug in this group, blocks some ion channels and α- and β-adrenergic receptors of the heart. They are used for treating ventricular arrhythmias, which do not respond to other antiarrhythmic drugs in life-threatening cases.

Amiodarone: Amiodarone, 2-butyl-3-benzofuranyl-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone (18.1.21), is synthesized in the following manner. Benzofuran is acylated by butyric acid anhydride in the presence of phosphorous acid, forming 2-butyroylbenzfuran (18.1.16). Reduction of the carbonyl group in a Wolff–Kizhner reaction using hydrazine hydrate gives 2-butylbenzofurane (18.1.17). This is acylated with 4-methoxybenzoic acid chloride, giving 2-butyl-3-(4-methoxybenzoyl)benzofuran (18.1.18), which undergoes demethylation by pyridine hydrochloride, forming 2-butyl-3-(4-hydroxy-benzoyl)-benzofuran (18.1.19). The resulting product is iodized in the presence of potassium iodide, forming 2-butyl-3-benzofuranyl-4-(2-hydroxy-3,5-diiodophenyl) ketone (18.1.20), which is reacted further with 2-diethylaminoethylchoride, giving desired amiodarone (18.1.21) [28,29].

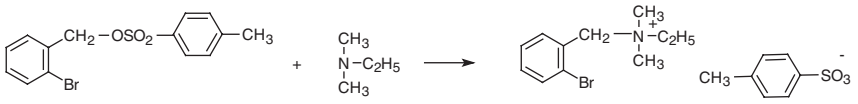


From the chemical point of view, amiodarone is completely different from other antiarrhythmics. It has two iodide atoms and a diethylaminoethanol group as substituents in the benzoyl part, and overall it is very similar to the structure of thyroxin-like molecules.

Amiodarone's antiarrhythmic action is connected to its ability to block K^+, Na^+, and Ca^{2+} channels while noncompetitively blocking α- and β-adrenergic receptors of the heart, thus prolonging the action potential and effective refractive period of atrial cells, atrioventricular junctions, and ventricles of the heart, which is accompanied by decreased automatism of sinus node and slowing of atrioventricular conductivity.

Clinical use of amiodarone is limited because of its high toxicity, which consists of cardiac block, bradycardia, cardiac insufficiency, damaged thyroid gland function, neuropathology, and increased sensitivity to light, all of which significantly limit use of amiodarona, and it is only used in therapy for extremely serious tachyarrhythmias such as reoccurring ventricular fibrillation and hemodynamic unstable ventricular tachycardia, and only under supervision of a physician in a clinical situation. Synonyms of amiodarone are cordarone, rythmarone, and others.

Bretylium: Bretylium, *N*-(*o*-bromobenzyl)-*N*-ethyl-*N*,*N*-dimethylammonium tosylate (18.1.22), is synthesized by reacting o-bromobenzyltosylate with ethyldimethylamine [30].



18.1.22

Bretylium is poorly absorbed when taken orally, and it is used only in the form of intravenous or intramuscular injections. However, like many other quaternary ammonium salts, it initiates a response of neuronal catechoamines, which can cause tachycardia, elevate blood pressure, and so on.

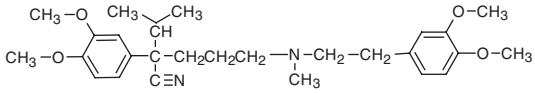
Bretylium possesses sympatholytic action, which is associated with blockage of norepinephrine (noradrenaline) from presynaptic nerve endings. It also has a direct effect on ischemic myocytes. Bretylium is an urgent treatment that is used in situations of ventricular tachycardia and ventricular fibrillation, primarily in the severe phase of a myocardial infarction, during which use of other medications or procedures have proven unsuccessful. It requires great caution and should be used only in urgent situations. Synonyms of this drug are vretilol, ornid, and others.

18.4 GROUP IV DRUGS

Drugs of this group are calcium channel blockers that inhibit slow transmembrane calcium ion flow in the cell of the conductive system of the heart during depolarization, which causes a slowing of atrioventricular conductivity and increased effective refractive period of atrioventricular ganglia, which eventually leads to the relaxation of smooth muscle of heart musculature and restores normal sinus rhythm during supraventricular tachycardias.

Today, this group is represented by a single calcium channel-blocking drug, verapamil, which is primarily used as an antianginal drug as well as for controlling hypertension.

Verapamil: Synthesis of verapamil, 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)isopropylvaleronitrile (19.3.15) will be described in Chapter 19.



19.3.15

Verapamil is used as an antiarrhythmic drug in treating supraventricular arrythmia such as paroxysmal atrial tachycardia, and for controlling atrial fibrillation. By blocking entrance of Ca^{2+} in the cell, verapamil exhibits a negative inotropic effect, and therefore it cannot be combined with β-adrenoblockers or cynidine since that would lead to an increased inotropic effect. Verapamil is primarily used as an antiarrhythmic for treating ventricular arrhythmias; however, currently it is being forced out gradually by adenosine. Synonyms of this drug are isoptin, calan, finoptin, falicard, manidon, and many others.

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– 19 –

Antianginal Drugs

An antianginal is any drug used in the treatment of angina pectoris, a symptom of ischaemic heart disease. So, medicinal agents used for relieving or preventing pathological conditions associated with coronary insufficiency and the related ischemic heart disease are referred to as antianginal drugs.

Ischemic heart disease includes angina pectoris and myocardial infarction. Angina pectoris results from an imbalance between oxygen required and oxygen supplied to the ischemic region of the myocardium. Therefore, drugs that either reduce the need for oxygen in the myocardium or enhance oxygen supply are theoretically necessary for treating these states.

This can be accomplished either by reducing the load on the heart, or by lowering systemic venous and arterial pressure (nitrates and nitrites), or by partial suppression of adrenergic innervation of the heart (β-adrenoreceptors), or by suppressing calcium ion transport in myocardial cells since the contraction of smooth muscles vessels is controlled by the concentration of calcium ions in the cytoplasm (Ca^{2+} channel blockers). The resulting effect of the aforementioned drugs is that they reduce the need for oxygen in the heart.

The main drugs used for myocardial ischema therapy and for relieving pain in angina pectoris are: nitrates and nitrites (nitroglycerin, isosorbide dinitrate, and pentaerythritol tetranitrate); substances that suppress adrenergic systems of the heart—β-adrenoblockers (atenolol, methoprolol, propranolol, and nadolol), and Ca^{2+} channel blockers (verapamil, diltiazem, nifedipine, and nicardipine); as well as a few older drugs, in particular papaverine and dipyridamole.

19.1 NITRATES AND NITRITES

More than 100 years ago, it was observed that amylnitrate and nitroglycerine relieve pain in angina pectoris, and since nitrites and nitrates have the ability to dilate vessels, thus moderately increasing blood flow to the myocardium, it became customary to think that dilation of coronary vessels alleviates the condition of angina pectoris.

It seems likely that the mechanism of action of all of the organic nitrates and nitrites should be analogous. They exhibit direct relaxant effects on vascular, smooth musculature, which results in general dilation of vessels—predominantly veins, but also arteries to a

lesser degree. As a result, vascular conductivity is reduced, which leads to reduced heart load and myocardial need of oxygen, thus relieving the hypoxic condition. Moreover, it is presumed that nitroglycerine and other nitrates reduce the size of ischemic lesions, which are linked to an increase of myocardial blood flow.

The mechanism of the action of nitrates is not completely known, though it is reasonably likely that within smooth muscle cells, nitrates are transformed into nitrites, which then release NO. This, in turn, reacts with guanylatecyclase, causing increased synthesis of guanosine 3′,5′-monophosphate (cyclic GMP). As a result, a GMP-requiring protein kinase is activated, which results in less phosphorylation of muscle protein. Dephosphorylated muscle proteins are less able to contract, which ultimately results in a reduction of the heart's need for oxygen.

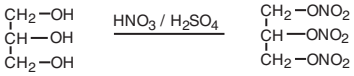
Thus, nitrates relax all smooth musculature including the liver, urinary bladder, and bronchial systems. However, the most active relaxation takes place in blood vessels.

Nevertheless, selective dilation of coronary vessels cannot completely explain the therapeutic action of coronary vasodilating agents. In stable forms of angina pectoris, rigid vascular structures incapable of widening are formed because of damaged vessels. Moreover, coronary blood circulation itself responds to ischemia by dilating vessels. Vessels that are not affected by atherosclerosis increase blood flow to a normal myocardium by way of dilation, and consequently, they reduce blood flow to the ischemic region. This is referred to as vascular theft, and is more harmful than positive.

As antianginal drugs, medicinal forms of nitrates are fast-acting drugs used for relieving severe angina pectoris attacks as well as drugs with prolonged action that are used for preventing angina pectoris attacks. Nitroglycerine—glyceryltrinitrate, and amylnitite are drugs that act quickly, yet briefly. Other organic nitrates used for more prolonged action are erythrite tetranitrate, isosorbide dinitrate, and pentaerythritol tetranitrate. Of the organic nitrites, amylnitrite is used in medicine.

Over the past 10 years, coronary vasodilating agents have been recommended as the primary compounds for treating cardiac insufficiency.

Nitroglycerine: Nitroglycerine, 1,2,3-propantrioltrinitrate (19.1.1), is synthesized by nitrating glycerol with nitric acid [1–3].



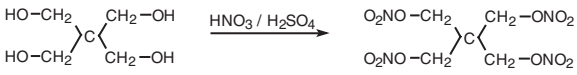
19.1.1

Nitroglycerine reduces the load on the heart by dilating peripheral veins, reducing the myocardial need for oxygen, and facilitating redistribution of coronary blood flow in the region of the myocardium with reduced blood flow.

Nitroglycerine is used mainly for relieving severe and chronic angina pectoris attacks and myocardial infractions.Synonyms of this drug are trinitroglycerine, trinitrol, trinitrin, and many others.

Pentaerythritol tetranitrate: Pentaerythritol tetranitrate, 2,2-bis(hydroxymethyl)-1,3-propandioltetranitrate (19.1.2), is also synthesized by a nitration reaction of pentaerythritol

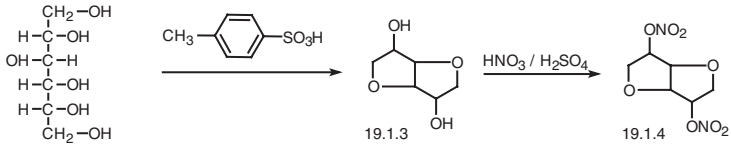
with nitric acid, but using 2,2-bis(hydroxymethyl)-1,3-propandiol instead of glycerol as the starting material [4].



19.1.2

Pentaerythritol tetranitrate is used for chronic cardiac insufficiency. It prevents angina pectoris attacks and eases their course. Synonyms of this drug are nitropentan, nitrinal, vasocor, vasolat, pentilan, erinit, and many others.

Isosorbide Dinitrate: Isosorbiddinitrate, 1,4:3,6-dianhydrosorbate-2,5-dinitrate (19.1.4), is synthesized by intermolecular dehydration of D-sorbite into isosorbide (19.1.3) using paratoluenesulfonic acid and subsequent nitration of the two hydroxyl groups by nitric acid [5–7].



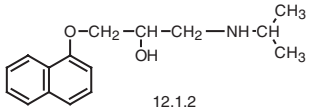
19.1.3 19.1.4

Isosorbide dinitrate is also used in chronic cardiac insufficiency for preventing angina pectoris attacks. It is a long-lasting drug. Synonyms of this drug are isordil, metronitron, vascardin, and others.

19.2 β-ADRENOBLOCKERS

Possessing the ability to reduce the heart's need for oxygen, β-adrenoblockers, in particular atenolol, metoprolol, propranolol, and nadolol, are recommended for treating chronic angina pectoris, which frequently develops after a myocardial infarction takes place. The reduction of the heart's need for oxygen using β-adrenoblockers is achieved by lowering the heart rate, blood pressure, and contractability of the myocardium. It should be noted that severe angina pectoris attacks are alleviated best with nitroglycerol. However, therapy with β-adrenoblockers is undoubtedly complemented by therapy with nitrates. Moreover, nitrates often counteract a few undesirable effects of β-adrenoblockers, and therefore combination therapy using nitrates and β-adrenoblockers are frequently used.

Propranolol: Propranolol is 1-(*iso*-propylamino)-3-(1-naphthoxy)-2-propanol (12.1.2). The synthesis of this drug is described in Chapter 12.

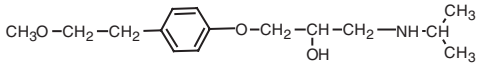


12.1.2

Propranolol is a nonselective β-adrenoblocker that affects both the mechanical and electrophysiological properties of the myocardium. It lowers myocardial contractibility, heart rate, blood pressure, and the myocardial need for oxygen. These properties make propranolol and other β-adrenoblockers useful antianginal drugs.

Propranolol is used for treating hypertension, angina pectoris, supraventricular arrhythmia, ventricular tachycardia, migraines, hypertrophic subaortal stenosis, and pheochromocytosis. It is used following a myocardial infraction. Generally accepted synonyms of this drug are anaprilin, obsidan, inderal, novapranol, and defensol.

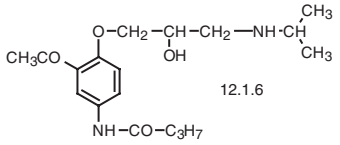
Metroprolol: Metroprolol is 1-(*iso*-propylamino)-3-[4′ (2-methoxyethyl)phenoxy]-2-propanol (12.1.5). The synthesis of this drug is described in Chapter 12.



12.1.5

Unlike propranolol, which blocks both β_1 and β_2-adrenoreceptors, metroprolol exhibits cardioselective action, i.e. in therapeutic doses, it blocks β_1-adrenoreceptors with insignificant effects on β_2-adrenoreceptors. Metroprolol is used for myocardial infarctions, for preventing cardiovascular tissue death, and in angina pectoris. The most common synonym of this drug is lopresor.

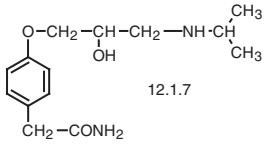
Acebutol: Acebutol is 3′-acetyl-4′-[2-hydroxy-3-(*iso*-propylamino)propoxy] butyranilide (12.1.6). The synthesis of this drug also is described in Chapter 12.



12.1.6

It is used for preventing angina pectoris. A synonym of this drug is sectral.

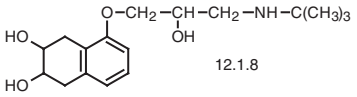
Atenolol: Atenolol is 2-[4′[2-hydroxy-3-(*iso*-propylamino)propoxy]phenyl]acetamide (12.1.7). The synthesis of this drug is described in Chapter 12.



12.1.7

It is used for preventing angina pectoris. A synonym of this drug is tenormin.

Nadolol: Nadolol is 1-(tert-butylamino)-3-[(5,6,7,8-tetrahydro-*cis*-6,7-dihydroxy-1-napthyl)-oxy]-2-propanol (12.1.8). The synthesis of this drug is described in Chapter 12.



12.1.8

It is used for preventing chronic angina pectoris. A synonym of this drug is corgard.

19.3 CALCIUM CHANNEL BLOCKERS

These drugs were developed as coronary vasodilating agents and were used for that purpose for some time, until it was discovered that they inhibit the contractile effect of calcium on smooth musculature and cardiac muscle, and that they affect calcium channels on the cell surface that permit calcium ions to enter. At first, they were called calcium antagonists; however, later on this class of compounds was given the preferred name of calcium channel blockers.

Chemically, calcium channel blockers are synthesized up of a fairly diverse group of compounds, which testifies of the diverse receptive regions both on the cell membrane surface as well as within the cell. Verapamil, which can be viewed as a benzylcyanide derivative, is one of the oldest and most actively used compounds of this class up to the present day. Diltiazem is a thiodiazepine, while nifedipin and nicardipine are derivatives of dihydropyridine.

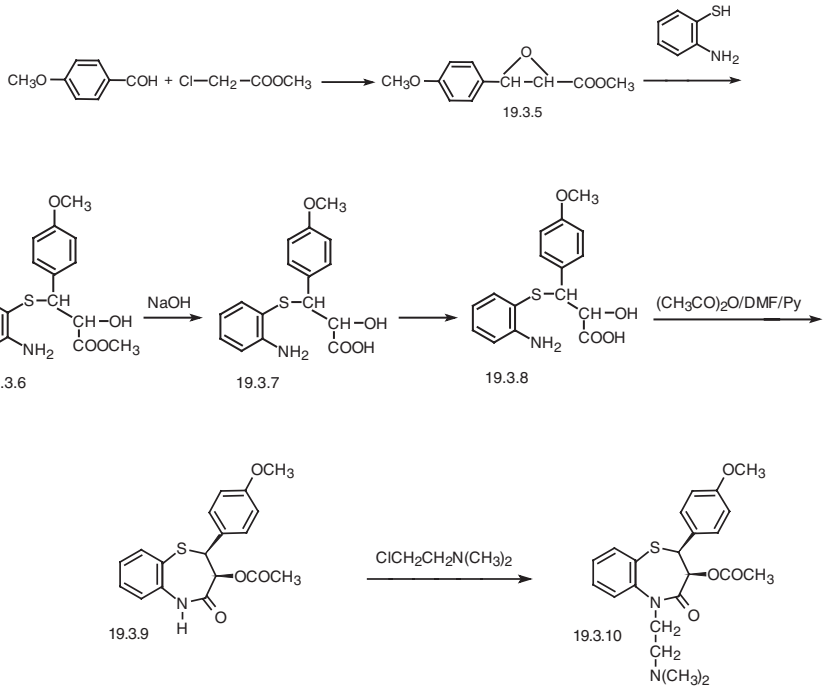
It is now obvious that the contraction of smooth muscle is controlled by the concentration of calcium in the cytoplasm. A basic principle of calcium-channel blocker action is that they disturb diffusion of calcium into muscle cells of the heart and vessels. Reduction of calcium ions entering the cells of the myocardium leads to a reduced use of the energy of phosphate bonds for mechanical heart work. As a result, strength of cardiac contractions and heart work are reduced, which in turn leads to a reduction in the heart's need of oxygen.

Two mechanisms of regulating cellular concentrations of calcium have been proposed. The first is called the electromechanical coupling mechanism. It is believed that voltage-gated calcium channels open in response to depolarization of the membrane and in response to extracellular calcium ions rushing into the cell. The second of the proposed mechanisms is not dependent on membrane depolarization. It is believed that calcium ions are released from sarcoplasmic reticulum, which causes an influx of extracellular calcium ions into the cell through open voltage-gated calcium channels. An increased concentration of calcium ions leads to binding with calmodulin. In turn the Ca^{2+}–calmodulin complex initiates phosphorylation of the myosin light chain by activating light chain kinases. Reaction of phosphorylated myosin light chains with actin, in turn, causes smooth muscle contraction.

Calcium channel blockers can block the flow of calcium ions into the cell by any of the stated mechanisms. However, voltage-gated channels respond to lower concentrations of Ca^{2+} than do nonvoltage-gated channels. This implies that the ratio of voltage-gated/nonvoltage-gated channels determines the selectivity of vein and artery responses. In

clinically used doses, calcium channel blockers relax the smooth musculature of arteries while having little effect on veins. It is necessary to point out that the process of excitation–contraction in cardiac myocytes depends more on the flow of sodium ions into the cell than calcium ions. Consequently, calcium channel blockers have relatively little effect on contractibility of the heart in doses that relax smooth muscle.

Diltiazem: Diltiazem, 5-[2-(diethylamino)ethyl]-*cis*-2,3-dihydro-3-hydroxy-2-(4-methoxy-phenyl)-1,5-benzothiazepin-4(5*H*)-one (19.3.10), is synthesized in the following manner. The condensation of 4-methoxybenzaldehyde with methylchoroacetate in the presence of sodium methoxide in Darzens reaction conditions gives methyl ester of 3-(4-methoxyphenyl)-glycidylic acid (19.3.5). Reacting it with 2-aminothiophenol with the opening of epoxide ring gives methyl ester of 2-hydroxy-3-(2′-aminophenylthio)-3- (4″-methoxyphenyl)propionic acid (19.3.6). Hydrolysis of the resulting compound with alkali leads to the formation of the corresponding acid (19.3.7) in the form of a racemic mixture, which when on interaction with (+)-α-phenylethylamine gives *threo*-(+)-2-hydroxy-3-(2′-aminophenylthio)-3-(4″-methoxyphenylpropionic acid (19.3.8). Boiling this in a mixture of acetic anhydride/dimethylformamide/pyridine system brings to cyclization to the thiazepine ring and simultaneously acylates the hydroxyl group, forming (+)-*cis*-2-(4-methoxyphenyl)-3-acetoxy-2,3-dihydro-1,5-benzothiazepin-4-(5*H*)-one (19.3.9). Alkylation of the resulting product with 2,2-dimethylaminoethylchloride forms diltiazem (19.3.10) [8–15].

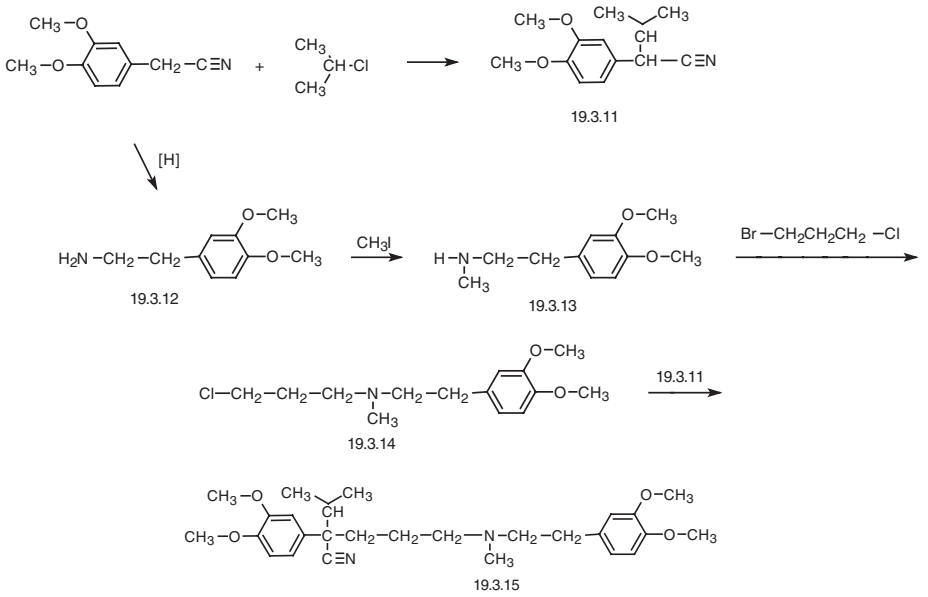


Diltiazem reduces the transmembrane influx of calcium ions into cells of cardiac muscle and smooth musculature of vessels. It causes dilation of coronary and peripheral vessels,

increases coronary blood flow, and prevents development of coronary artery spasms. It lowers elevated arterial pressure and reduces tachycardia.

It is used for stable and nonstable angina pectoris (including after myocardial infarctions) as well as in arterial hypertension. Universally accepted synonyms of this drug are cardizem, dilacor, tiazac, iproventaril, and others.

Verapamil: Verapamil, 5-[(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)isopropylvaleronitrile (19.3.15), is synthesized by a scheme using 3,4-dimethoxyphenylacetonitrile as the initial substance. The synthesis of the final product (19.3.15) is accomplished by alkylating 2-(3.4-dimethoxyphenyl)-3-methylbutyronitrile (19.3.11) with *N*-[2-(3,4-dimethoxyphenyl)-ethyl]-*N*-3-(chloropropyl)-*N*-methylamine (19.3.14). The initial 2-(3.4-dimethoxyphenyl)-3-methylbutyronitrile (19.3.11) is synthesized by alkylating 3,4-dimethoxyphenylacetonitrile with isopropyl chloride in the presence of sodium amide. The alkylating agent, *N*-[2-(3,4-dimethoxyphenyl)-ethyl]-*N*-3-(chloropropyl)-*N*-methylamine (19.3.14), is also synthesized from 3,4-dimethoxyphenylacetonitrile followed by reduction into 3,4-dimethoxyphenylethylamine (19.3.12), with subsequent methylation into *N*-methyl-*N*-3,4-dimethoxyphenylethylamine (19.3.13). Next, the resulting *N*-[2-(3,4-dimethoxyphenyl)-ethyl] -*N*-methylamine (19.3.12) is alkylated by 1-chloro-3-bromopropane into the desired *N*-[2-(3,4-dimethoxyphenyl)-ethyl]-*N*-3-(chloropropyl)-*N*-methylamine (19.3.14), which is alkylated by 2-(3.4-dimethoxyphenyl)-3-methylbutyronitrile (19.3.11) to give the final product, verapamil (19.3.15) [16–19].

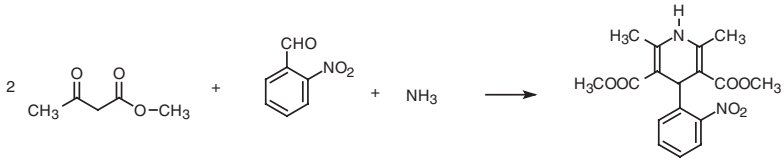


Verapamil possesses antiarrhythmic, antianginal, and hypotensive activity. It reduces the myocardial need of oxygen by reducing contractibility of the myocardium and slowing the frequency of cardiac contractions. It causes dilation of coronary arteries and increases

coronary blood flow. It lessens tonicity of smooth musculature, peripheral arteries, and general peripheral vascular resistance. It expresses antiarrhythmic action in supraventricular arrhythmias.

Verapamil is used for preventing angina pectoris attacks, arterial hypertension, and treating and preventing supraventricular arrhythmia (paroxysmal supraventricular tachycardia, atrial fibrillation, atrial flutter, extrasystole). Synonyms of this drug are isoptin, calan, finoptin, falicard, manidone, and many others.

Nifedipin: Nifedipine, dimethyl ether 1,4-dihydro-2,6-dimethyl-4-(2′-nitrophenyl)-3,5-piridindicarboxylic acid (19.3.16), is synthesized by a Hantsch synthesis from two molecules of a β-dicarbonyl compound—methyl acetoacetate, using as the aldehyde component—2-nitrobenzaldehyde and ammonia. The sequence of the intermediate stages of synthesis has not been completely established [20–23].

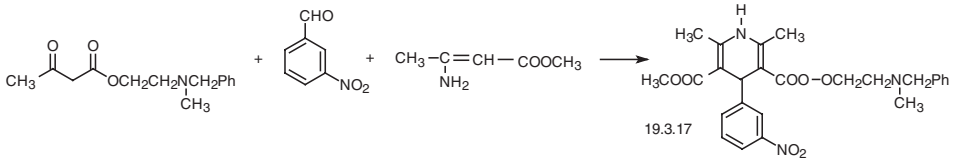


19.3.16

Nifedipine causes relaxation of smooth musculature of vessels, dilates coronary and peripheral arteries, and reduces peripheral resistance, arterial pressure, and the oxygen supply to the heart.

Nifedipine is used for preventing and relieving angina pectoris attacks, for hypertension, and as an ingredient in combination therapy for chronic cardiac insufficiency. Synonyms of this drug are adalat, corinfar, procardia, and nifecor.

Nicardipine: Nicardipine, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-methyl-2-[(methylphenylmethyl)-amino]ethyl ester 3,5-pirididincarboxylic acid (19.3.7), is synthesized in a manner analogous to the synthesis of nifedipine, the only difference being that in the Hantsch synthesis, two different β-dicarbonyl compounds are used simultaneously with *o*-nitrobenzaldehyde. During this, one of these in the enamine form of acetoacetic ester is simultaneously used as an amine component. A heterocyclization reaction is accomplished by reacting, the methyl ester of β-aminocrotonic acid with the 2-methyl-2-benzylaminoethyl ester of acetoacetic acid [24–27].



19.3.17

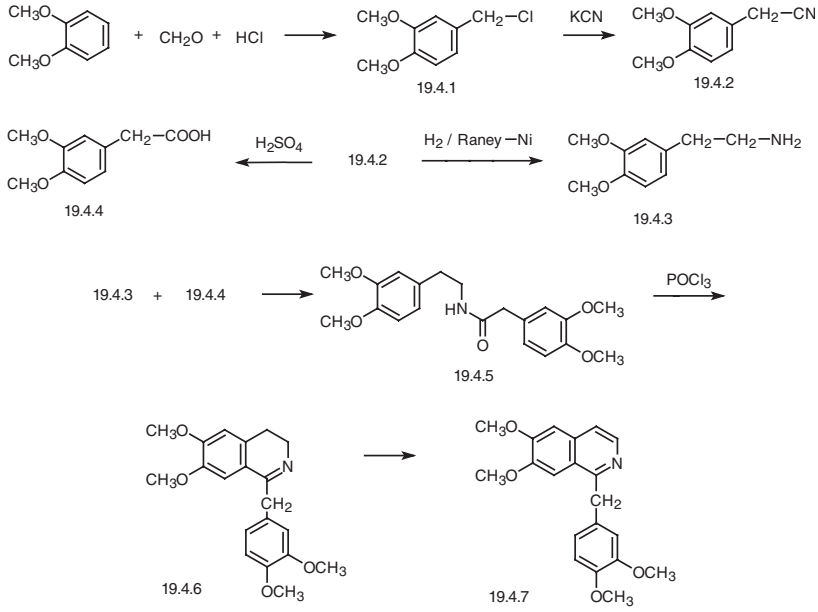
Nicardipin relaxes smooth musculature of vessels, lowers resistance of coronary and peripheral vessels, increases blood flow in vessels of the brain, causes a moderate and stable hypotensive effect, and reduces the myocardial need for oxygen.

It is used for arterial hypertension, chronic, stable angina pectoris, preventing angina pectoris, and for ischemic-type abnormalities of brain blood flow. Synonyms of this drug are nerdipina, carden, and others.

19.4 OTHER DRUGS

Modern drugs that are used for treating angina pectoris are described above. However, there are some very old drugs and ways for treating angina pectoris, such as using papaverine and dipyridamole, which are successfully used even today.

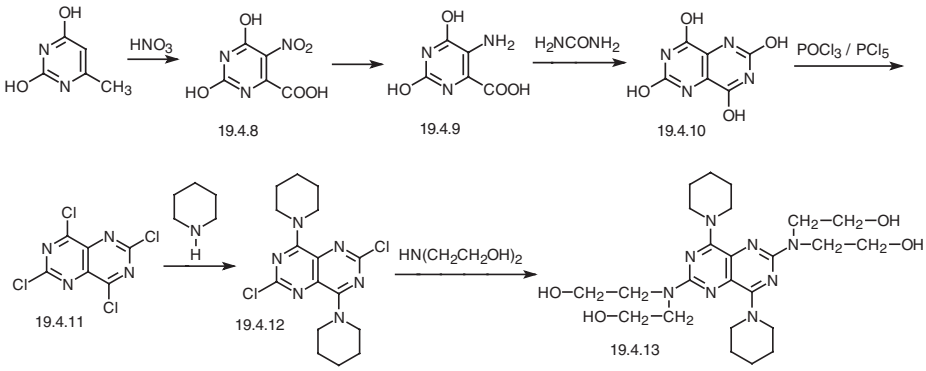
Papaverine: Papaverine, 1-veratryl-6,7-dimethoxyisoquinolin (19.4.7), is synthesized from veratrol. Veratrol undergoes chloromethylation, forming 3,4-dimethoxybenzylchloride (19.4.1). Reacting this with potassium cyanide gives 3,4-dimethoxybenzylcyanide (19.4.2). The resulting 3,4-dimethoxybenzylcyanide undergoes reduction by hydrogen over Raney nickel, forming homoveratrylamine (19.4.3). At the same time 3,4-dimethoxybenzylcyanide (19.4.2) undergoes acidic hydrolysis giving 3,4-dimethoxyphenylacetic acid (19.4.4). The interaction of the resulting compounds brings to corresponding amide (19.4.5). The cyclization of this by Bischler–Napieralski method, using phosphorous oxychloride, gives 3,4-dihydropapaverine (19.4.6), which is dehydrated into the desired papverine when heated in tetraline at high temperatures [28–31].



Papaverine is an alkaloid of unripe poppies; however, it is not related to compounds in the morphine class and does not possess analgesic properties. It is a peripheral vasodilator and has a direct effect on vessels. It causes dilation of coronary, cerebral, and pulmonary

arteries. It facilitates an increase in cerebral blood flow and a decrease in cerebral vascular resistance. In therapeutic doses, it raises blood pressure. In large doses, it can cause arrhythmia. Despite the fact that it lacks a clear-cut therapeutic effect, it nevertheless continues to be widely used for peripheral and cerebral blood flow abnormalities and as a coronary dilating agent in general, and also for spasm of peripheral vessels and vessels of the brain and bronchi. Synonyms of this drug are papvin, cerebid, miobid, pavacen, vasospan, and many others.

Dipyridamole: Dipyridamole, 2,2′,2″,2‴-[(4,8-dipiperidinopirimido[5,4-d]pirimidin-2,6-diyl)-diimino]-tetraethanol (19.4.13), is easily synthesized from 5-nitroorotic acid (19.4.8), easily obtained, in turn, by nitrating of 2,4-dihydroxy-6-methylpyrimidine, which is usually synthesized by the condensation of urea with acetoacetic ether. Reduction of the nitro group in 5-nitroorotic acid by various reducing agents gives 5-aminoorotic acid (19.4.9), which is reacted with urea or with potassium cyanide to give 2,4,6,8-tetrahydroxypyrimido[5,4-d]pyrimidine (19.4.10). This undergoes a reaction with a mixture of phosphorous oxychloride and phosphorous pentachloride, which forms 2,4,6,8- tetrachloropyrimido[5,4-d]pyrimidine (19.4.11). Reacting the resulting tetrachloride with piperidine replaces the chlorine atoms at C_4 and C_8 of the heterocyclic system with piperidine, giving 2,6-dichloropyrimido-4,8-dipiperidino[5,4-d]pyrimidine (19.4.12). Reacting the resulting product with diethanolamine gives dipyridamole (19.4.13) [32,33].



Dipyridamole increases coronary blood circulation, increases oxygen flow to the myocardium, potentiates adenosine activity, and impedes its metabolization. It inhibits aggregation of thrombocytes, blocks phosphodiesterase, increases microcirculation, and inhibits the formation of thrombocytes.

It is used for chronic coronary insufficiency, as well as for preventing and treating thrombosis. Synonyms of this drug are anginal, curantyl, stenocor, thrompresantin, and many others.

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– 20 –

Hypolipidemic Agents

Drugs that lower the concentration of lipoproteins in the plasma by inhibiting their production in the organism or by removing them from the plasma are called hypolipidemic or antisclerotic drugs.

Atherosclerosis is a condition of the organism characterized by elevated levels of atherogenic lipoproteins in blood plasma, lipid deposits (including cholesterol) in the form of esters inside walls of the arterial system, and it is expressed by a gradual difficulty of blood circulation. The most appropriate name for this disease is lipoproteinemia. Clinically, it is manifested in the form of ischemic heart disease, stroke, abnormal cerebral blood flow, and peripheral ischemia.

Atherosclerosis is a much more complex disease than simply knowing that there is a high concentration of lipoproteins in the blood and that there is a constriction of vessels.

The primary developmental mechanism of the atherosclerotic process is not completely understood. It seems likely that the development of atherosclerosis is preceded by metabolic abnormalities of the synthesis, transport, and utilization of lipids. Lipids such as triglycerides and cholesterol esters are circulated in the blood in the form of particles (lipoproteins) wrapped in hydrophilic membranes that are synthesized from phospholipids and free cholesterol. Cholesterol is transported by particles of various sizes synthesized from triglycerides, cholesterol esters, and phospholipids, each of which plays a very specific role.

Lipoproteins are divided into five basic types. The largest particles are the chylomicrons, followed by the very low-density lipoproteins, intermediate lipoproteins, low-density proteins, and finally the smallest—high-density lipoproteins. Separation of the aforementioned cholesterol-containing complexes is accomplished by ultracentrifugation.

Thus, chylomicrons are the largest particles with the lowest density, and they are formed in the epithelial cells of the small intestine and are synthesized from exogenic triglycerides (fats) which are used for carrying out transport functions. Very low-density lipoproteins are formed in the liver and include primarily endogenic triglycerides and cholesterol esters with unsaturated fatty acids. They undergo lipolysis in the organism, forming short-lived lipoproteins of intermediate density that contain approximately equal quantities of triglycerides and cholesterol esters. These undergo lipolysis once again, thus, transforming into low-density lipoproteins, in which cholesterol esters are already predominant.

High-density lipoproteins are formed in the liver and intestines as a result of catabolism of chylomicrons and very low-density lipoproteins, and in comparison with other lipoproteins, they contain considerably more cholesterol esters with unsaturated fatty acids, as well as phospholipids and specific proteins.

However, unlike atherogenic low-density lipoproteins and very low-density lipoproteins, which when metabolized release cholesterol that is in the form of esters and is deposited in tissue, chylomicrons and high-density lipoproteins are not atherogenic. There is a direct link between the concentration of high-density lipoproteins in blood plasma and expressed atherosclerotic changes in medium and large arteries.

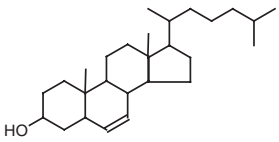
The likely progression of the process of atherosclerotic plaque formation can be briefly described in the following manner. Over time, usually years, endothelium at a certain spot of a vessel is somehow damaged by turbulent blood flow. Thrombocytes are attracted to the damaged region. The combined action of endothelial growth, thrombocytes moving in, and growth factor attracting macrophages to the region, causing an inflammatory reaction which leads to hypertrophy of middle artery muscles, which constricts the whole length of the vessel and forms plaque. Endothelia are never completely restored and can be a region of thrombosis formation in a constricted vessel.

Reducing the level of cholesterol in the organism mainly consists of either removing the excess amount from the plasma, or inhibiting low-density and very low-density lipoprotein synthesis. Hypolipidemic agents are accordingly subdivided into drugs that enhance catabolism and removal of atherogenic lipoproteins and lipids from the organism (colestipol and cholestyramine), and drugs that inhibit the formation of atherogenic lipoproteins—fibrates (clofibrate and henfibrozil); natural compounds—statines (lovastatin, mevastatin, and their analogs), as well as probucol and nicotinic acid. In addition, drugs are sometimes used that lower cholesterol levels in the organism by mechanisms that are not completely explainable—dextrotiroxin and neomycin.

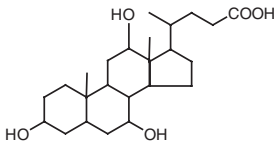
However, along with the aforementioned negative properties associated with cholesterol, it should be noted that a specific portion of it is transformed into adrenal hormones, sex hormones, and vitamin D all of which are necessary for good health.

20.1 BILE ACID SEQUESTERS

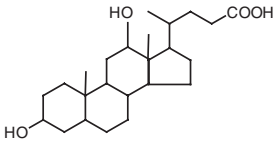
One of the ways in which cholesterol is catabolized in the organism is by its transformation into bile acids, the most important of which are cholic, deoxycholic, lithocholic, and cholanic acids.



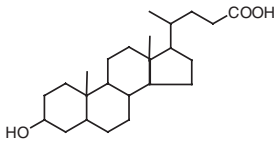
cholesterol



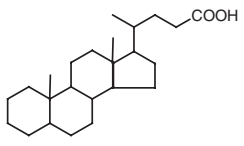
cholic acid



deoxycholic acid



lithocholic acid



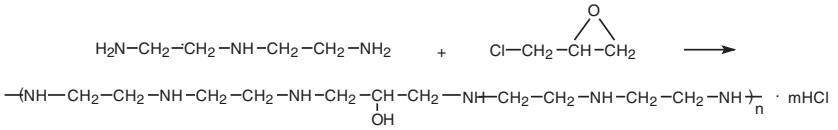
cholanic acid

Binding of bile acids and their removal from the organism disturbs the balance of cholesterol and bile acids, and a compensatory increase of the transformation of cholesterol into

bile acids begins, which results in a decreased content of cholesterol. Drugs that remove cholesterol in the form of insoluble bile acid derivatives stimulate transformation of cholesterol into bile acids by the organism. The resulting effect is an overall reduction in the amount of cholesterol in the organism.

Currently, there are two drugs that bind with the gastric tract and release bile acids from the organism—colestipol and cholestyrolramine. Both are macromolecular compounds—anion-exchange resins. They differ from one another in that they have different chemical structures; however, they have the same mechanism of action. Being insoluble in water, they are not absorbed from the gastrointestinal tract and bind with bile acids at their quaternary ammonium regions, where they are removed with feces in the form of an ion-exchange resin to which they are bound.

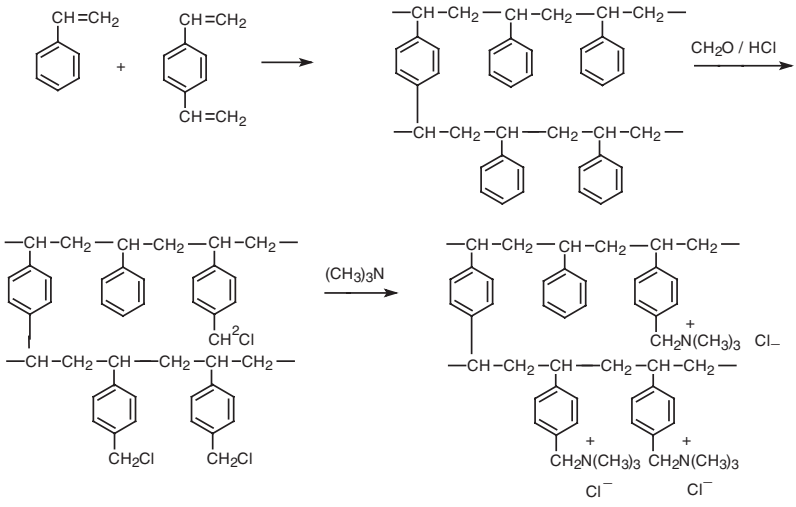
Colestipol: Colestipol (20.1.1) is a hydrochloride of the product of copolymerization of epichlorohydrine with diethylentriamine that contains varying numbers of quaternary nitrogen atoms. There is no exact formula of the product of copolymerization, but its approximate structure can be expressed as 20.1.1 [1–4].



20.1.1

Colestipol binds to bile acids, which are secreted from the organism in a form which bunds to the ion-exchange resin. It lowers the overall level of cholesterol and cholesterol-containing low-density lipoproteins in blood plasma while not affecting the level of high-density lipoproteins. Colestipol is used for hypercholesterolemia (including atherosclerosis and arterial hypertension). Synonyms of this drug are colestabil, colestid, lestid, and others.

Cholestyramine: Cholestyramine (20.1.2) is a copolymer of divinylbenzene and styrene, which undergoes chloromethylation and afterwards is reacted with triethylamine [5].



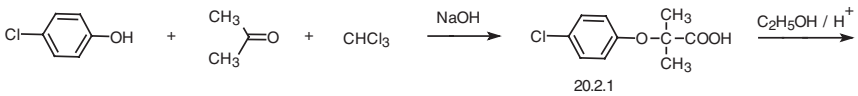
20.1.2

Cholestyramine, like colestipol, binds bile acids, which are removed from the organism in a form bound to the ion-exchange resin. They are used for the same indications. Synonyms of this drug are colibar, quantalan, questran, and others.

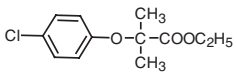
20.2 DRUGS THAT INHIBIT CHOLESTEROL SYNTHESIS

Drugs of this series include clofibrate and gemfibrozil, which are derivatives of phenoxycarboxylic acids—fibrates; probucol, which is a substituted *bis*-mercaptophenol; and also natural compounds lovastatin, mevastatin, and their analogs. They will be examined separately because it is difficult to explain their action via the entire mechanism.

Clofibrate: Clofibrate, ethyl ether 2-(4-chloropheoxy)-*iso*-butyric acid (20.2.2), is synthesized by esterifying 2-(4-chlorophenoxy)-*iso*-butyric acid (20.2.1) with ethyl alcohol. This is synthesized in a single-stage reaction from 4-chlorophenol, acetone, and chloroform in the presence of an alkali, evidently by initial formation of chlorethone-trichloro-*tert*-butyl alcohol, which under the reaction conditions is converted into (4-chlorophenoxy)trichloro-*tert*-butyl ether, and further hydrolyzed to the desired acid 20.2.1, which is further esterified with ethanol in the presence of inorganic acid [6–8].



20.2.1



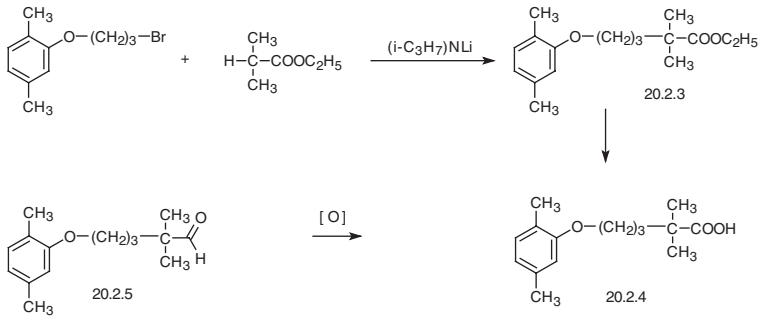
20.2.2

This aryloxyisobutyric derivative turned out to be more active than all of the known sulfur compounds in the early 1960s for lowering the overall concentration of lipids and cholesterol in the plasma. The exact effector region of clofibrate has not been determined. By quickly and completely transforming into para-chlorophenoxybutyric acid in the organism, it enhances the activity of lipoprotein lipase, which increases the rate of transforming a certain number of very low-density proteins into intermediate-density proteins and further into low-density proteins. Clofibrate directly reduces synthesis (in the liver) as well as the distribution of low-density proteins. Clofibrate also lowers the concentration of triglycerides in the plasma. It is generally observed that clofibrate reduces the level of cholesterol by 5–10%, and the level of triglycerides by 20–25%. The level of high-density proteins does not change.

This drug is generally used for the presence of a high quantity of high-density lipoproteins. Synonyms of this drug are miscleron, acolestol, atherosol, lisiterol, regelan, and others.

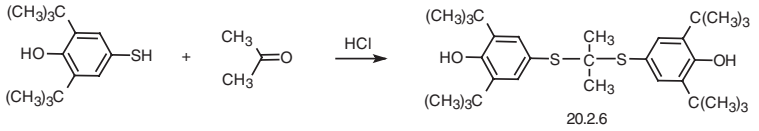
Gemfibrozil: Gemfibrozil, 2,2-dimethyl-5-(2,5-dimethylphenoxy)valeric acid (20.2.4), is synthesized either by hydrolysis of ethyl ester of 2,2-dimethyl-5-(2,5-dimethylphenoxy)valeric acid (20.2.3), which is synthesized by alkylation 2,2-dimethylvaleric acid

ethyl ester with 3-(2,5-dimethylphenoxy)propylbromide-1 in the presence of lithium diisopropylamide, or by oxidation of the corresponding aldehyde (20.2.4) [9–11].



From the chemical point of view, gemfibrozil is somewhat related to clofibrate and has analogous pharmacological use. The primary action of gemibrozil as well as clofibrate consists of a significant reduction in the level of very low-density proteins in the plasma and an increase in high-density protein formation. This drug is used for hyperlipoproteinemia that cannot be corrected by a special diet or by physical exertion. Synonyms of this drug are lopid, ipolipid, normolip, and others.

Probucol: Probucol, *bis*(3,5-*tert*-butyl-4-hydroxyphenyl)mercaptol acetone (20.2.6), is synthesized by thioketalizing acetone with 2,6-di-*tert*-butyl-4-mercaptophenol in the presence of hydrogen chloride [12–16].

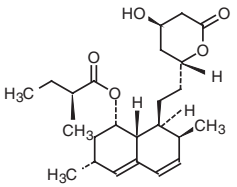


Probucol, introduced relatively recently as an antihypercholesteremic drug, differs chemically from other drugs. Chemically, probucol is *ortho*-di-*tert*butyl substituted *bis*-mercaptophenol. The mechanism of action of probucol is unknown. Being a lipophilic compound, it is easily distributed into fatty tissue and, as a result, approximately 20% of its maximum concentration in the blood is still maintained for 6 months.

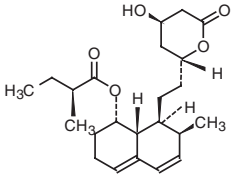
Probucol reduces the overall level of cholesterol—primarily low-density lipoproteins—without having an effect on triglycerides and very low-density lipoproteins. It has been suggested that it inhibits synthesis of cholesterol itself and increases removal of bile salts. Upon using this drug, a fraction of low-density proteins is reduced; however, even more significant is the reduction of high-density proteins. From the epidemiological point of view, this is dangerous, because lowering the concentration of high-density proteins means less cholesterol is removed from tissues. However, in any case, probucol lowers the level of cholesterol in the plasma by 10–15%. Moreover, it has been shown that probucol facilitates reduction of necrotic zones in myocardial ischemia. It is used for problems with lipid exchange associated with an elevated level of cholesterol and low-density lipoproteins when diet and physical exertion do not have a sufficient hypocholesterinemic effect. Synonyms of this drug are bifenabid and lorelco.

Lovastatin and mevastatin: Lovastatin, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[-[2R,4R]-[tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthyl (S)-2-methylbutyrate (20.2.7) is isolated from *Monascus rubber* [17] and *Aspergillus terreus* [18], as is mevastatin (1S,3R,7S,8S,8aR)-1,2,3,7,8, 8a-hexahydro-7-methyl-8-[-(2R,4R)-[tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthyl (S)-2-methylbutyrate (20.2.8), which is isolated from *Penicillium citrinum* [19, 20] as well as from *Penicillium brevicompactum* [21].

Lovastatin and mevastatin are new-generation drugs that were introduced into medicine for treating hyperlipocholesterolemia, and they are unique compounds. Lovastatin is isolated from *Aspergillus terreus* mushrooms. Mevastatin is a chemically analogous compound that differs only in the absence of a methyl group at C_3 of the naphthaline system, and it is isolated from *Penicillium citrinum* mushrooms.



20.2.7

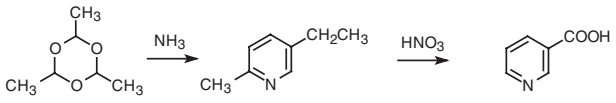


20.2.8

These hypolipidemic agents are noncompetitive inhibitors of the enzyme that limit the rate of cholesterol synthesis in the liver at the levalonic acid stage.

It is considered the most effective drug for lowering levels of cholesterol, triglycerides, and very low-density lipoproteins in the plasma and for moderately increasing the number of high-density lipoproteins. It is used for treating hyperlipoproteinemia that cannot be corrected by a special diet or physical exertion. Synonyms of lovastatin are lovalip, mevacor, mevinacor, and sivlor; and those of mevastatin are CS-500 and ML-236 B.

Nicotinic acid: Nicotinic acid, pyridine-3-carboxylic acid (20.2.9) is synthesized industrially by heating a paraldehyde trimer of acetaldehyde, under pressure with ammonia, which leads to the formation of 2-methyl-5-ethylpyridine, followed by oxidation with nitric acid which gives the desired product [22–25].



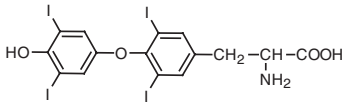
20.2.9

In large doses, nicotinic acid, or vitamin B_3 or vitamin PP, lowers the levels of both cholesterol and triglycerides in the plasma. Despite the fact that it has extremely problematic side effects, it has a long and successful history as an antihyperlipoproteinemic drug. However, it is not taken as a vitamin. Its action is connected with a reduction of very low-density protein production, which evidently is linked to inhibition of lipolysis in fatty tissue. It is important to notice that nicotinic acid does not have an effect on the general synthesis of cholesterol in the organism. Nicotinic acid or nicotinic acid in combination with bile acid-reducing drugs can lower the level of cholesterol and triglycerides by

10–30%. It is used for pellagra (avitaminosis PP), atherosclerosis, liver disease, stomach and duodenum ulcers, and prolonged, nonhealing wounds and ulcers. Synonyms of this drug are niconacid, pernivit, enzycol, niacin, and others.

20.3 OTHER DRUGS

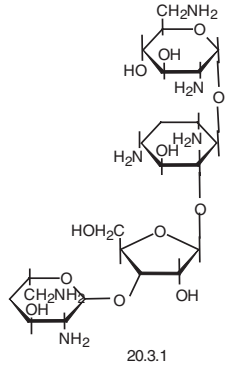
Dextrothyroxine: Dextrothyroxine is D-3,3′,5,5′-tetraiodothyronine (25.1.10). The synthesis of this drug is described in Chapter 25.



25.1.10

Dextrothyroxine speeds up the decomposition of cholesterol and lipoproteins, thus activating catabolism of cholesterol in the liver, which results in cholesterol being more intensively transformed into bile salts. It lowers the level of low-density lipoproteins in the plasma and very low-density lipoproteins in fatty tissue. It is recommended for treating hyperlipoproteinemia. Synonyms of this drug are choloxin, lizolipin, natexin, travenon, and others.

Neomycin: Neomycin is a complex of aminoglycoside antibiotics (neomycin A, neomycin B, and neomycin C) that is synthesized by the actinomycete *Streptomyces fradiae*. [26–30]. For example, neomycin B is *O*-2,6-diamino-2,6-didesoxy-α-D-glucopyranosyl-(1→4)-*O*-[*O*-2,6-diamino-2,6-didesoxy-β-L-idopyranosyl(1→3)-β-D-ribofuranosyl-(1→5)]-2-desoxy-D-streptamine (20.3.1).



20.3.1

Neomycin has a wide spectrum of antibacterial action. It is effective against both a number of Gram-positive as well as Gram-negative microorganisms. However, it is able to bind with cholesterol and bile salts. In combination with other bile salt-reducing drugs or nicotinic acid, neomycin is able to block cholesterol and bile salt absorption, which significantly increases the level of cholesterol in the plasma. Synonyms of this drug are miacin, neosporin, endomixin, corisporin, topisporin, and others.

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– 21 –

Diuretics

Diuretics are drugs that increase secretion of excess water and salt that accumulates in tissues and urine. An excess quantity of intercellular fluid is formed in the organism as a result of an inability of the kidneys to release sodium ions fast enough to ensure that a sufficient quantity of water is excreted along with them. Therefore, efficacy of a diuretic depends first and foremost on its ability to release sodium ions from the body, since they are accompanied by an osmotically equivalent amount of water that is released from interstitial fluids. The exceptions are diuretics classified as carbonic anhydrase inhibitors.

The primary therapeutic use of diuretics is to reduce the overall swelling, correct specific ion imbalance, lower blood pressure, lower the rate of intraocular fluid formation, and to lower pressure on pulmonary vessels.

Diuretics are widely used in medicine for very diverse pathologies, primarily for relieving edema, treating hypertension, cardiac insufficiency, hypercalcinuria, glaucoma, and a few forms of epilepsy, liver cirrhosis, and nephrosis.

The nephronic parts of the kidney are the principal diuretic active sites for secreting edematic fluid from the organism. Diuretics basically increase secretion of water and salts from the kidneys by suppressing reabsorption of a few main ions (primarily sodium and chloride ions); however, secretion of calcium, potassium, magnesium, and hydrocarbonate ions also increases to some degree.

A large number of chemically related compounds exhibit diuretic effects. According to the proposed mechanism of action, diuretic drugs are classified into five groups. Drugs used as osmotic diuretics (mannitol, glycerol, urea, isosorbide). Diuretics that suppress carbonic anhydrase activity (acetazolamide, methazolamide, dichorphenamide). Thiazides (chlorothiazide, hydrochlorothiazide, chlorthalidone, indapamide, and others). Loop diuretics (bumethanide, ethacrynic acid, furosemide). Potassium sparing diuretics (amyloride, spironolactone, canrenon, triamterene).

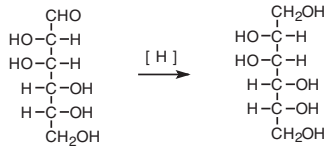
21.1 OSMOTIC DIURETICS

Osmotic diuretics are the only group of compounds whose action is not associated with a reaction to corresponding receptors, or with direct blocking of any renal transport mechanism. Pharmacological activity of this group depends solely on the osmotic pressure

caused by the presence of the drug molecules in a solution. Located in the intracellular fluid, these compounds force intermolecular water molecules into the extracellular space and prevent them from returning into the cell. There is a linear relationship between the magnitude of the diuretic effect and the concentration of osmotic diuretic drugs.

Along with glycerol, urea, and isosorbide, the most important drug of this group is mannitol.

Mannitol: Mannitol, D (−)-mannitol (21.1.1) is made by reducing D (−)-mannose [1–4].



21.1.1

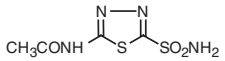
Today, mannitol is the most widely used osmotic diuretic. It raises osmotic pressure in renal tubules, thus reducing reabsorption of water in the nephrons. As a result, a large quantity of free water is released, sodium secretion increases, and as a rule, an insignificant amount of potassium is secreted. Mannitol is used as an adjuvant drug for preventing oliguria and anuriua. It can be used to lower intraocular pressure and in the postoperational period in ophthalomological procedures as well as during brain edema. Synonyms of this drug are osmosal, osmitrol, renitrol, and others.

21.2 CARBONIC ANHYDRASE ACTIVITY SUPPRESSING DIURETICS

Drugs of this group inhibit activity of carbonic anhydrase, an enzyme that catalyzes the reversible reaction of water and carbon dioxide, which forms carbonic acid. The mechanism of action of this group of drugs is not fully understood. However, inhibition of carbonic anhydrase activity leads to a reduction of carbonic acid formation and an increase in bicarbonate, sodium, and potassium excretion with urine, which eventually leads to a significant increase in the process of excreting water from the organism.

Symptoms for using carbonic anhydrase inhibitors are: edema in cardiopulmonary insufficiency, glaucoma (wide angle, secondary, and preoperational narrow-angle glaucoma), minor epileptic attacks, premenstrual high blood pressure, and severe altitude sickness. It is believed that in glaucoma, the effect of drugs is possibly linked to suppression of carbonic anhydrase in ciliary bodies, which can result in decreased secretion of cerebrospinal fluid. Of the drugs that suppress carbonic anhydrase activity, acetazolamide, methazolamide, and dichlorphenamide are used in medical practice.

Acetazolamide: Acetazolamide, 5-acetamido-1,3,4-thiadiazol-2-sulfonamide (9.7.5), is synthesized according to a scheme given in Chapter 9.

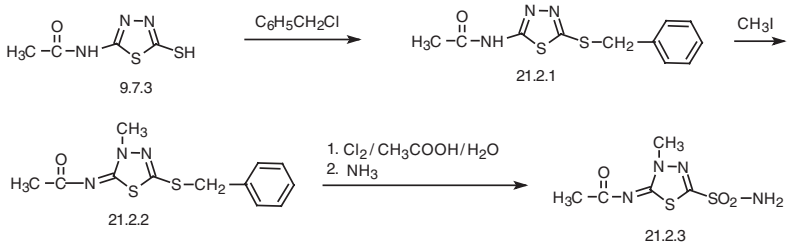


9.7.5

Acetazolamide is an aromatic sulfonamide used as a carbonic anhydrase inhibitor. It facilitates production of alkaline urine with an elevated biocarbonate, sodium, and potassium ion concentrations. By inhibiting carbonic anhydrase, the drug suppresses reabsorption of sodium ions in exchange for hydrogen ions, increases reflux of bicarbonate and sodium ions and reduces reflux of chloride ions. During this process, chloride ions are kept in the kidneys to cover of insufficiency of bicarbonate ions, and for keeping an ion balance. Electrolytic contents of fluid secreted by the kidneys in patients taking carbonic anhydrase inhibitors are characterized by elevated levels of sodium, potassium, and bicarbonate ions and a moderate increase in water level. Urine becomes basic, and the concentration of bicarbonate in the plasma is reduced.

Acetazolamide is a weak diuretic with limited use in edema associated with cardiac insufficiency, glaucoma, minor epileptic attacks, and altitude sickness. Synonyms of this drug are midamor, modamide, cetazol, diamox, dicarb, and others.

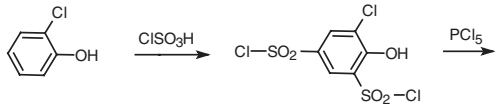
Methazolamide: Methazolamide, N-(4-methyl-2-sulfamoyl-1,3,4-thiadiazol-5-yliden) acetamide (21.2.3), is made by an intermediate product of acetazolamide synthesis—2-acetylamino-5-mercapto-1,3,4-thadiazol (9.7.3). This is benzylated with benzylchloride at the mercapto group, forming 2-acetylamino-5-benzylthio-1,3,4-thiadiazole (21.2.1). Further methylation of the product with methyl iodide leads to the formation of N-(4-methyl-2-benzylthio-1,3,4-thiadiazol-5-yliden)acetamide (21.2.2). Oxidation and simultaneous chlorination of the resulting product with chlorine in an aqueous solution of acetic acid, and reacting the resulting chlorosulfonic derivative with ammonia gives (21.2.3) [5–7].



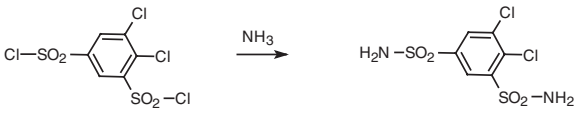
9.7.3 21.2.1 21.2.2 21.2.3

Action of this drug is similar to that of acetazolamide, and it is used for lowering intraocular pressure in treating wide-angle and secondary glaucoma, and before surgical intervention for severe wide-angle glaucoma. Synonyms of this drug are naptazane and others.

Dichlorphenamide: Dichlorphenamide, 4,5-dichlorbenzol-1,3-disulfonamide (21.2.6), is made in a relatively simple way from 2-chlorophenol. 2-Chlorophenol undergoes sulfochlorination by chlorosulfonic acid, forming 4-hydroxy-5-chlorobenzol-1,3-disulfonylchloride (21.2.4). The hydroxyl group is replaced by a chlorine atom using phosphorous pentachloride, giving 4,5-dichlorobenzol-1,3-disulfonylchoride (21.2.5), the reaction of which with ammonia gives the desired dichlorphenamide (21.2.6) [8].



21.2.4



21.2.5 21.2.6

Like the drugs described above, dichlorphenamide is used for secreting excess water in cases of elevated intraocular pressure, and it is used for treating wide-angle and secondary glaucoma as well as in cases where it is necessary to lower intraocular pressure before surgical intervention in severe wide-angle glaucoma. Synonyms of this drug are daranide and others.

21.3 THIAZIDE DIURETICS

Most of the diuretics of the thiazide class are structurally related to antibacterial drugs of the sulfonamide class; however, these compounds exhibit no antibacterial activity.

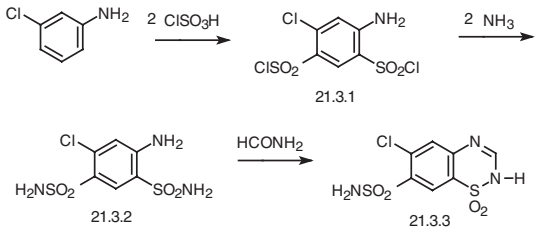
Drugs of this group are derivatives of benzothiadiazine, and as a rule they are substituted at C_7 of the benzol ring by a sulfonamide group and a chlorine atom, or by another electron-accepting group (trifluoromethyl) at C_6. A hydrogenated thiadiazine ring of the benzothiadiazine system permits the introduction of various substituents at C_3, which allows for a significant number of drugs to be created and to make specific correlations between structure and activity in this series of compounds. In particular, it has been established that in the majority of cases, reduction of the double bond at C_3–C_4 of thiazide drugs increases their diuretic activity.

The exact mechanism of action is not known; however, qualitatively, thiazide diuretics act analogously, and their differences are generally quantitative in character. The effector regions of thiazide diuretics are the distal nephron tubules. Drugs of this group inhibit reabsorption of sodium, chloride, magnesium, and calcium ions and cause increased excretion from the organism along with an osmotically equivalent amount of water. Thiazides are also effective in acidosis or alkalosis, inhibiting carbonic anhydrase *in vitro*, and lowering arterial pressure in hypertensive patients.

The antihypertensive effect of thiazides can be explained by their diuretic action, i.e. by lowering the volume of circulated blood. It is also possible that the antihypertensive action of thiazides occurs as a result of their spasmolytic action on the walls of vessels, possibly as a result of changing sodium ion contents in muscle fibers. Reactivity of the vascular system changes under thiazide action, and pressor reactions on vasoconstricting substances (adrenaline and others) are reduced. The majority of side effects of thiazides occur along with hypertension or electrolytic irregularities such as hyponatremia, hypkalemia, or hypomagnesemia. Around 1% of patients using thiazide diuretics develop skin rashes. Thiazides are used either independently, or in combination with other antihypertensive drugs to treat hypertension.

In medical practice, the most frequently used are hydrochorthiazide, chorthiazide, benthiazide, bendroflumethiazide, hydroflumethiazid, polythiazide, trichlormethiazide, as well as related thiazides, but not those named chlortalidon, metolazone, and indapamide.

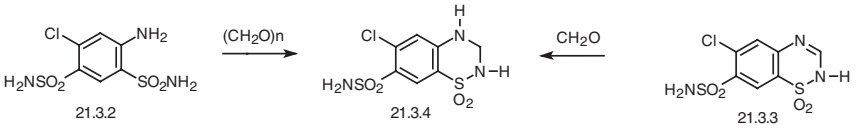
Chlorothiazide: Chlorothiazide, 1,1-dioxide 6-chloro-2*H*-1,2,4-benzothiadiazin-7-sulfonamide (21.3.3) is synthesized in the exact same manner, is all thiazide diuretics. 3-Chloroaniline (or 3-trifluoromethylaniline) undergoes sulfoylchlorination by chlorosulfonic acid, forming 4,6-sulfonochloride-3-chloroaniline (21.3.1), the reaction of which with ammonia gives 4,6-sulfonylamido-3-chloroaniline (21.3.2). Heating this with formamide leads to formation of chlorothiazide (21.3.3) [9–11].



The diuretic action of chlorothiazide, like other drugs of this series, is caused by reduced absorption of sodium and chloride ions by the kidneys during their simultaneous, intense excretion from the organism.

This drug exhibits strong diuretic action during both acidosis and alkalosis. It is used for arterial hypertension, in edematous syndromes of various genesis, congestive effects in cardiovascular insufficiency, nephrosis and nephritis, and toxicosis. It is especially recommended for hypertonic illnesses. It lowers intraocular pressure in a number of cases. Synonyms of this drug are clotride, diupres, diuril, and others.

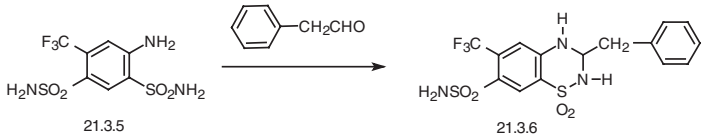
Hydrochlorothiazide: Hydrochlorothiazide, 1,1-dioxide 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazin-7-sulfonamide (21.3.4), is synthesized either by cyclization of 4,6-sulfonamido-3-chloroaniline (21.3.2) using paraformaldehyde, during which simultaneous reduction of the double bond occurs at position C_3–C_4, or the drug is synthesized by reduction of the same double bond in chlorothiazide (21.3.3) by formaldehyde. This small change in structure increases activity of the drug in comparison with chlorothiazide, and increases its absorbability when used orally [12–17].



Hydrochlorothiazide is one of the most widely used drugs of this series, and it is used for the same indications, as is chlorothiazide. Hydrochlorothiazide causes less inhibition of carbonic anhydrase, but causes 5–10 times more diuresis of sodium ions than chlorothiazide using the same dose. Synonyms of this drug are chlorozide, diaqua, esidrix, hydrodiuril, hydrozide, hypothiazide, novohydrazide, urozide, and others.

Bendroflumethiazide: Bendroflumethiazide, 1,1-dioxide 3-benzyl-6-(trifluoromethyl)-3,4-dihydro-2*H*-1,2,4-benzothiadiazin-7-sulfonamide (21.3.6), is synthesized by the same

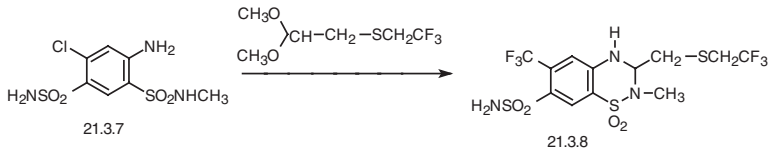
scheme of making the aforementioned drugs using phenylacetaldehyde or its acetale as a carbonyl component, and using 2,4-disulfonamido-5-trifluoromethylaniline (21.3.5) as an o-aminosulfonamide component [18–21].



21.3.5 21.3.6

Bendroflumethiazide may be used for the same indications as the aforementioned drugs; however, it is primarily used as an adjuvant agent for relieving edema associated with cardiac insufficiency, liver cirrhosis, and edema caused by taking corticosteroids. Synonyms of this drug are sinesalin, docidrazine, tensionorm, aprinox, naturetin, and others.

Polythiazide: Polythiazide, 1,1-dioxide 2-methyl-3-(2,2,2-trifluoroethylthiomethyl)-6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazin-7-sulfonamide (21.3.8), is also synthesized by an analogous scheme, which is by condensing 4-aminosulfonyl-5-chloro-2-methylaminosulfonylaniline (21.3.7) with 2,2,2-trifluoroethylthioacetaldehyde dimethylacetal [22].

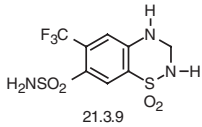


21.3.7 21.3.8

Polythiazide exhibits a more pronounced antihypertensive effect than chlorothiazide and it may be used independently for the same indications as the aforementioned drugs. However, it is primarily used as an ingredient of a combination drugs intended for lowering pressure, in particular in minizide, which is a combination of prazozine and polythiazide. Synonyms of this drug are drenusil, nephril, renis, and others.

There are a number of extremely important thiazide diuretics not listed above. These widely used drugs include hydroflumethiazid, trichlormethiazide, methylcyclothiazide, cyclothiazide, benzothiazide, diazoxide, and others, whose methods of synthesis and pharmacological action are practically identical to those listed above.

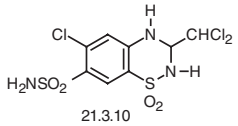
Hydroflumethiazid: Hydroflumethiazid, 1,1-dioxide 3,4-dihydro-6-trifluoromethyl-2*H*-1,2,4-benzothiadiazin-7-sulfonamide (21.3.9) [21,23–25].



21.3.9

Synonyms of this drug are leodrine, diuritens, hydrenox, riosyl, rontyl, diucardyn, calurin, salutenzine, and others.

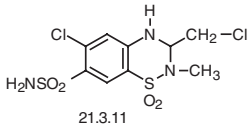
Trichlormethiazide: Trichlormethiazide is 1,1-dioxide 3,4-dihydro-3-(dichlormethyl)-6-chloro-2*H*-1,2,4-benzothiadiazin-7-sulfonamide (21.3.10) [26–31].



21.3.10

Synonyms of this drug are esmarin, esmalorid, anatran, carvacron, intromene, sanamirone, methahydrin, naqua, triazide, and others.

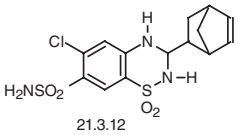
Methylcyclothiazide: Methylcyclothiazide is 1,1-dioxide 3,4-dihydro-3-(chloromethyl)-6-chloro-2*H*-1,2,4-benzothiadiazin-7-sulfonamide (21.3.11) [23].



21.3.11

Synonyms of this drug are thiaidyl, enduron, and others.

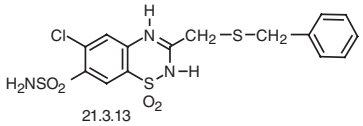
Cyclothiazide: Cyclothiazide is 1,1-dioxide 3,4-dihydro-3-(5-norbornen-2-yl)-6-chloro-2*H*-1,2,4-benzothiadiazin-7-sulfonamide (21.3.12) [32–34].



21.3.12

Synonyms of this drug are diampres, cyclotheriam, anhydron, and others.

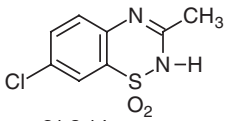
Benzothiazide: Benzothiazide is 1,1-dioxide 3,4-dihydro-3-benzylthiomethyl-6-chloro-2*H*-1,2,4-benzothiadiazin-7-sulfonamide (21.3.13) [35–37].



21.3.13

Synonyms of this drug are diteriam, ditide, regulan, aquatag, hydrex, and others.

Diazoxide: 1,1-dioxide 3-Methyl-7-chloro-1,2,4-benzothiadiazine (21.3.14) [38–40].



21.3.14

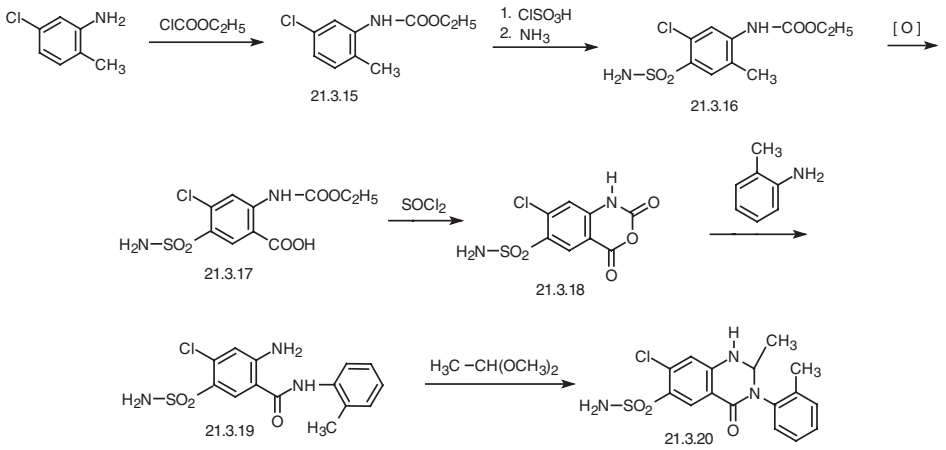
Synonyms of this drug are dizoxide; eudemine, hyperstat, hypertonalum, mutabase, proglicem.

21.3.1 Drugs related to thiazide diuretics

Diuretic drugs metolazone, chlorothalidon, and indapamide are diuretics and antihypertensive drugs. Chemically they are not thiazides; however, being sulfonamide derivatives and having, in a certain sense, structural similarities and a similar mechanism of action common among thiazides, with the exception being that they do not inhibit carbonic anhydrase. Therefore, they are formally seen in the same group as thiazide diuretics.

The ability of metolazone, chlorothalidone, and indapamide to remove edematous liquid from the body is practically identical to that of thiazide diuretics. These drugs are used for relieving edema associated with hepatic, renal, and cardiac diseases, as well as for treating general hypertension either independently, or in combination with other drugs.

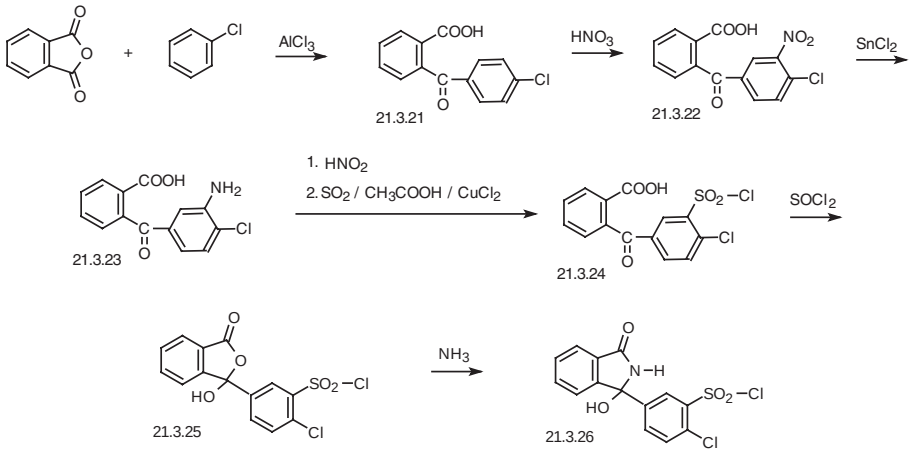
Metolazone: Metolazone, 7-chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-*o*-tolyl-6-quinazolinsulfonamide (21.3.20), is synthesized from 5-chloro-2-methylaniline. The amino group is acylated by ethyl chloroformate, forming 5-chloro-*N*-ethoxycarbonyl-2-methylaniline (21.3.15). The product, upon subsequent reaction with chlorosulfonic acid and ammonia, is transformed in the usual manner into 4-sulfonamido-5-chloro-*N*-ethoxycarbonyl-2-methylaniline (21.3.16). The methyl group of this product is oxidized by potassium permanganate, giving 5-sulfonamido-4-chloro-*N*-ethoxycarbonyl anthranylic acid (21.3.17). Upon treating this with thionyl chloride it cycles into the corresponding anhydride (21.3.18). This reacts with *o*-toluidine, turning it into 2-amino-5-aminosulfonyl-4-chloro-*o*-toluolbenzamide (21.3.19). Finally, reacting this with dimethylacetal acetic acid gives metolazone (21.3.20) [41–47].



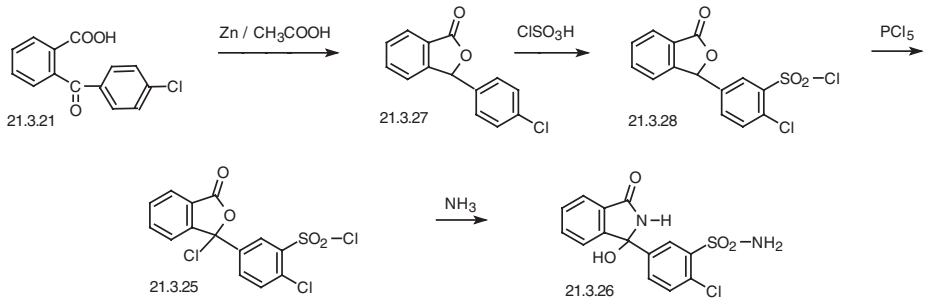
Metolazone acts on the distal tubules, thus increasing excretion of water and sodium, potassium, and chloride ions. It is used for treating edema caused by cardiac insufficiency and adrenal irregularities, including nephrotic syndrome. Synonyms of this drug are diulo, matenix, and zaroxolyn.

Chlorothalidone: Chlorothalidone, 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzolsulfamide (21.3.26), is synthesized by two proposed methods from 2′-carboxy-4-chlorobenzophenone (21.3.21), which is easily synthesized by acylating chlorobenzol with phthalic anhydride in the presence of aluminum chloride. The resulting benzophenone (21.3.21)

undergoes nitration by nitric acid, which gives 2′-carboxy-3-nitro-4-chlorobenzophenone (21.3.22). The nitro group in the resulting compound is reduced by tin dichloride to 2′-carboxy-3-amino-4-chlorobenzophenone (21.3.23). Next, subsequent diazotation and reaction with sulfur dioxide in the presence of copper dichloride gives the corresponding sulfonylchloride (21.3.24). Upon reaction with thionyl chloride, this compound undergoes cyclization into phtahlide (21.3.25), which when reacted with aqueous ammonia rearranges into a derivative of isoindoline with simultaneous substitution of the chloride atom in the sulfogroup with an amino group, which results in chlorothalidone (21.3.26) [48,49].

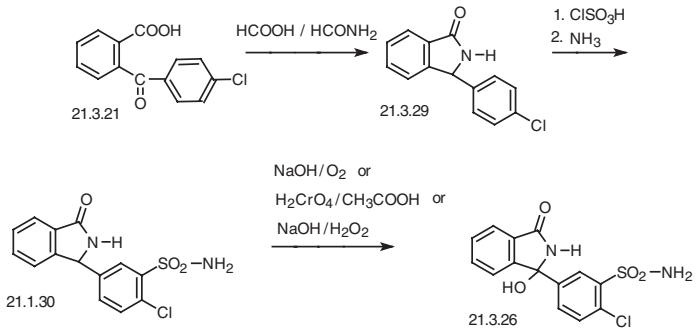


A second way of synthesizing it is from 2′-carboxy-4-chlorobenzophenone (21.3.21), which during reduction with zinc in acetic acid transforms into 3-(4′-chlorophenyl)phthalide (21.3.27). Sulfonylchlorination of this gives the corresponding sulfonylchloride (21.3.28), which upon reaction with phosphorous pentachloride is chlorinated into 3-(4′-chlorophenyl-3′-chlorosulfo)-3-chlorophtalide (21.3.25). This is reacted with aqueous ammonia in the aforementioned manner, and it rearranges into chlorothalidone (21.3.26) [50].



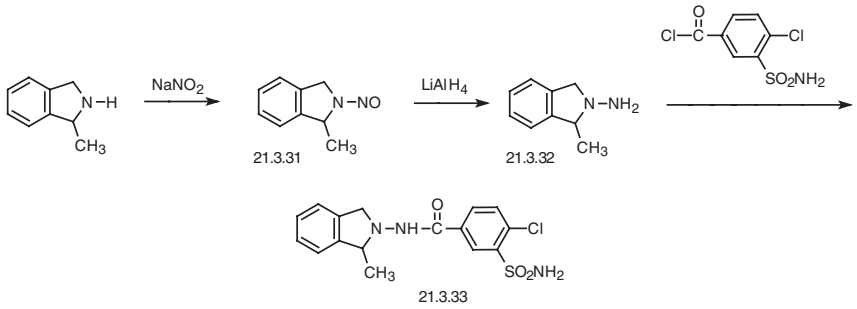
The third way of synthesis is started from 2′-carboxy-4-chlorobenzophenone (21.3.21), and it consists of direct cyclization of the indicated carboxy benzophenone into 3-(4[1]-chlorophenyl)phthalimidine (21.3.29). Subsequent sulfochlorination and amination of this product gives 2-chloro-5-(3-oxo-1-isoindolinyl)-benzolsulfonamide (21.3.29), which is

oxidized by various oxidizers such as oxygen or hydrogen peroxide in alkaline or chromic acid in acetic acid into chlorothalidone (21.3.26) [51,52].



In terms of activity, chlorothalidone is very similar to benzothiadiazide (21.3.13) and is used as an independent drug or in combination with other antihypertensive agents for lowering arterial blood pressure, and also as an adjuvant drug for treating edema caused by cardiac insufficiency and renal irregularities, including nephrotic syndrome. Synonyms of this drug are gigroton, novatalidon, uridon and others.

Indapamide: Indapamide, 4-chloro-N-(2-methyl-1-indolinyl)-3-sulfamoylbenzamide (21.3.33), is synthesized from 2-methylendoline, the nitrosation of which gives 2-methyl-1-nitrosoindoline (21.3.31). Reducing this with lithium aluminum hydride leads to formation of 1-amino-2-methylendoline (21.3.32). Acylating this with 3-sulfonylamino-4-chlorbenzoic acid chloride leads to (21.3.33) [53,54].



Indapamide is a derivative of benzolsulfonamide and its mechanism of action is analogous to that of thiazides. It is intended for lowering arterial blood pressure and as an adjuvant drug for treating edema caused by cardiac insufficiency. Synonyms of this drug are lozol and others.

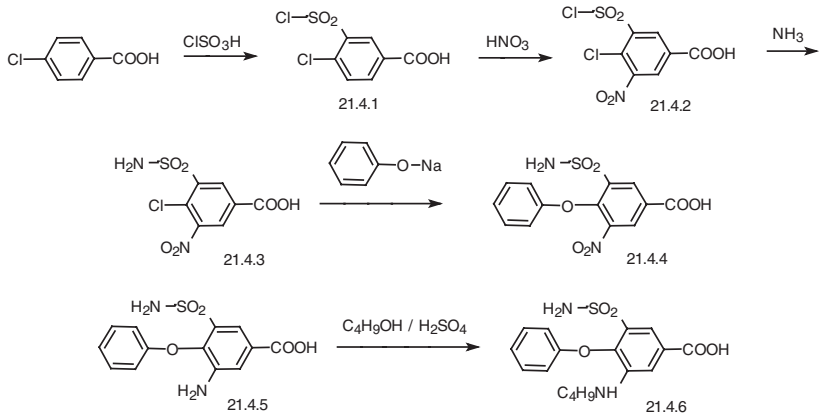
21.4 LOOP DIURETICS

The most powerful diuretic effect is provided by loop diuretics, which severely inhibit reabsorption of sodium and chloride ions from renal tubules in cortical and cerebral

regions and the ascending region of Henle's loop. In both oral and intravenous introduction, they cause a rapid rise in excretion of sodium and chloride ions from the kidneys and an increase in secreted urine volume.

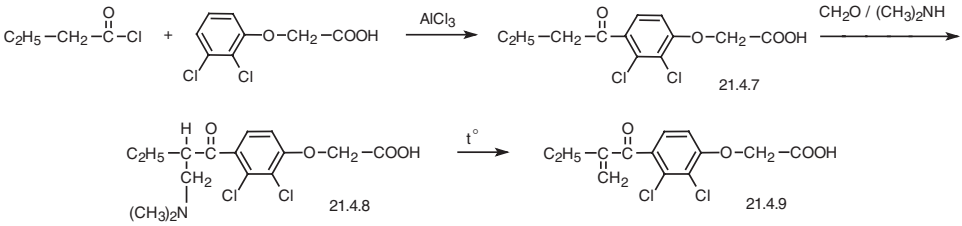
An increase in potassium, hydrogen, magnesium, and calcium ions is observed simultaneously with the increase of sodium and chloride ions being excreted. Urine becomes more acidic, and the concentration of ammonia ions falls. This can result in hypochloremic alkalosis. The most widely used loop diuretics are bumetanide (derivative of monosulfamoyl methanylamide), ethacrynic acid (a derivative of aryloxyacetic acid), and furosemide (derivative of monosulfamoylanthranylic acid), which have more diuretic efficacy than thiazides. Bumetanide, ethacrynic acid, and furosemide are used in treating edema associated with severe and chronic cardiac insufficiency, cirrhosis of the liver, nephrotic syndrome, and renal diseases. They are frequently used by patients unable to tolerate thiazides. They are also used to treat chronic hypertension both independently as well as in combination with other antihypertensive drugs. The efficacy and safety of bumetanide and ethacrynic acid in chronic hypertension has not been proven. Loop diuretics are effective in treating severe hyperkalemia.

Bumetanide: Bumetanide, 3-butylamino-4-phenoxy-5-sulfamoylbenzoic acid (21.4.6), is synthesized from 4-chlorobenzoic acid. In the first stage of synthesis, it undergoes sulfonylchlorination by chlorosulfonic acid, forming 4-chloro-3-chlorosulfonylbenzoic acid (21.4.1), which is further nitrated with nitric acid to 4-chloro-3-chlorosulfonyl-5-nitrobenzoic acid (21.4.2). Reacting this with ammonia gives 5-aminosulfonyl-4-chloro-3-nitrobenzoic acid (21.4.3), which when reacted with sodium phenolate is transformed into 5-amino-sulfonyl-3-nitro-5-phenoxybenzoid acid (21.4.4). Reduction of the nitro group in this product by hydrogen using a palladium on carbon catalyst gives 3-amino-5-aminosulfonyl-5-phenoxybenzoic acid (21.4.5). Finally, reacting this with butyl alcohol in the presence of sulfuric acid gives the desired bumetanide (21.4.6) [55–59].



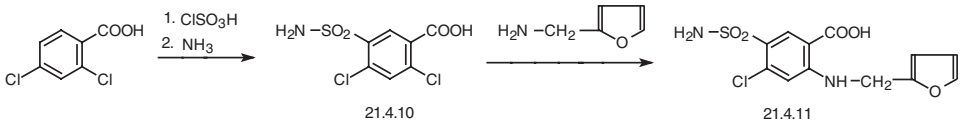
Bumetanide is used for relieving edema associated with cardiac insufficiency, for liver and kidney diseases including nephrotic syndrome, for ascites, and hypertension. Synonyms of this drug are bumex and others.

Ethacrynic acid: Ethacrynic acid—[2,3-dichloro-4-(2-methylenbutyryl)phenoxy]acetic acid (21.4.9), is synthesized from 2,3-dichlorophenoxyacetic acid. This is acylated with butyroyl chloride, forming 4-butyroyl-2,3-dichlorophenoxyacetic acid (21.4.7), which is further aminomethylated under Mannich reaction conditions using dimethylamine and formaldehyde. The resulting product (21.4.8) undergoes further thermal degredation, forming an unsaturated ketone—ethacrynic acid (21.4.9) [60–62].



Ethacrynic acid is a powerful diuretic prescribed for edema associated with cardiac insufficiency, renal edema that does not respond to other diuretics, and edema of the brain and lungs. Synonyms of this drug are uregit, edecrin, and others.

Furosemide: Furosemide, 4-chloro-N-furfuryl-5-sulfamoylanthranylic acid (21.4.11), is synthesized in a relatively simple manner from 2,4-dichlorobenzoic acid, which is converted into 5-aminosulfonyl-4,6-dichlorobenzoic acid (21.4.10) during subsequent reaction with chlorosulfonic acid and ammonia. Reacting this with furfurylamine gives furosemide (21.4.11) [63–66].



Furosemide is a highly effective and quick-acting diuretic whose action, like all of the examined loop diuretics, is associated with blocking reabsorption of ions in the ascending bend of Henle's loop. It is used for edema syndrome of various origins, edema of the lungs and brain, chronic renal insufficiency, some forms of hypertonic crises, and poisoning by barbiturates and other compounds excreted mainly with urine.

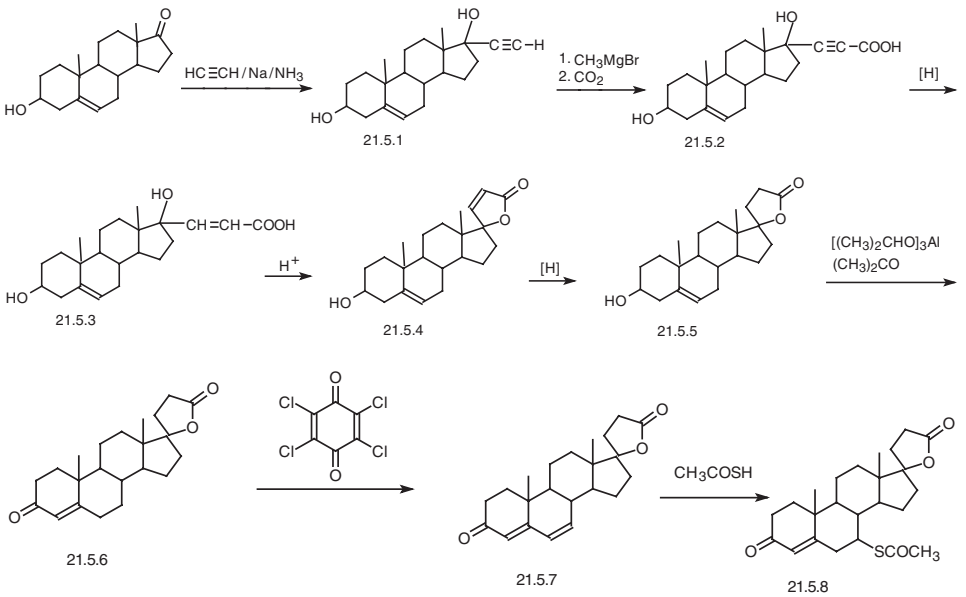
In a number of cases, furosemide has proven more effective than other diuretics. Besides a diuretic effect, it also dilates peripheral vessels. It is frequently used in combination with other antihypertensive drugs. Synonyms of this drug are lazix, lazizix, franil, urosemide, and many others.

21.5 POTASSIUM SPARING DIURETICS

Potassium sparing diuretics differ from other diuretics in that they increase excretion of sodium ions from the body while simultaneously reducing excretion of potassium ions. In general, when used as independent agents, drugs of this class are not powerful diuretics

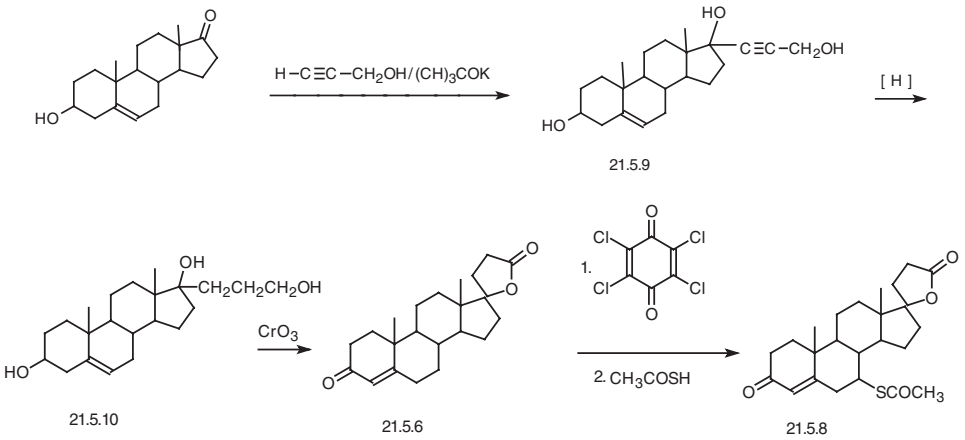
and they are only used specifically in cases of hypercalemia. They are primarily used in combination with other diuretics for increasing diuresis and for preventing development of hypokalemia. Because of completely different structures and the presence of specifically unique characteristics, properties of drugs of this series (spironolactone, triamterene, and amiloride) will be examined individually.

Spironolactone: Spironolactone is the 7-acetate of the γ-lactone of 17-hydroxy-7-mercapto-3-oxo-17-α-pregn-4-ene-21-carboxylic acid (21.5.8). Spironolactone is synthesized industrially in two different ways from androstenolone—3β-hydroxy-5-androsten-17-one. According to the first method, androstenolone undergoes ethynylation by acetylene in a Normant reaction condition using sodium amide in liquid ammonia, which forms 17 α-ethynyl-3β-,17β-dihydroxy-5-androstene (21.5.1). Subsequent reaction of this with methylmagnesiumbromide and then with carbon dioxide gives the corresponding propenal acid (21.5.2). Reduction of the triple bond in this product with hydrogen using a palladium on calcium carbonate catalyst forms the corresponding acrylic acid derivative (21.5.3), which is treated with acid without being isolated, which leads to cyclization into an unsaturated lactone derivative (21.5.4). The double bond is reduced by hydrogen, in this case using a palladium on carbon catalyst. The resulting lactone 21.5.5 undergoes oxidation in an Oppenauer reaction, giving an unsaturated keto-derivative—4-androsten-3,17-dione (21.5.6). Further oxidation of the product (21.5.6) using chloroanyl gives dienone (21.5.7), which when reacted with thioacetic acid gives the desired spionolactone (21.5.8) [67–71].



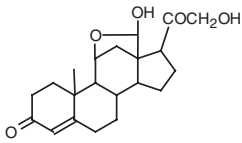
The second way is from 4-androsten-3,17-dione (21.5.6), which undergoes ethynylation by propargyl alcohol in the presence of potassium *tert*-butylate, forming 17β-hydroxy-17α-(3-hydroxypropinyl)-4-androsten-3-one (21.5.9), the triple bond of which is completely reduced by hydrogen using as a catalyst a complex of triphenylphospine and

rhodium chloride, which forms 17β-hydroxy-17α-(3-hydroxypropyl)-4-androsten-3-one (21.5.10). Oxidation of this product with chromium (VI) oxide in pyridine gives lactone (21.5.6), which is oxidized in the manner described above by chloranyl to (21.5.9) and reacted further with thioacetic acid to the desired spironolactone (21.5.8) [72].



Spironolactone is a potassium sparing diuretic that has a different mechanism of action than other drugs of this class.

It is a competitive antagonist of aldosterone, and its action is most effective when the level of circulated aldosterone in the organism is high.

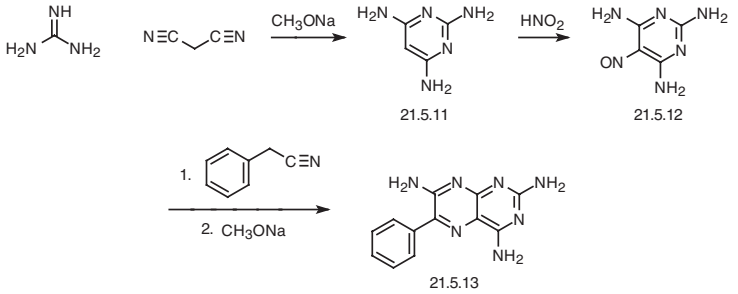


aldosterone

Aldosterone is a mineralocorticosteroid that takes part in the regulation of electrolytic balance in the organism. Aldosterone lowers excretion of sodium ions from the body, thus increasing their reabsorption and increasing secretion of potassium ions in renal tubules. Being a competitive antagonist of aldosterone, spironlactone blocks aldosterone receptors, thus increasing excretion of sodium, chloride, and corresponding equivalents of water with urine, thus retaining the amount of potassium ions in the organism. Spironolactone is used both individually as well as in combination with thiazides, since it lowers kaliuresis caused by thiazide diuretics. It is used for edema syndrome caused by chronic cardiac insufficiency, liver cirrhosis, hyperaldosteronism, and hypokalemia caused by other diuretics. Synonyms of this drug are aldactone, verospirone, and others.

Triamterene: Triamterene, 2,4,7-triamino-6-phenylpteridine (21.5.13), is synthesized in by the following scheme. Reacting guanidine with malonodinitrile gives 2,4,6-triaminopyrimidine (21.5.11). This undergoes nitrosation by reacting it with nitric acid, which results in the

formation of 5-nitroso-2,4,6-triaminopyrimidine (21.5.12), which upon condensation with benzyl cyanide in the presence of sodium methoxide cyclizes into triamterene (21.5.13) [73–76].

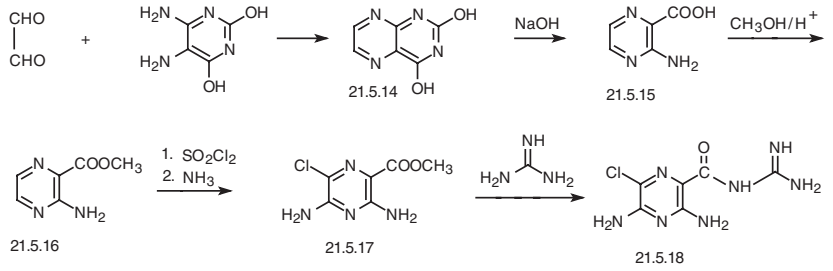


Triamterene is a pyrazine derivative that inhibits reabsorption of sodium ions without increasing excretion of potassium ions. It exhibits the same approximate effect as spironolactone; however, it does not competitively bind with aldosterone receptors. Its action does not have an effect on secretion of aldosterone or its antagonists, which are a result of direct action on renal tubules.

This potassium sparing diuretic causes a moderate increase in excretion of sodium and bicarbonate ions in urine, and it raises excretion of potassium and ammonia ions. It has little effect on urine volume.

This drug is recommended in combination with other diuretics for treating edema caused by usual reasons such as circulatory insufficiency, cirrhosis of the liver, and nephrotic syndrome. Synonyms of this drug are diazide, reviten, pterophene, and others.

Amyloride: Amyloride, N-amidino-3,5-diamino-6-chloropirazincarboxamide (21.5.18), is synthesized from 5,6-diaminouracil, which upon reaction with glyoxal transforms into a pyrazineopyrimidine derivative (21.5.14), which decomposes upon further reaction with a strong alkaline, forming 3-aminopirazin-2-carboxylic acid (21.5.15). This is esterified into the corresponding methyl ester (21.5.16), and subsequently treated with sulfonyl chloride and ammonia, which gives the methyl ester of 3,5-diamino-6-chloropirazin-2-carboxylic acid (21.5.17). Reacting this with guanidine gives amyloride (21.5.18) [77–82].



Amyloride is also a potassium sparing diuretic that exhibits moderate activity. It is not an antagonist of aldosterone. It inhibits reabsorption of sodium ions and reduces excretion of

potassium ions. Amyloride is rarely used individually—as a rule it is used in combination with thiazides or loop diuretics. It is mainly used in combination with thiazide diuretics for cardiac insufficiency and hypertension, especially in cases where it is necessary to prevent hypokalemia. Synonyms of this drug are arumil, diursan, modamid, frumil, and others.

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– 22 –

Antihypertensive Drugs

Drugs that are used for treating hypertonic diseases as well as symptomatic hypertensions are called antihypertensive drugs.

Hypertension is a syndrome characterized by elevated arterial blood pressure that depends on a number of factors. Some of the main factors that determine arterial blood pressure are parameters of heart rate, volume, viscosity, and electrolytic contents of circulating blood.

Normal range of blood pressure varies depending on sex and age. Moreover, various medical schools themselves determine what an acceptable value is. The etiology of 90–95% of cases of this disease are unknown, and these cases are referred to as primary or essential hypertension; treatment is of a palliative nature that is directed to lowering systolic and diastolic blood pressure, and in general, effectively permitting control of a patient's arterial blood pressure over a long period of time. During such treatment, antihypertensive agents can be directed at various sections of physiological systems that regulate arterial blood pressure.

The remaining 5–10% of cases of hypertension originate because of stenosis of renal arteries or constriction of the aorta, Cushing's syndrome, and pheochromocytosis. Hypertension originating from these latter conditions is called secondary hypertension. The main systems controlling the body's arterial blood pressure are the central nervous system (CNS), sympathetic ganglia, adrenergic nerve endings, vascular smooth musculature, kidneys and arterioles, and lastly, the renin–angiotensin system. Lowering arterial blood pressure can be accomplished by affecting vascular smooth musculature using hydralazine, diazoxide, minoxidil, sodium nitroprusside, diuretics, and calcium channel blockers, which relax vascular smooth musculature, thus lowering both systolic and diastolic blood pressure.

H-cholinoblockers (ganglioblockers) such as mecamylamine and trimethaphan act on autonomic ganglia to reduce blood pressure.

Lowering arterial blood pressure by acting on the adrenergic system can be accomplished by stimulating α-adrenoreceptors (clonidine, guanabenz, guanacin, and methyldopa), which leads to a reduction of sympathetic impulses to vessels and the heart, thus reducing cardiac output and heart rate, which consequently lowers arterial blood pressure; blocking α_1-adrenoreceptors (prazosin, terazosine), the main importance of which is dilating peripheral vessels, which leads to reduced blood pressure; blocking β-adrenoreceptors (propranolol, athenolol, nadolol, and others), which reduce cardiac output and peripheral resistance of vessels, resulting in lower blood pressure.

Lowering blood pressure can also be done by acting on the renin–-angiotensin system by using angiotensin-converting enzyme (cartopril, enalapril). These drugs block action of the angiotensin-converting enzyme, which results in less production of angiotensin II and inhibits its vasoconstricting action on arterial and venous blood vessels. Diuretics can act on the kidneys and arterioles for the purpose of lowering blood pressure. Finally, calcium channel blockers can act on smooth musculature in order to lower blood pressure (verapamil, diltiazem, and nifedipine).

Antihypertensive drugs can be divided into eight classes based on the mechanism of action: diuretics, β-adrenoblockers, centrally acting sympatholytics, peripherally acting sympatholytics, calcium channel blockers, myotropic hypotensive drugs, angiotensin-converting enzyme inhibitors, and calcium channel activators.

Depending on the severity of the hypertension, treatment with antihypertensive drugs proceeds strategically in a specific order. It is understood that this order should be flexible and open to alternative ways, but a few general principles must be adhered to.

Diuretics, β-adrenoblockers, or small doses of angiotensin-converting enzyme inhibitors should be used first for minor hypertension to lower blood pressure. In treating weak and moderate hypertension, it is recommended to use β-adrenoblockers, angiotensin-converting enzymes inhibitors, clonidine, guanabenz, guanfacine, methyldopa, prazosin, terazosin, calcium channel blockers, or reserpine. In moderate to severe hypertension, it is recommended to use hydralazine and large doses of angiotensin-converting enzyme inhibitors. In severe hypertension, guanethidine, guanadrel, and also minoxidil are used. Finally, in urgent cases of hypertension, it is recommended to use sodium nitroprusside, diazoxide, trimethaphan, or labetalol.

A universally accepted principle of antihypertension therapy is the simultaneous use of several drugs that act on the primary regions controlling arterial blood pressure, and it is generally recommended to use a combination of diuretics, adrenoblockers, angiotensin-converting enzyme inhibitors, or calcium channel blockers.

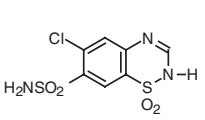
22.1 DIURETICS

Hypertension therapy suggests wide use of diuretics, including thiazide diuretics, drugs related to them, such as metolazone (21.3.20) and indapamide (21.3.26), furosemide (21.4.11), loop diuretics, as well as potassium sparing diuretics—spironolactone (21.5.8), triamterene (21.5.13), and amyloride (21.5.18).

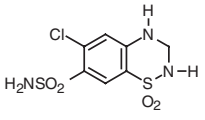
The molecular mechanism of diuretics acting as antihypertensive agents is not completely clear; however, use of diuretics causes a significant increase in the amount of water and electrolytes excreted in urine, which leads to a reduction in the volume of extracellular fluid and plasma. This in turn leads to a reduction of cardiac output, which is the main parameter responsible for a drop in arterial blood pressure and venous blood return. Cardiac output is gradually restored, but the hypotensive effect remains, possibly because of the reduced peripheral resistance of vessels. It is also possible that diuretics somehow lower vascular activity of noradrenaline and other factors of pressure in the organism. Methods of synthesizing thiazide diuretics used for hypertension are described in the preceding chapter, Chapter 21.

22.1.1 Thiazide diuretics

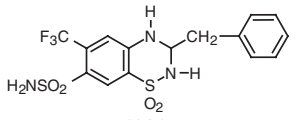
The most widely used thiazide diuretics are chlorothiazide (21.3.3), hydrochlorothiazide (21.3.4), bendroflumethiazide (21.3.6), polythiazide (21.3.8), hydrofluthiazide (21.3.9), trichlorometazide (21.3.10), methylcycloothiazide (21.3.11), cyclothiazide (21.3.12), and benzthiazide (21.3.13).



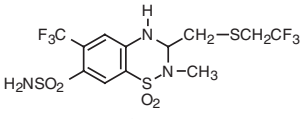
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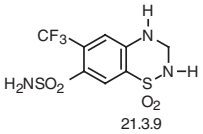
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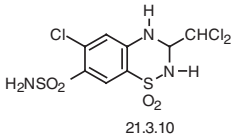
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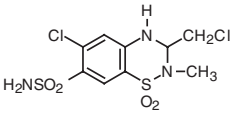
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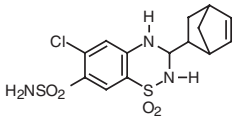
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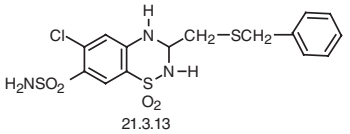
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21.3.11



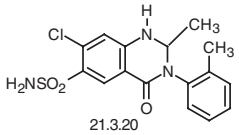
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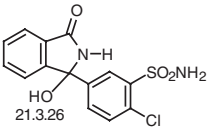
21.3.13

22.1.2 Thiazide-related drugs

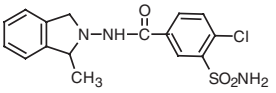
Metolazone (21.3.20), chlorotanidone (21.3.26), indapamide (21.3.33), and also loop diuretics, bumetanide (21.4.6), ethacrynic acid (21.4.9), and furosemide (21.4.1).



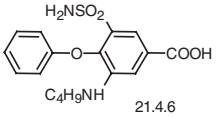
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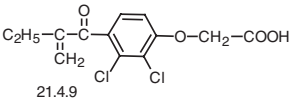
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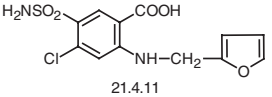
21.3.33



21.4.6



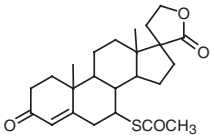
21.4.9



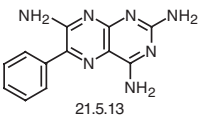
21.4.11

22.1.3 Potassium sparing diuretics

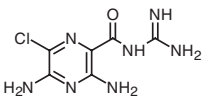
Spironolactone (21.5.8), triamterene (21.5.13), and amyloride (21.5.18).



21.5.8



21.5.13



21.5.18

The effects of these drugs are practically identical. This group of drugs is characterized by three main side effects: (1) hyperuricemia, (2) hyperglycemia, and (3) irregular electrolytic balance that can be characterized by hypercalcemia, hypochloremia, and metabolic alkalosis.

Furosemide is the most effective one, although when compared to thiazides, it is not the most powerful antihypertensive drug.

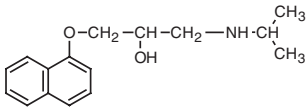
22.2 β-ADRENOBLOCKERS

The most frequently used antiadrenergic drugs for hypertension therapy are the β-adrenoblockers. Despite the fact that they have been used for many years, their mechanism of action is not completely understood. Only one thing is clear—they are competitive antagonists of adrenaline and noradrenaline on cardiac β-adrenergic receptors.

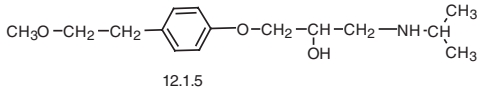
It is believed that, like diuretics, using β-adrenoblockers leads to a reduction of cardiac output. Heart rate and overall peripheral vascular resistance declines.

Also, as with diuretics, cardiac output is gradually restored, yet the hypotensive effect remains. Labetalol, a unique β-adrenoblocker best suited to lower blood pressure, combines nonselective β-adrenergic blocking action on both β_1- and β_2-receptors with simultaneous blockage of α_1-receptors.

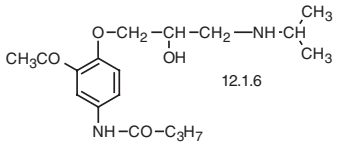
Unlike other adrenoblockers, labetalol lowers blood pressure more by lowering resistance of peripheral vessels than by suppressing myocardial function. This, along with a reduction in pressure, fails to change heart rate. Currently, eight of the most frequently used β-adrenoblockers in medicine are used for hypertension therapy, and their syntheses are described in Chapter 12. They are propranolol (12.1.3), metoprolol (12.1.5), acebutol (12.1.6), athenolol (12.1.7), nadolol (12.1.8), pindolol (12.1.9), timolol (12.1.10), and labetalol (12.1.12).



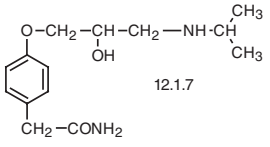
12.1.2



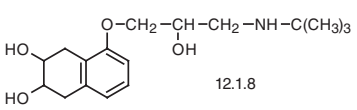
12.1.5



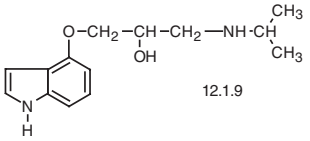
12.1.6



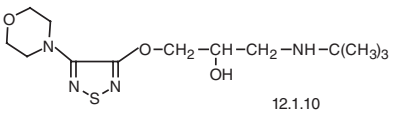
12.1.7



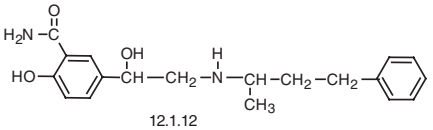
12.1.8



12.1.9



12.1.10



12.1.12

The most frequent side effects when using β-adrenoblockers are feelings of fatigue, coldness in the extremities, and also an increase in the level of triglycerides and lipoproteins in the blood.

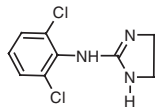
22.3 CENTRALLY ACTING ADRENERGIC DRUGS (SYMPATHOLYTICS)

The stimulation of α-adrenergic receptors in specific regions of the CNS leads to hypotension.

The mechanism of action of these drugs is caused by stimulation of α_2-adrenoreceptors in the inhibitory structure of the brain. It is believed that interaction of these drugs with α_2-adrenergic receptors is expressed in the suppression of vasomotor center neurons of the medulla, and reduction of hypothalamus activity, which leads to a decline in sympathetic impulses to the vessels and the heart. In summary, cardiac output and heart rate are moderately reduced, and consequently arterial pressure is reduced.

The clinically beneficial antihypertensive drugs of this series such as clonidine, guanabenz, and guanfacin evidently act identically by affecting α_2-adrenergic receptors. Methyldopa, examined together with the aforementioned drugs, is transformed in the body into α-methylnoradrenaline, which, by stimulating α_2-adrenergic receptors, inhibits sympathetic impulses, thus lowering arterial pressure.

Clonidine (11.1.34)***:*** The synthesis is described in Chapter 11.

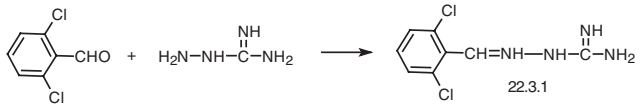


11.1.34

Clonidine is a selective α_2-adrenergic agonist that exhibits pronounced hypotensive action that is associated with a reduction of overall peripheral vascular resistance, decline in frequency of cardiac contraction, and reduced cardiac output. Clonidine is the drug of choice for treating various degrees of hypertension when used in combination with oral diuretics.

Clonidine is used in various forms of hypertonic diseases and for relieving hypertonic crises. It is also used in ophthalmological practice for treating wide-angle glaucoma. Synonyms of clonidine are gemiton, catapresan, and clofeline.

Guanabenz: Guanabenz, [(2,6-dichlorobenzyliden) amino] guanidine (22.3.1), is synthesized in one step by reacting 2,6-dichlorobenzaldehyde with amino guanidine [1–3].

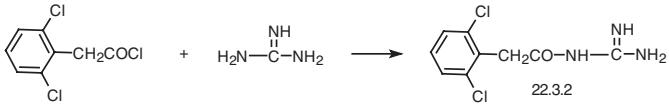


22.3.1

Guanabenz is an α_2-adrenergic agonist that exhibits pronounced hypotensive action, and that is associated with a reduction of overall peripheral vascular resistance, decline in frequency of cardiac contractions, and reduced cardiac output.

It is used both independently and in combination with oral diuretics for treating various degrees of hypertension. A synonym of this drug is vitensin.

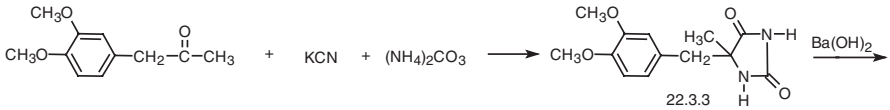
Guanfacin: Guanfacin, *N*-amidino-2-(2,6-dichlorophenyl)acetamide (22.3.2), is also synthesized in a very easy synthesis of reacting the acid chloride or ester of 2,6-dichlorophenylacetic acid with guanidine [4–7].



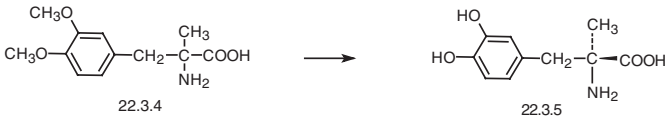
22.3.2

Guanidine operates exactly by the same mechanism as clonidine and guanabenz, and it is used for the same indications. A synonym of this drug is estulic.

Methyldopa: Methyldopa, (-)-3-(3,4-dihydroxyphenyl)-2-methylalanine (22.2.5), is synthesized by a few methods that are only slightly different. The first method is from 3,4-dimethoxyphenylacetone, which undergoes a Strecker–Zelinski reaction using potassium cyanide and ammonium carbonate, to give 4-methyl-4-(3,4-dimethoxybenzyl-hydantoine (22.3.3), which is further hydrolyzed in the presence of barium hydroxide to give (±)-3-(3,4-dimethoxyphenyl)-2-methylalanine (22.3.4). This undergoes acetylation at the amino group, and the racemic mixture is then separated using (-)-1-phenylethylamine. The isolated isomer is hydrolyzed using hydrobromic acid, which simultaneously removes the methoxy- and acetyl groups to give the desired (-)-3-(3,4-dihydroxyphenyl)-2-methylalanine (22.3.5) [8–10]. Alternative syntheses have been proposed [11–13].



22.3.3



22.3.4

22.3.5

Methyldopa is an α-methoxylated derivative of levodopa that exhibits hypotensive action by reducing overall peripheral vascular resistance and reducing heart work. Antihypertensive action of methyldopa consists of the biotransformation of methyldopa into methylnoradrenaline (methylnorepinephrine), which acts as a "pseudo neurotransmitter." The current, universally accepted point of view is that the action of methyldopa is carried out through the CNS, where methylnorepinephrine, a powerful stimulant of α-adrenergic receptors of the medulla, inhibits the vasomotor center.

It is prescribed for arterial hypertension and hypertensive crises. Synonyms of this drug are aldomet, dopegit, mopatil, and others.

22.4 PERIPHERALLY ACTING SYMPATHOLYTICS (α-ADRENOBLOCKERS)

As was already mentioned (Chapter 12), the characteristic uniqueness of α-adrenoblockers is their ability to reduce the pressor effect of adrenaline (epinephrine). In particular,

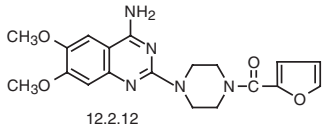
postsynaptic α_1-blockers act on α-receptive regions located on vascular smooth musculature and counteract the pressor, vasoconstricting effect of adrenaline (epinephrine) and noradrenaline (norepinephrine). In addition, they exhibit a direct relaxant effect on the smooth musculature, which leads to peripheral dilation of vessels, and as a result, leads to lower blood pressure. Dilation of peripheral vessels is probably the most important effect of α-adrenoblockers. However, they also exhibit a cardiostimulatory effect, which often becomes the reason for tachycardia. Attempts to treat hypertension with drugs such as phentolamine (12.2.1) and phenoxibenzamine (12.2.6), which block α-adrenergic receptors, have been unsuccessful because of a large number of hindering side effects, and also because of the possibility of developing tolerance to them.

However, a number of α_1-selective adrenoblockers and adrenergic neuron blockers are used to treat hypertension.

22.4.1 Reversible competitive α_1-selective adrenoblockers

Drugs with α-adrenergic blocking activity are peripheral coronary-dilating agents that only differ in specificity with α_1-adrenergic receptors. Prazozin and tetrazin are selective α_1-adrenoblockers that are used in therapeutic doses to lower arterial pressure.

Prazosin (12.2.12)***:*** Its synthesis is described in Chapter 12.

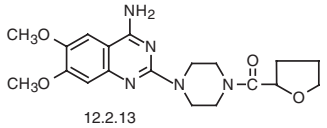


12.2.12

Prazosin is used to treat average or moderate hypertension. Upon taking this drug, blood pressure drops without substantial changes in indicators of heart work, such as rate, coronary flow, and cardiac output.

Prazosin is used for weak to moderate hypertension. Synonyms of this drug are minipress and minizide.

Terazosin (12.2.13)***:*** Its synthesis is described in Chapter 12.



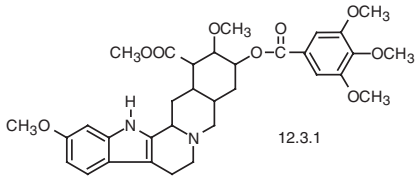
12.2.13

Terazosin is used for the same indications as prazosin; however, it has the advantage of being able to be taken once per day. Synonyms of this drug are heitrin and vasocard.

22.4.2 Adrenergic neuron blockers

Adrenergic neuron blockers cause a release of biogenic amines at neuron terminals. These drugs can interfere in the synthesis, storage, and release of norepinephrine, dopamine, and serotonin.

Reserpine (12.3.1)***:*** Its synthesis is described in Chapter 12.



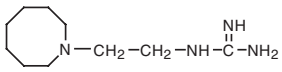
12.3.1

Reserpine causes release of norepinephrine, dopamine, and serotonin at neuronal termini. It weakens the intracellular uptake of biogenic amines and decreases the ability to store them in vesicles.

Reserpine is used to treat hypertension; however, it is not the drug of choice because of a number of side effects; however, it is the basis for many combined hypertensive drugs, in particular, for diuretic drugs.

Reserpine is prescribed under a number of synonyms, including serpasil, brinerdin, diupres, and others.

Guanethidine (12.3.2)***:*** The synthesis of this drug is described in Chapter 12.



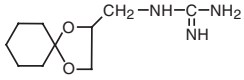
12.3.4

Guanethidine, whose synthesis is described in Chapter 12, does not act on effector cells. It enters the neuron, where it accumulates and replaces norepinephrine. As a result, guanethidine itself can be released during stimulation of the nerve, which, however, is not an adrenergic receptor stimulant.

Guanethidine is used for severe hypertension when the use of the more generally accepted drugs turns out to be unsuccessful. It is a powerful, long-lasting antihypertensive drug; however, it affects a patient's blood pressure only in the orthostatic position, and not when lying down.

Guanethidine is a very powerful and long-lasting drug, and its action often lasts 2–3 days after its use has been stopped. Synonyms of this drug are octadin, ismelin, sanotensin, and others.

Guanadrel (12.3.8)***:*** The synthesis of this drug is described in Chapter 12.



12.3.8

Guanadrel is an adrenergic neuron blocker used for essential hypertension. Its mechanism of action and side effects are similar to those of guanethidine.

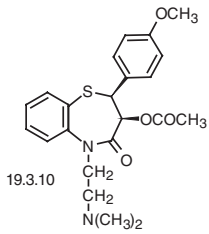
It is used to treat hypertension in patients who do not adequately respond to thiazide diuretics. It can be used as an adjuvant in thiazide treatment for reaching an optimal level of blood pressure. A synonym of this drug is hylodrel.

22.5 CALCIUM CHANNEL BLOCKERS

In addition to being used as antianginal and antiarrhythmic agents, calcium channel blockers are used to treat weak and moderate hypertension. These drugs prevent calcium ions from entering into the smooth muscle cells of peripheral vessels, and they cause relaxation of peripheral vessels, which leads to lowering of arterial blood pressure. In clinically used doses, calcium channel blockers relax smooth musculature of arteries and have little effect on veins. In doses that relax smooth musculature, calcium channel blockers have relatively little effect on cardiac contractility.

In antihypertension therapy, the most frequently used drugs are diltiazem (19.3.10), verapamil (19.3.15), and nifedipin (19.3.16), which appear to be equally effective drugs for treating hypertension. Methods of syntheses have already been discussed in Chapter 19.

Diltiazem (19.3.10)**:** The synthesis of this drug is described in Chapter 19.

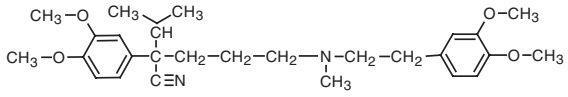


19.3.10

Diltiazem reduces transmembrane influx of calcium ions into cardiac muscle cells and vascular smooth musculature. It causes widening of coronary and peripheral vessels. It increases coronary blood flow, thus, preventing the development of coronary artery spasms. It lowers elevated blood pressure and reduces tachycardia.

It is used for stable and unstable stenocardia (including after myocardial infarctions), and for arterial hypertension.

Verapamil (19.3.15)**:** The synthesis of this drug is described in Chapter 19.

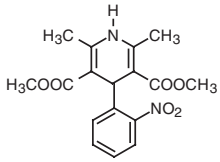


19.3.15

Verapamil possesses antiarrhythmic, antianginal, and hypotensive activity. It reduces the myocardial need for oxygen by reducing contractility of the myocardium and slowing the frequency of cardiac contractions. It causes dilation of coronary arteries and increased coronary blood flow. It reduces tonicity of smooth musculature, peripheral arteries, and overall peripheral vascular resistance. It provides antiarrhythmic action in supraventricular arrhythmia.

Verapamil is used to prevent attacks of stenocardia, arterial hypertension, and to treat and prevent supraventricular arrhythmia.

Nifedipin (19.3.16)***:*** The synthesis of this drug is described in Chapter 19.



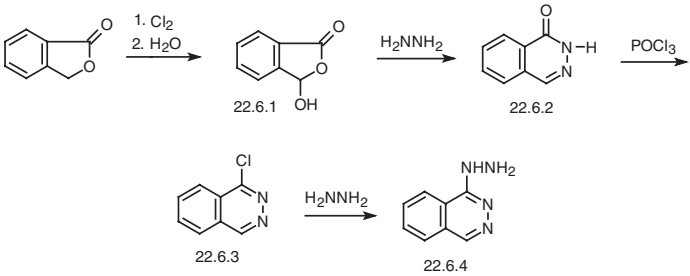
19.3.16

Nifedipin causes relaxation of smooth musculature, dilation of coronary and peripheral arteries, and reduction of peripheral resistance and arterial blood pressure, and enhances oxygen supply to the heart.

22.6 MYOTROPIC HYPOTENSIVE DRUGS

The drugs of this class (hydralazine and sodium nitroprusside) lower arterial blood pressure primarily by direct spasmolytic action on smooth musculature of arterioles, which leads to a reduction of resistance of peripheral vessels by causing dilation. Diastolic pressure is usually lowered more than the systolic pressure.

Hydralazine: Hydralazine, 1-hydrazinonaphthalazine (22.6.4), is synthesized by the oxidative chlorination of phthalide with simultaneous hydrolysis of product, which results in hydroxyphthalide (22.6.1), which upon reaction with hydrazine changes to phthalazone (22.6.2). This undergoes a reaction with phosphorous oxychloride, forming 1-chlorophthalazine (22.6.3), in which substitution of the chlorine atom with hydrazine gives the desired hydralazine (22.6.4) [14–16].



22.6.1 22.6.2 22.6.3 22.6.4

Hydralazine exhibits an antihypertensive effect by directly relaxing smooth muscles of the vessels. It has an effect on arterial vessels while having a minimal effect on venous vessels. As a result, resistance of peripheral vessels decreases, and blood pressure is reduced (diastolic more than systolic).

It does not have a substantial effect on nonvascular smooth musculature or cardiac tissues. Homeostatic circulatory reflexes remain natural, and the resulting hypotension activates cardiovascular reflexes, which are expressed as an increase of heart work, power, and volume of cardiac output. Therefore, it is most effectively used in combination with β-blockers.

By itself, hydralazine is used for hypertension; however, it is not even the drug of choice for weak forms of this condition. Synonyms of this drug are apressin, hypatol, depressan, and others.

Sodium Nitroprusside, $Na_2Fe(CN)_5NO$ (22.6.7)***:*** It is synthesized by successive reactions including the reaction of potassium ferrocyanide with nitric acid, which forms potassium nitroprusside (22.6.5), which is further transformed to copper nitroprusside (22.6.6), and reaction of this with sodium carbonate gives sodium nitroprusside (22.6.7).

$$2K_4Fe(CN)_6 + 4HNO_2 + 2H_2SO_4 \rightarrow K_2Fe(CN)_5NO + 2NO + 2(CN)_2 + 2K_2SO_4 + 4H_2O$$
22.6.5

$$K_2Fe(CN)_5NO + CuSO_4 \rightarrow CuFe(CN)_5NO + K_2SO_4$$
22.6.6

$$CuFe(CN)_5NO + Na_2CO_3 \rightarrow Na_2Fe(CN)_5NO + CuCO_3$$
22.6.7

Sodium nitroprusside is a powerful, instantaneous-acting intravenous drug used to lower blood pressure in hypertensive crises. The hypotensive effect is caused by peripheral vasodilation resulting from a direct effect on both arterial and venous vessels.

Side effects also appear very quickly; however, they last for a very short time because of their extremely short half-life. Sodium nitroprusside is biotransformed to cyanide and thiocyanate, which upon overdose can result in thiocyanate and cyanide intoxication. The presence of drugs such as diazoxide and sodium nitroprusside has significantly decreased the possibility of a sharp drop in arterial blood pressure and urgent situations; which, however, should be used under the constant care of medical personnel. Synonyms of this drug are nipride, nipruton, and others.

22.7 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme inhibitors have turned out to be very effective antihypertensive drugs that have begun to overtake β-adrenoblockers, especially in monotherapy of hypertension.

These drugs inhibit angiotensin-converting enzyme by blocking the hydrolysis of angiotensin I into active angiotensin II, which is an active, endogenic vasopressor substance.

Angiotensin I is a prohormone that is formed as a result of the action of renin on a peptide substrate produced by the liver.

Renin, in turn, is a proteolytic enzyme that is produced by the kidneys, and it controls the physiological functions of other organs.

The secretion of renin itself is controlled by the nervous system, and possibly by a recently discovered cardiac peptide hormone.

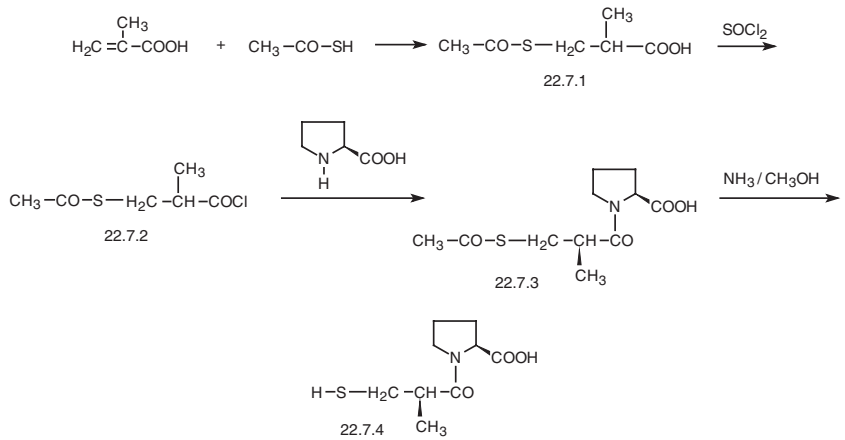
Angiotensin I is relatively inactive and is activated by being turned into angiotensin II by angiotensin-converting enzyme. Membrane receptors of smooth muscle cells of the

arterioles and adrenal cortex (aldecterone secretion) are specifically stimulated by angiotensin II. As a result, peripheral resistance of vessels increases as heart rate increases, cardiac output increases, and water and sodium ion retention takes place. In turn, induced elevation of pressure by reverse binding causes a decrease in renin secretion.

There is a hypothesis that irregularity of the rennin–angiotensin system lies at the base of etiology of all cases of essential hypertension. However, despite all of the apparent attractiveness of this theory, there is still not enough proof for it to be accepted as the single reason of elevated arterial blood pressure.

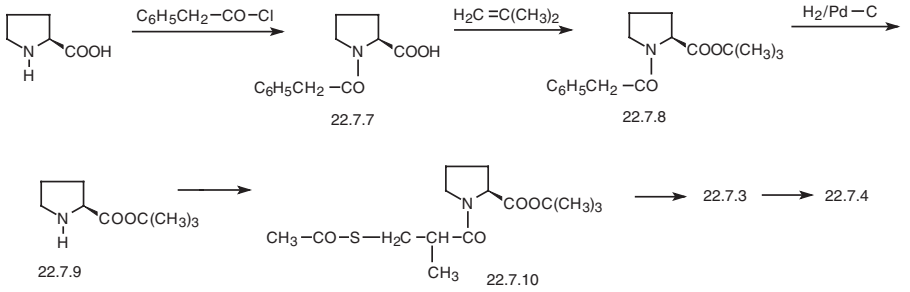
Moreover, whether or not hypertension is caused by an elevated level of renin or other reasons, angiotensin-converting enzyme inhibitors lower both systolic and diastolic arterial pressure in hypertensive patients, and their effects are enhanced by diuretics. Angiotensin-converting drugs of this series (captopril, enalapril) are effective antihypertensive drugs used both independently and in combination with other drugs to treat all types of hypertension as well as to treat cardiac insufficiency.

Captopril: Captopril, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline (22.7.4), is synthesized by direct acylation of L-proline with 3-acetylthio-2-methylpropionic acid chloride (22.7.2), which is synthesized from 3-acetylthio-2-methylpropionic acid (22.7.1), which is in turn synthesized by reacting methacrylic and thioacetic acid. 1-(3-Acetylthio-2-D-methylpropanoyl)-L-proline (22.7.3) is formed by reacting L-proline with 3-acetylthio-2-methylpropionic acid chloride, and it undergoes further ammonolysis with ammonia, to give the desired captopril (22.7.4).



An alternative method differs from the first only in that a previously protected *tert*-butyl ester of L-proline (22.7.6) undergoes acylation using 3-acetylthio-2-methylpropionic acid chloride (22.7.2). This is synthesized by the following scheme. L-proline is acylated by phenylacetyl chloride, giving *N*-benzyloxycarbonyl L-proline (22.7.7), which is reacted with isobutylene in order to obtain *tert*-butyl ester of *N*-benzyloxycarbonyl—L-proline (22.7.8). This is reduced using hydrogen and a palladium-on-carbon catalyst, which gives the L-proline *tert*-butyl ester 22.7.9. After acylation of the resulting 22.7.9 with the acid chloride 22.7.2, *tert*-butyl ester of 1-(3-actylthio-2-methylpropanoyl)-L-proline (22.7.10)

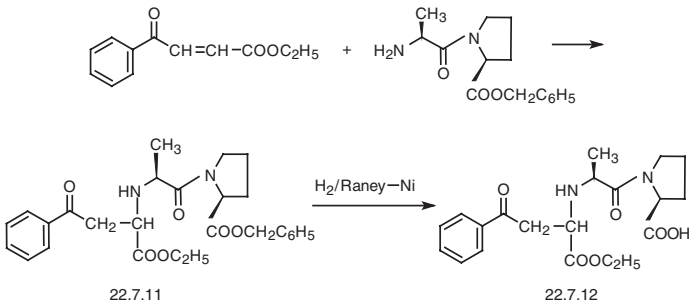
is synthesized, from which the protecting groups are subsequently removed. The ester part of the molecule is hydrolyzed using trifluoroacetic acid, giving 1-(3-acetylthio-2-methylpropanoyl)-L-proline (22.7.3), after separation of diastereomers of which, 1-(3-acetylthio-2-D-methylpropanoyl)-L-proline is isolated, which undergoes ammonolysis analogous to that mentioned earlier, forming captopril (22.7.4) [17–23].



Captopril is the most studied of the angiotensin-converting enzyme inhibitors proposed as an antihypertensive drug. It blocks angiotensin-converting enzyme, which suppresses formation of angiotensin II and relieves its vasoconstricting effect on arterial and venous vessels. Overall vascular peripheral tension is reduced, which results in the lowering of arterial pressure.

It is used for hypertension and chronic cardiac insufficiency. Synonyms of this drug are capoten, capril, and others.

Enalapril: Enalapril, (S)-1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline (22.7.12), is synthesized by reacting the benzyl ester of L-alanyl-L-proline with the ethyl ester of 3-benzoylacrylic acid, which forms the product 22.7.11, the reduction of which with hydrogen using a Raney nickel catalyst removes the protective benzyl group, giving the desired enalapril (22.7.12) [24]. Alternative methods of syntheses have also been proposed [25–29].

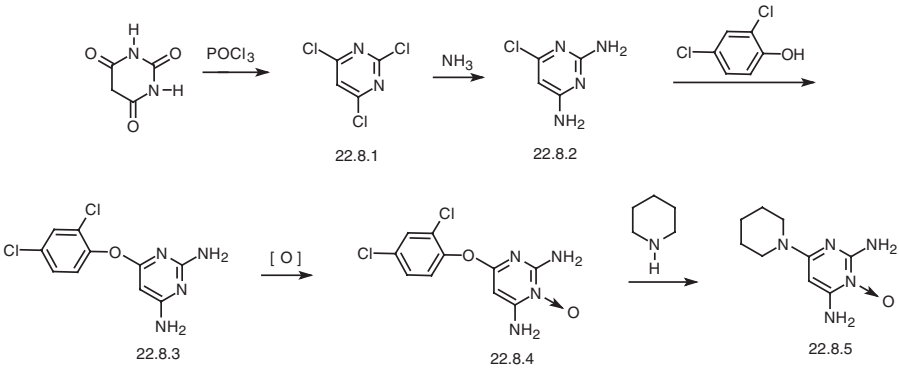


Like captopril, enalapril selectively suppresses the rennin–angiotensin–aldosterone system, inhibits angiotensin-converting enzyme, and prevents conversion of angiotensin I into angiotensin II.

It is used for hypertension and chronic cardiac insufficiency. Synonyms of this drug are vasotec, tenitec, naprilene, and others.

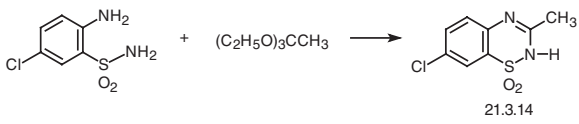
22.8 CALCIUM CHANNEL ACTIVATORS

Minoxidil: Minoxidil, 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine (22.8.5), is synthesized from barbituric acid, the reaction of which with phosphorous oxychloride gives 2,4,6-trichloropyrimidine (22.8.1). Upon reaction with ammonium, this turns into 2,4-diamino-6-chloropyrimidine (22.8.2). Next, the resulting 2,4-diamino-6-chloropyrimidine (22.8.2) undergoes reaction with 2,4-dichlorophenol in the presence of potassium hydroxide, giving 2,4-diamino-6-(2,4-dichlorophenoxy)-pyrimidine (22.8.3). Oxidation of this product with 3-chloroperbenzoic acid gives 2,4-diamino-6-(2,4-dichlorophenoxy)pyrimidine-3-oxide (22.8.4), the 2,4-dichlorophenoxyl group of which is replaced with a piperidine group at high temperature, giving minoxidil (22.8.5) [30–33].



Minoxidil is a peripheral vasodilator that directly relaxes vascular smooth musculature, thus, lowering systolic and diastolic pressure. Its action is linked to the activation of calcium channels. Open calcium channels cause hyperpolarization of smooth muscle cells, which in turn, reduces the flow of calcium ions into the cell, which is necessary for supporting vascular tonicity. However, when taking minoxidil, tachycardia, elevated renin secretion, and water and sodium ion retention all appear simultaneously with hypotension. Because of potentially serious side effects, it is used only for severe hypertension that does not respond to treatment with other drugs, and absolutely in combination with two other antihypertensive drugs. A synonym of this drug is loniten.

Diazoxide: 7-chloro-3-methyl-2-*H*-1,2,4-benzothiadiazin-1,1-dioxide (21.3.14), is synthesized by condensating 2-aminosulfonyl-4-chloroaniline with triethyl orthoacetate [34–36].



Diazoxide is a nondiuretic derivative of thiazides that dramatically reduces blood pressure by direct relaxation of smooth muscles of the arterioles, possibly as a result of calcium

channel activation of smooth musculature in arterioles. It has a weak effect on the venous system and on the heart. In addition to hypotensive action, diazoxide causes a sharp increase in the level of glucose in the blood as a result of the inhibition of insulin release from adrenal glands. Some of the undesirable effects are water and sodium ion retention in the body and increased concentrations of uric acid in the blood. It is used in urgent situations where blood pressure needs to be reduced in severe hypertension. Diazoxide is not used for essential hypertension. A synonym of this drug is hyperstat.

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– 23 –

Drugs for Treating Respiratory System Illnesses

Respiratory system diseases can originate as a result of infection, foreign agents of various natures including dust, chemical substances, and smoking; aging, genetic factors, severe injury, or as a result of a hypersensitive reaction. Therapy of respiratory system illnesses generally consists of restoring appropriate physiological functions. In particular, antibiotics remove infections that have invaded the respiratory tract, glucocorticoids relieve inflammation, bronchodilators (broncholytics) relax smooth musculature of the bronchioles and open blocked air channel regions, and so on.

Asthma has a particular place among pulmonary illnesses—it is a chronic lung condition with clinical syndromes characterized by elevated excitability and contraction of the respiratory tract, and consequently, resulting in shortness of breath, breathing difficulties, and coughing. Patients suffering from asthma can develop signs of chronic bronchitis or pulmonary emphysema.

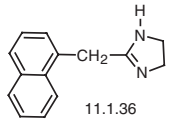
Mainly because the molecular mechanism of these pathological changes has not been sufficiently studied, therapy of asthma, pulmonary illnesses, and other respiratory system illnesses are generally aimed at preventing and relieving symptoms that accompany the disease.

Therefore, drugs for treating respiratory system illnesses can be examined as antiedematous drugs whose vasoconstricting action can be taken in the form of nasal sprays, anticough and expectorant agents, as well as bronchiolytics and other drugs used to treat bronchial asthma, such as methylxanthine, anticholinergic drugs, adrenergic drugs, allergy mediator releasing inhibitors, and corticosteroids.

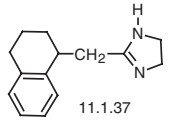
23.1 ANTIEDEMA, VASOCONSTRICTING DRUGS

Vasoconstricting drugs, as a rule α-adrenomimetics, are used as temporarily relieving agents for severe rhinitis of both viral and allergic origin, for sinitus, and for eustachitis. When locally administered in the form of drops or sprays, arterioles of nasal mucous membranes constrict, leading to reduced edema, hyperemia, and exudation. Sympatomimetics with pronounced antiedema action are frequently taken for this purpose, and they include

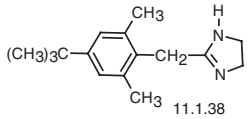
naphazoline (11.1.36), tetrahydrozoline (11.1.37), xylomethazoline (11.1.38), oxymethazoline (11.1.40), and others whose properties and synthesis are described in Chapter 11.



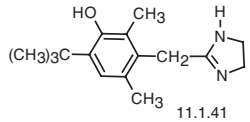
11.1.36



11.1.37



11.1.38



11.1.41

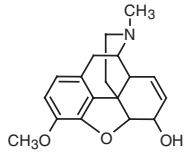
23.2 ANTICOUGH AND EXPECTORANT AGENTS

Respiratory system illness, as a rule, is accompanied by a cough—a protective mechanism by which foreign substances, irritants, and mucous are discharged from the respiratory tract.

Anticough drugs can have an effect at the 'cough center' level in the medulla, as well as an effect on various regions of the tracheobronchial tree. Drugs that exhibit anticough effects are divided into two groups. They are centrally acting drugs—narcotic anticough drugs or opiates such as codeine and hydrocodone, as well as various groups of drugs displaying both central and peripheral effects that suppress coughing, and the so-called nonnarcotic anticough drugs (dextromethorphan, benzonatate).

23.2.1 Narcotic anticough drugs

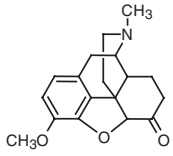
Codeine (3.1.20): Synthesis of this drug is described in Chapter 3.



3.1.20

It suppresses the cough reflex in the cough center of the medulla, and it is used for severe and chronic reflex coughing.

Hydrocodone (3.1.27): Synthesis of this drug is described in Chapter 3.

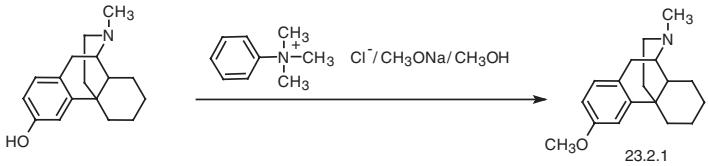


3.1.27

Hydrocodone is a powerful anticough drug that is widely used for suppressing the cough reflex. It is widely used in effective commercial anticough drugs in combination with guaiphenesin (entuss), with homatropine (hycodan), with phenylpropanolamine (hycomine), phenyltoloxamine (tussionex), and pseudoephedrine and guaiphenesin (tussened).

23.2.2 Non-narcotic anticough drugs

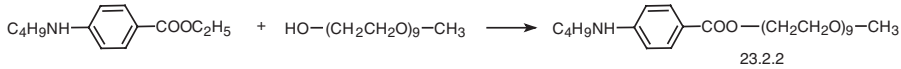
Dextromethorphan: Dextromethorphan, (9α,13α,14α)-3-methoxy-17-methylmorphinane (23.2.1), is synthesized from (±)-3-hydroxy-*N*-methylmorphinane by methylating the phenol hydroxyl group using phenyltrimethylammonium chloride and sodium methoxide in methanol. The resulting racemic product (±)-3-methoxy-*N*-methylmorphinane is separated into isomers using D-tartaric acid, which produces dextromethor-phan [1,2].



23.2.1

This drug possesses a pronounced anticough effect and minimal action on the CNS. It is not addictive. Synonyms of this drug are coffex, robidex, seatuss, and others.

Benzonatate: Benzonatate, *p*-butylaminobenzoate 2,5,8,11,14,17,20,23,26-nonaoctacozan-28-ol (23.2.2), is synthesized by reesterifying the ethyl ester of 4-butylaminobenzoic acid with the monomethyl ether nonaethylenglycol. It is a structural analog of the local anesthetic tetracaine [3,4].



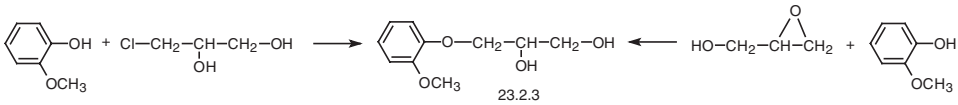
23.2.2

It is believed that it acts by two mechanisms: selective anesthesia of irritated receptors in the lungs and simultaneous suppression of the cough center. Synonyms of this drug are tessalon, ventussin, and others.

23.2.3 Expectorant drugs

For thick, dry secretion of bronchial glands, a cough can be alleviated through: (1) reflexes, by increasing mucous membrane secretion, possibly by increased activity of ciliary epithelium and strengthening bronchial muscle contractions (guaiphenesin, potassium iodide, and terpinhydrate); or (2) by diluting the secretion with mucolytics—drugs that reduce the thickness of phlegm by depolymerization of polysaccharides contained therein. Acetylcysteine is the most used drug for this purpose.

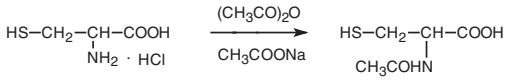
Guaiphenesin: Guaiphenesin, 3-(*o*-methoxyphenoxy)-1,2-propandiol (23.2.3), is synthesized by reacting guiacol with 3-chloropropan-1,2-diol or with glycidol [5–10].



23.2.3

Guaiphenesin facilitates secretion from bronchial mucous membranes, thus relieving a cough in colds, bronchitis, and bronchial asthma. Synonyms of this drug are robitussin, lotussin, and others.

Acetylcysteine: Acetylcysteine, *N*-acetyl-L-cysteine (23.2.4), is synthesized by reacting L-cysteine hydrochloride with acetic anhydride in the presence of sodium acetate [11–13].



23.2.4

Acetylcysteine is a drug taken for a cough in order to reduce thickness of phlegm. Synonyms of this drug are flumucetin, mucomyst, and others.

23.3 BRONCHODILATORS (BRONCHOLYTICS)

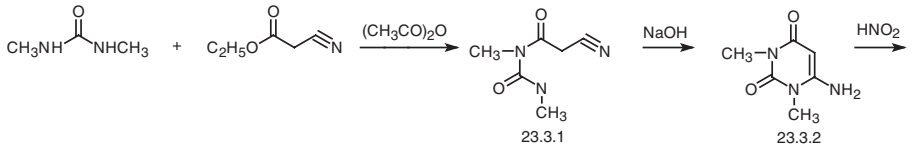
23.3.1 Methylxanthines

Xanthenes belong to a family of compounds containing a purine cyclic system, one of the most important heterocyclic systems found in nature that can be synthesized by combining pyrimidine and imidazole rings.

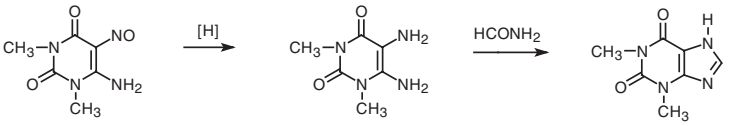
Three of the most important methylxanthenes are theophylline, theobromine, and caffeine. Methylxanthenes exhibit a similar range of biological activity.

The main sources of these compounds are tea, cocoa, and coffee. Theophylline has the highest interest as a broncholytic.

Theophylline: Theophylline, 1,3-dimethylxanthine (23.3.5), is present in small quantities in tea leaves. It is synthesized synthetically by the Traube method, a general method suggested for making purine bases. In the given example, reacting *N*,*N*-dimethylurea with cyanoacetic ether in the presence of acetic anhydride gives cyanoacetylmethylurea (23.3.1), which cyclizes into 6-amino-1,3-dimethyluracil (23.3.2). The resulting compound transforms into 5-nitroso-6-amino-1,3-dimethyluracil (23.3.3) upon reaction with nitric acid. Reduction of the nitroso group gives 5,6-diamino-1,3-dimethyluracil (23.3.4), the subsequent reaction of which with formamide gives the desired theophylline (23.3.5) [14–17].



23.3.1 23.3.2



23.3.3 23.3.4 23.3.5

The mechanism of action of theophylline as a broncholytic is unknown. However, some hypotheses are based on its structural similarity to adenosine and $3^1,5^1$-cyclic adenosinemonophosphate.

Adenosine is an endogenic mediator that, reacting with membrane receptors, can cause bronchial contractions. Theophylline inhibits this reaction, thus preventing substrate–receptor reactions of bronchospasms caused therein.

It is believed that theophylline can inhibit phosphodiesterase, which in turn can lead to elevated levels of cellular cyclic adenosine monophosphate, and subsequently, to the weakening of smooth musculature of the respiratory tract. However, theophylline is not a powerful phosphodiesterase inhibitor, and the necessary concentrations for this cannot be achieved *in vivo*.

On the other hand, theophylline inhibits reverse uptake catecholamine uptake, which can elevate the level of cyclic adenosine monophosphate, thus causing a broncholytic effect. Finally, theophylline is an adenosine receptor blocker, and this may be responsible for its broncholytic effect.

Despite the fact that the last mechanism may be basic for theophylline, a few xanthines, which in general lack the ability to bind with adenosine receptors, express the same, if not more broncholytic activity than theophylline.

Theophylline and other methylxanthines also display a pharmacological effect on a number of other organ systems. Of course the most pronounced effect is relaxation of smooth musculature in the respiratory tract. However, theophylline is a CNS stimulant, and it lowers arterial blood pressure, increases diuresis, displays cardiotonic activity, and has a specific effect on the gastrointestinal tract. The effects listed are the most frequently encountered side effects upon taking theophylline as a broncholytic.

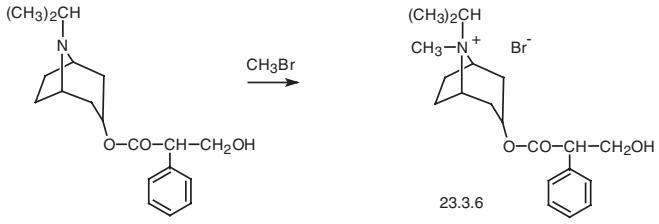
Action on the CNS depends directly on the dose of administered drug, and can be manifested as fatigue, anxiety, tremors, and even convulsions in relatively high doses. Theophylline acts on the cardiovascular system by displaying positive ionotropic and chronotropic effects on the heart, which, can likely be linked to the elevated influx of calcium ions by modulated cyclic adenosine monophosphate and its action on specific cardiac phosphodiesterases. In the gastrointestinal system, methylxanthines simultaneously stimulate secretion of both gastric juice and digestive enzymes.

Theophylline reduces contractile activity of smooth musculature, widens bronchi and blood vessels, reduces pulmonary vascular resistance, stimulates the respiratory center, and increases the frequency and power of cardiac contractions. It is used for bronchial asthma, preventing attacks, and systematic treatment. Theophylline is also used for symptomatic treatment of bronchospastic syndrome of a different etiology (chronic obstructive pulmonary disease, chronic bronchitis, and pulmonary emphysema). A large number of combined drugs are based on theophylline. Synonyms of theophylline are adophyllin, asthmophyllin, theocin, and many others.

23.3.2 Anticholinergic drugs

Cholinergic drugs, in particular atropine (14.1.4) or scopolamine (14.1.6), have been used for centuries to treat obstructive pulmonary diseases. By inhibiting the action of acetylcholine on smooth musculature of the respiratory system, anticholinergic drugs prevent bronchospasms resulting from vagus nerve discharge. However, they have an effect on many tissues and systems, and consequently exhibit a wide range of side effects. Currently, they are rarely used to treat coughs that result from certain irritants. However, a quaternary derivative of atropine, ipratropium bromide, is frequently used for chronic bronchitis, pulmonary emphysema, and asthma.

Ipratropium bromide: Ipratropium bromide, 3α-hydroxy-8-isopropyl-1αH,5αH-tropanium bromide (23.3.6), is synthesized by reacting *N*-isopropylnoratropine with methyl bromide [18–20].



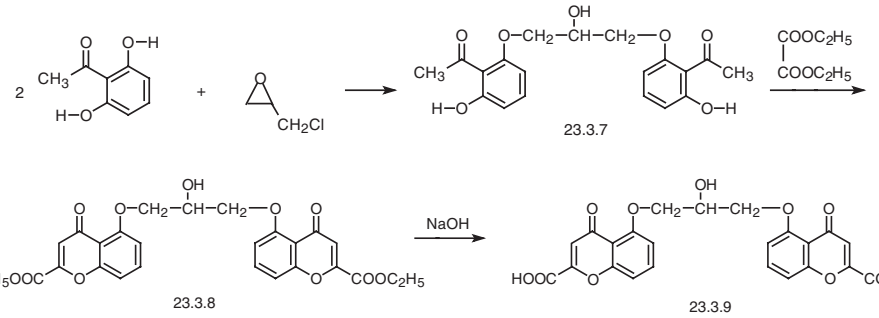
23.3.6

This drug exhibits broncholytic action by reducing cholinergic influence on bronchial musculature (*m*-cholinoblocking action). It relieves bronchial spasms. It is used to treat and prevent minor and moderate bronchial asthma, especially asthma that is accompanied by cardiovascular system diseases. Synonyms of this drug are atrovent, introp, iprafen, and others.

23.3.3 Inhibitors of allergy mediator release

Allergy mediators (histamine, leukotrienes, and others) take part in the formation of bronchospasms. By blocking allergy mediator release in allergic subjects, a few drugs, in particular cromolyn, are a prototype of drugs of this kind, and they block both early and late phases of reactions in the organism in response to exposure to allergens. These drugs do not have bronchodilating properties; however, they inhibit bronchospasms caused by antigens or for other reasons.

Cromolyn: Cromolyn, 5,5′[(2-hydroxytrimethylen)dioxy] *bis* 4-oxo-4*H*-1-benzopiran-2-carboxylic acid (23.3.9), are synthesized by reacting 2,6-dihydroxyacetophenone with epichlorohydrine, during which the chlorine atom in epichlorohydrine is replaced and an opening of the epoxide ring takes place, resulting in a *bis*-product 23.3.7. Cyclization of this product into a *bis*-derivative 23.3.8 is accomplished using diethyloxalate, subsequent alkaline hydrolysis of the ester groups of which gives the desired cromolyn (23.3.9) [21–23].



Cromolyn stabilizes the membranes of mast cells, stopping the release of allergy mediators and suppressing activation of eosinophiles, neutrophilis, thrombocytes, and macrophages, which take part in the formation of bronchospasms.

Cromylyn differs from the majority of medications taken for obstructive diseases of the respiratory tract in that it is used only as a preventative agent.

It is used for bronchial asthma, as well as prevention of seasonal, constant, and physically caused asthma attacks and allergic rhinitis. Synonyms of this drug are intal, opticrom, allergospasmin, lomuren, and many others.

23.3.4 Corticosteroids

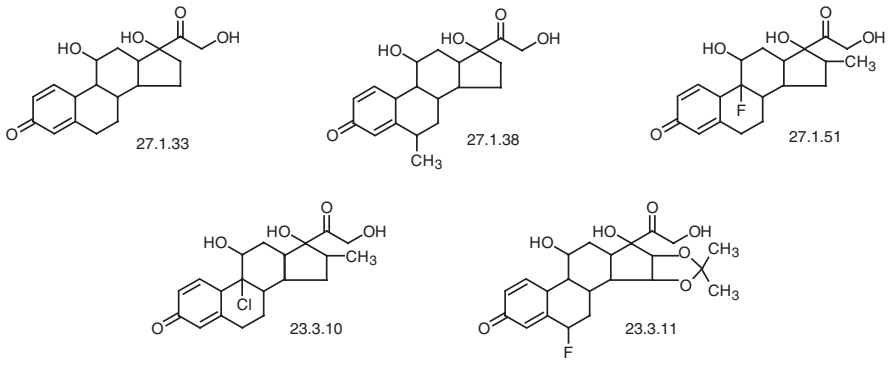
Many corticosteroids are used as inhalation drugs for bronchial asthma.

Corticosteroids are not bronchodilators, and it is reasonable to think that their action is simply relayted to the anti-inflammatory immunodepressive effect of corticosteroids, which is quite positively manifested in the course of relieving bronchial asthma.

They are widely used for obstructive diseases of the respiratory tract; however, they are not used for severe bronchial asthma attacks.

A number of side effects cased by their systematic use limit their use to some degree as drugs for treating bronchial asthma.

In obstructive pulmonary diseases, drugs mainly used are prednizolone (27.1.33), methylprednizolone (27.1.38), dexamethazone (27.1.51), beclomethazone (23.3.10), and flunizolide (23.3.11), the synthesis and detailed description of which will be discussed in Chapter 27.

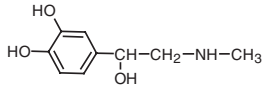


23.3.5 Adrenergic drugs (β_2-receptor agonists, sympathomimetics)

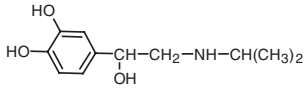
One of the most important uses of sympathomimetics—β_2-adrenoreceptor agonists—is treatment of obstructive respiratory tract diseases. It is highly likely that these drugs act by raising the level of cyclic adenosinemonophosphate, an excess quantity of which is formed as a result of adenylate cyclase activation. The result of β_2-adrenoreceptor agonist action is relaxation of smooth musculature, and in the given case, smooth musculature of the bronchi, and simultaneous inhibition of allergogenic mediator release.

One of the first β-adrenoreceptor agonists used both currently and in the past as a broncholytic is epinephrine or adrenaline, isoproterenol, and especially ephedrine. In treatment and prevention of obstructive respiratory tract diseases, other β-adrenoreceptor agonists also are used, such as isoetharine, terbutaline, albuterol, metaproterenol, and also those described in this section—fenoterol (23.3.16), pirbuterol (23.3.22), and procaterol (23.3.25).

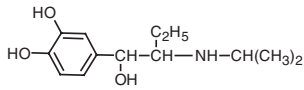
Synthesis and pharmacological properties of the first six drugs mentioned, epinephrine (adrenaline) (11.1.2), isoproterenol (11.1.8), albuterol (11.1.26), terbutaline (11.1.12), metaproterenol (11.1.15), isoetharine (11.1.11), and also ephedrine (11.3.4) are all described in Chapter 11.



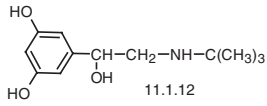
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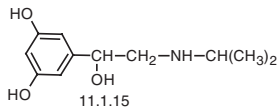
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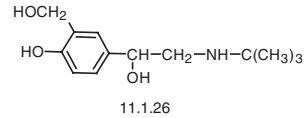
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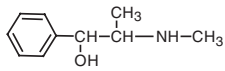
11.1.12



11.1.15

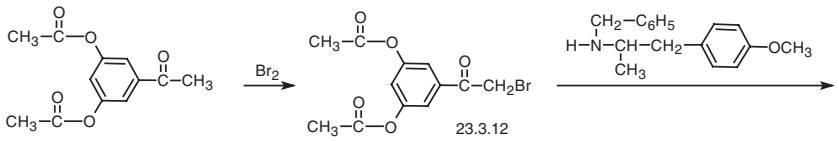


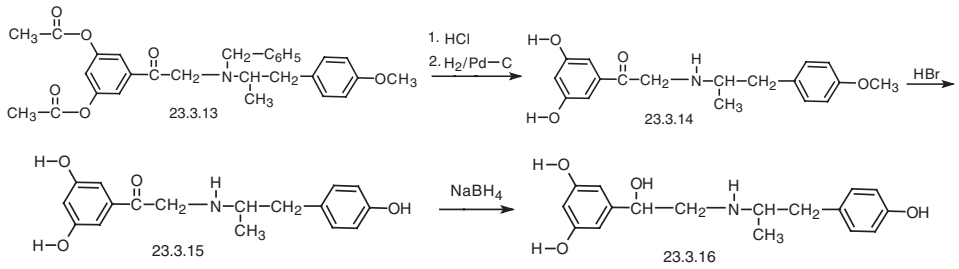
11.1.26



11.3.4

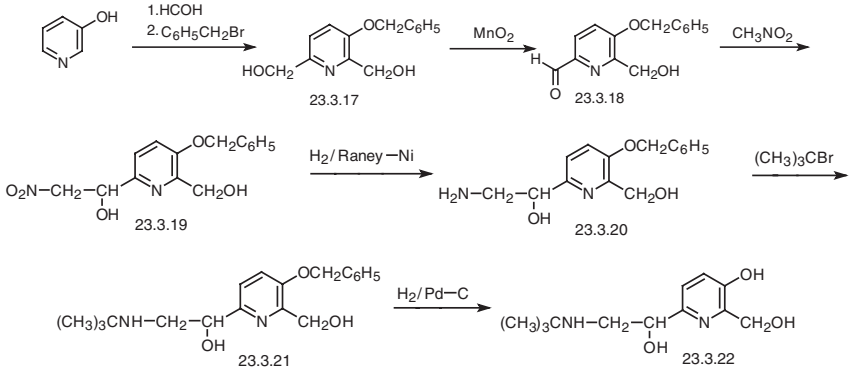
Fenoterol: Fenoterol, 3,5-dihydroxy-α[[(-p-hydroxy-α-methylphenethyl)amino]methyl]-benzyl alcohol (23.3.16), is synthesized from 3,5-diacetoxyacetophenone, which is brominated to give 3,5-diacetoxybromacetophenone (23.3.12). This is reacted with 2-benzylamino-1-(4-methoxyphenyl)-propane, giving the corresponding tertiary amine 23.3.13. Hydrolysis of the acetyl group of this product and removal of the protective benzyl group by hydrogen reduction using a palladium on carbon catalyst gives a secondary amine 23.3.14. This is reacted with hydrobromic acid, which cleaves the ether bond in the benzene ring, producing phenol derivative 23.3.15. Finally, reduction of the carbonyl group with hydrogen gives the desired fenoterol (23.3.16) [24–26].





Fenoterol is a selective stimulant of β_2-adrenoreceptors. It dilates bronchi and blood vessels, has a pronounced tocolytic action, lowers contractile activity and reduces uterus tonicity. It is mainly used in premature births. Synonyms of this drug are berodual, verotec, duovent, and others.

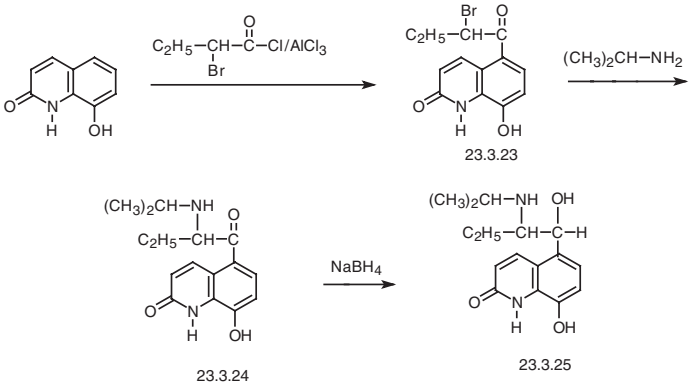
Pirbuterol: Pirbuterol, α(6)–[[[1,1-dimethylethyl]amino]methyl]-3-hydroxy-2,6-pyridindimethanol (23.3.22), is synthesized from 3-hydroxypyridine, which undergoes subsequent hydroxymethylation and further alkylation by benzylchloride at the aromatic hydroxyl group, giving 3-benzyloxy-2,6-*bis*-(hydroxymethyl)pyridine (23.3.17). Selective oxidation of the 6-hydroxymethyl group using manganese peroxide gives 3-benzyloxy-2-hydroxymethylpiperidine-6-aldehyde (23.3.18). Condensation of this with nitromethane gives the corresponding nitromethylcarbinol 23.3.19, the nitro group of which is reduced to an amine group by hydrogen using Raney nickel as a catalyst, which forms an aminoalcohol 23.3.20. Alkylation of the aminogroup with *tert*-butylbromide gives a secondary amine (23.3.21), and removing the protective benzyl group by hydrogen reduction forms pirbuterol (23.3.22) [27–33].



This relatively selective β_2-adrenergic receptor agonist is structurally very similar to albuterol, and it displays similar broncholytic properties. It is used as an inhaled drug for treating bronchial asthma. Synonyms of this drug are exirel and maxair.

Procaterol: Procaterol, 5-[1-hydroxy-2-[(1-methylethyl)amino]butyl]-8-hydroxy-2-(1*H*) quinolone (23.3.25), is synthesized by acylation of 8-hydroxy-2(1*H*)-quinolone with

2-bromobutyric acid chloride at the fifth position of the quinoline system, which gives the compound 23.3.23. This undergoes action of isopropylamine, forming an aminoketone 23.3.24, the carbonyl group of which is reduced by sodium borohydride, giving procaterol (23.3.25) [34–38].



Like pirbuterol, procaterol exhibits similar broncholytic properties as albuteral, but it has somewhat of a more prolonged action. It is recommended for use as an inhaled drug for treating bronchial asthma. Synonyms of this drug are onsukil, masacin, procadil, meptin, and others.

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– 24 –

Anticoagulants, Antiaggregants, Thrombolytics, and Hemostatics

Drugs that inhibit thrombus formation and prevent coagulation or formation of new blood clots are called anticoagulants. Drugs that reduce aggregation of blood thrombocytes are called antiaggregants. Drugs that speed up lysis of already formed blood clots are called thrombolytics or fibrinolytics. Drugs that facilitate reduction and stoppage of bleeding are called hemostatic drugs.

Coagulation and fibrinolytic processes are very important protective physiological mechanisms of the organism, and only a very fine regulatory interaction between them provides the required homeostatic condition of the vascular system. In normal conditions, microscopic blood clots are often necessary for restoration of damaged areas of vessels. During this, the damaged vessel is restored by renewing its endothelial surface, and insoluble clots formed are effectively removed by the fibrinolytic system by way of proteolytic digestion into soluble fragments.

The process of blood clot formation and their subsequent lysis is a very complex feature that depends on a number of substances (coagulation factors—fibrinogen, prothrombin, tromoplastin, calcium, antihemophylin factor, and others) that exist in the plasma, blood cells, and to a lesser degree in other tissues. The process of thrombocyte aggregation and its inhibition is very strictly regulated by a thromboxane–prostacyclin system. Thromboxane A_2 strengthens aggregation, while prostacyclin (prostaglandin I_2) inhibits aggregation. Prostaglandin E_2—collagen of vascular walls, thrombin, adenosine diphosphate, serotonin, and catecholamines are all aggregation stimulants. Prostaglandin E_1, adenosine monophosphate, adenosine, methylxanthines, serotonin antagonists, heparin, and others are aggregation inhibitors.

Disturbances in endogenic control over coagulation and fibrinolytic processes can have severe consequences. On one hand, initiation of unlimited coagulation can lead to thrombosis, and subsequently, to ischemia, stroke, or death. On the other, a malfunction of the coagulation mechanism can lead to hemorrhage. Therefore, depending on the character of the abnormality, which can result in clinical problems of various difficulties, both conditions require correction. Anticoagulants, antiaggregants, thrombolytics, and hemostatics are used for this purpose.

24.1 ANTICOAGULANTS

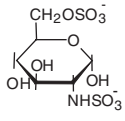
Anticoagulants prevent the development of the coagulation process of blood. Therapy using anticoagulants is first and foremost directed at preventing the formation of clots in blood vessels, which are the main cause of death in thromboembolic diseases. Anticoagulants are subdivided into direct-acting coagulants, i.e. those that have an effect on coagulation factors directly in the blood, and indirect-acting coagulants, i.e. those that have an effect on factors of synthesis or blood coagulation in the liver. On the other hand, anticoagulants are classified as parenteral and oral drugs. Heparin is the only representative of parenteral anticoagulants. Oral coagulants are made up of a number of coumarin derivatives (dicumarol, ethylbiscumacetate, warfarin, phenprocumon, and acenocumarol), and indanone (fenidion, anisindion).

24.1.1 Direct-acting coagulants or parenteral anticoagulants

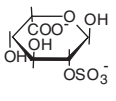
Heparin is one of the first types of direct-acting anticoagulants.

Heparin: Heparin, a natural anticoagulant, is formed in the body. The source of commercial heparin is the mucous membranes of pig intestine and ox lungs [1–5]. Heparin is a mixture of natural sulfated mucopolysaccharides, which are generally found in granules of mast cells. A lot of heparin is found especially in the liver and lungs. Lysosomes of mast cells contain proteases and glycosidases that evidently destroy heparin-proteoglucan that is contained in them, forming various sulfated oligosaccharides, of which heparin is one; it is present in extracellular fluid, and cleansed samples are used in clinics. Heparin is active only upon parenteral introduction. It is frequently used intravenously.

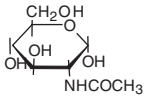
Heparin is a heterogenic mixture of sulfonated polysaccharides made from a repeating units of D-glucosamine, D-glucoronic, and L-iduronic acid. Commercial heparin is essentially a mixture of a number of compounds with various chain lengths and of molecular masses between 5000 and 30,000. Monosaccharides that form heparin are modified by either *N*-acetyl, or *N*- or *O*-sulfate groups, and are joined by glucoside bonds, thus forming polymers like 24.1.6 with different chain lengths. The main monosaccharides that form heparin are 6-sulfate-2-desoxy-2-sulfamino-α-D-glucose (24.1.1), 2-sulfate α-L-iduronic acid (24.1.2), 2-acetamido-2-desoxy α-D-glucose (23.1.3), β-D-glucoronic acid (24.1.4), and α-L-iduronic acid (24.1.5). These sugars are present in commercial heparin in descending order: (24.1.1) > (24.1.2) > (24.1.3) > (24.1.4) > (24.1.5). Because of the presence of sulfonate and carboxyl groups in the molecules, heparin is a strongly acidic compound that is partially neutralized in the body by substituting acidic hydrogen atoms in sulfate groups with sodium ions.



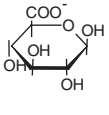
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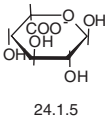
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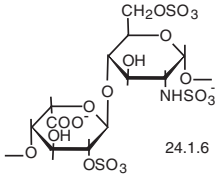
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24.1.4



24.1.5



24.1.6

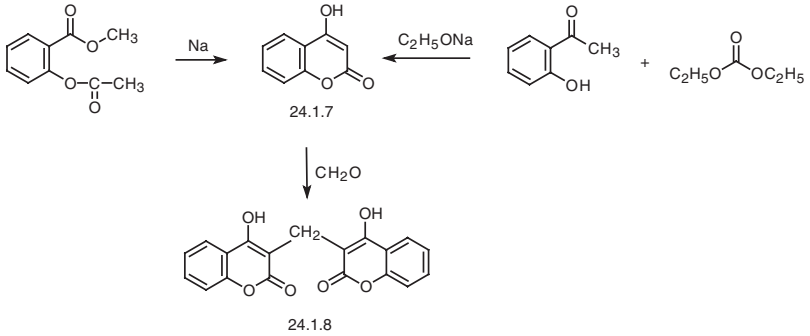
It is believed that heparin acts by neutralizing a number of active blood coagulation factors, thus disrupting the transformation of prothrombin into thrombin. Heparin is used to prevent thrombo-formation in myocardial infarctions, thrombosis, and embolism, for maintaining liquid conditions in the blood in artificial blood circulation and hemodialysis. Synonyms of this drug are arteven, hepalen, leparan, liquemin, panheprin, vetren, and many others.

Heparin antagonist: A heparin antagonist used for heparin overdose is protamin, a mixture of proteins that are isolated from fish sperm. Upon reaction, it inactivates heparin by forming an insoluble complex. Direct-acting coagulants include sodium citrate, which is used for stabilizing blood during its conservation. It is believed that its anticoagulant action consists of binding calcium ions necessary for preventing prothrombin from turning into thrombin.

24.1.2 Direct-acting coagulants, or enteral anticoagulants

The most widely used enteral anticoagulants in medicine are structural derivatives of 4-hydroxycoumarin, a compound that is isolated from sweet clover, and that was a cause of fatal hemorrhagic diathesis in flocks in the 1920s—the so-called 'sweet clover disease.' After discovering that coumarin is able to suppress prothrombin synthesis, intense studies in the area of coumarinic derivative synthesis occurred, and as a result drugs, such as dicoumarol (bishydroxycoumarin), ethyl biscoumacetate, warfarin, phenprocoumon, and acenocumarol were introduced into medicine. Their therapeutic action depends on the ability to suppress formation of a number of functional factors of blood coagulation in the liver. These factors are described as vitamin K-dependent factors since their biosynthesis by hepatocytes is partially linked with hepatic vitamin K metabolism. Oral anticoagulants are effective only *in vivo* because their principal effect is suppression of synthesis of prothrombin, proconvertin, and other blood coagulation factors in the liver. They are sometimes conventionally called vitamin K antagonists.

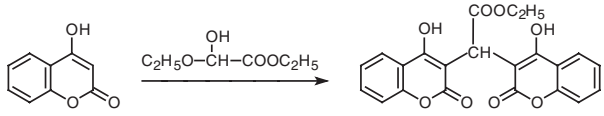
Dicoumarol: Dicoumarol, 3,3′-methylene-bis(4-hydroxycoumarin) (24.1.8), is synthesized from 4-hydroxycoumarine (24.1.7), which is in turn synthesized from salicylic acid methyl ester by cyclization to a chromone derivative using sodium or sodium methoxide; or from *o*-oxyacetophenone by reacting it with diethylcarbonate in the presence of sodium ethoxide. Condensation of the resulting 4-hydroxycoumarin with formaldehyde as a phenol component gives dicoumarol [6–9].



24.1.7 24.1.8

This drug is used for preventing and treating thrombosis, thrombophlebitis, thromboemolium, and for preventing thrombo-formation in post-operational periods. Synonyms of this drug are bishydroxycoumarin, dicumol, cromolyn, and others.

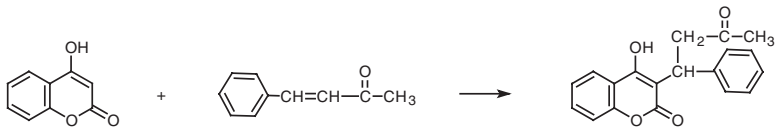
Ethyl biscoumacetate: Ethyl biscoumacetate, the ethyl ester of *bis*-(4-hydroxy-3-coumarinyl)-acetic acid (24.1.9), is synthesized analogously from 4-hydroxycoumarine, but using ethylglyoxylate, its semiacetal or glyoxylic acid instead of formaldehyde [10–13].



24.1.7 24.1.9

This drug is used for the same indications as dicoumarin. Synonyms of this drug are neodicoumarin, ethyldicourmarol, tremexan, dicumacyl, and others.

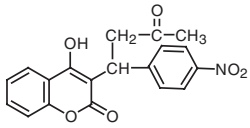
Warfarin: Warfarin, 3-(α-acetonylbenzyl)-4-hydroxycoumarin (24.1.10), is synthesized via Michael reaction by attaching 4-hydroxycoumarin (24.1.7) to benzalacetone in the presence of pyridine [14–19].



24.1.7 24.1.10

Warfarin is used as an anticoagulant for preventing and treating deep venous thromboses and pulmonary embolism. Synonyms of this drug are cumadin, panwarfin, sofrain, warnerin, and others.

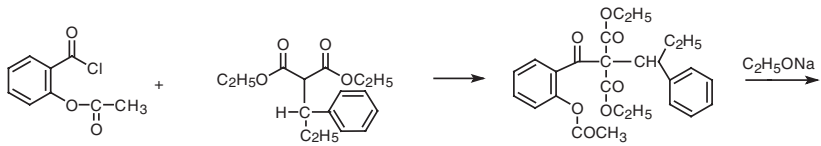
Acenocoumarin: Acenocoumarin, 3-(α-acetonyl-*p*-nitrobenzyl)-4-hydroxycoumarin (24.1.11), is synthesized by a scheme completely analogous to making warfarin, but using *p*-nitrobenzalacetone [20].



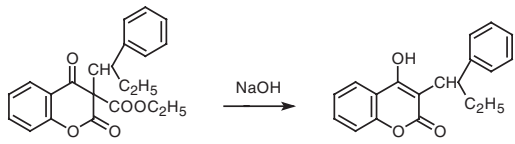
24.1.11

It is used for the same indications for preventing and treating thrombosis and pulmonary embolism. A synonym of this drug is sintrom.

Phenprocoumon: Phenprocoumon, 3-(α-ethylbenzyl)-4-hydroxycoumarin (24.1.14), is synthesized by acylating sodium salts of diethyl ester (1-phenylpropyl)butyric acid with acetylsalicylic acid chloride, which forms the compound 24.1.12, which upon reaction with sodium ethoxide cyclizes to 3-(α-ethylbenzyl)-2-carboethoxy-4-hydroxycoumarin (24.1.13). Alkaline hydrolysis of this product and further decarboxylation gives phenprocoumon (24.1.14) [21–28].



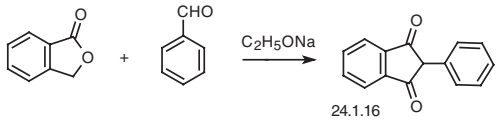
24.1.12



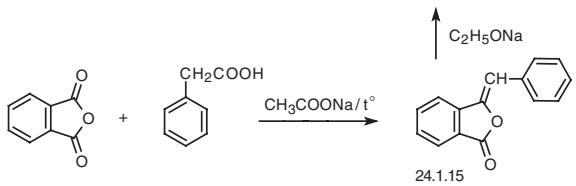
24.1.13 24.1.14

Phenprocoumon is used for the same indications as all of the aforementioned drugs. Synonyms of this drug are marcoumar and liquamar.

***Phenindione*:** Phenindione, 3-phenylindan-1,3-dion (24.1.16), is synthesized in two ways. The first consists of condensating benzaldehyde with phthalide in the presence of sodium ethoxide. Evidently, the resulting phenylmethylenphthalide (24.1.15) rearranges under the reaction conditions to give the desired phenindione (24.1.16). The second method consists of condensation of phenylacetic acid with phthalic anhydride, forming phenylmethylenphthalide (24.1.15), which rearranges further in the presence of sodium ethoxide to phenindione [29].



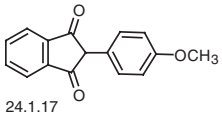
24.1.16



24.1.15

Like coumarin derivatives, phenindione, a compound of the indandione class, acts by altering biosynthesis of coagulant proteins in the liver. It is used for preventing and treating thrombosis, thrombophlebitis, and thromboembolism. However, because of a number of side effects such as polyurea, polydipsia, tachycardia, and others, it is rarely used in practical medicine. Synonyms of this drug are pindone, bindan, gevulin, indan, phenyline, and rectadione.

Anisindione: Anisindione, 3-(*p*-methoxyphenyl)indan-1,3-dion (24.2.11), differs from phenidione only in the presence of a *p*-methoxy group in the phenyl ring, and it is synthesized in the same manner as phenindione, but by using *p*-methoxybenzaldehyde or *p*-methoxyphenylacetic acid [30–32].



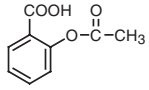
24.1.17

It is used for the same indications as phenindione. Synonyms of this drug are unidone and miradon.

24.2 ANTIAGGREGANTS

Inhibitors of aggregations of blood thrombocytes possess practical importance, and to a large degree are regulated by the thromboxane—prostacyclin system. Thromboxane A_2 enhances aggregation, while prostacycline (prostaglandin I_2) inhibits aggregation of blood thrombocytes. Prostaglandin E_2, collagen of vascular walls, thrombin, adenosindiphosphate, serotonin, and catecholamines are also aggregation stimulants. Prostaglandin E_1, adenosine monophosphate, adenosine, methylanthines, antagonists of serotonin, heparin, and others are also aggregant inhibitors. Nonsteroid anti-inflammatory, fever-reducing analgesics such as aspirin, indomethacin, ibuprofen, and others, which block cyclooxygenase and prevent transformation of arachidonic acid to thromboxane A_2, have gained practical importance in medicine as aggregant inhibitors of blood thrombocytes. Other aggregant inhibitors of blood thrombocytes, such as the coronary vasodilating drugs dipyridamole and ticlopidine, control activation of thrombocytes.

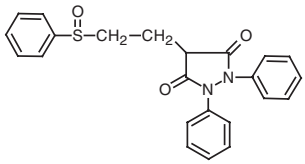
Aspirin (3.2.2)***:*** Synthesis and properties of this drug are described in Chapter 3.



3.2.2

Aspirin is a cyclooxygenase inhibitor that is expressed in the inhibition of synthesis of thromboxane A_2 and prostacyclin (prostaglandin I_2), which are functional antagonists. Synthesis of thromboxane A_2 is suppressed to a large degree when using aspirin in small doses. Using aspirin reduces the risk of myocardial infarction, and increases the survival of patients with myocardial infarction. It lowers the risk of stroke in cases of damaged brain blood circulation.

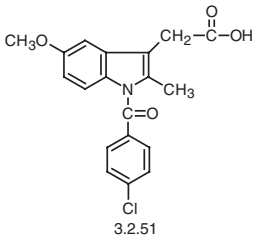
Sulfinpyrazone (3.2.8)***:*** Synthesis of this drug is described in Chapter 3.



3.2.8

Sulfinpyrazone is used in medicine as a nonsteroid anti-inflammatory, fever-reducing analgesic; however, it is believed, that it inhibits cyclooxygenase of thrombocytes. In addition, it is also possible that its action is also linked with the action on membrane of thrombocytes and reduced quantities of secreted adenosine diphosphate and serotonin, which facilitate thrombocyte aggregation. Unlike aspirin, it has no effect on those who do not have irregular aggregation systems.

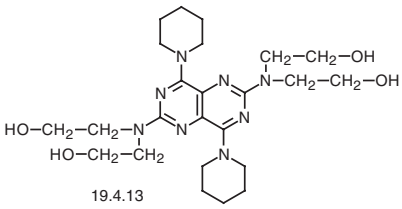
Indomethacin (3.2.51)***:*** Synthesis and properties of indomethacin are described in Chapter 3.



3.2.51

Indomethacin, like aspirin, reversibly inhibits cyclooxygenase action by blocking formation of thromboxane A_2.

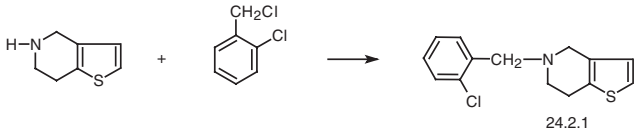
Dipiridamol (19.4.13)***:*** Synthesis of this drug is described in Chapter 19.



19.4.13

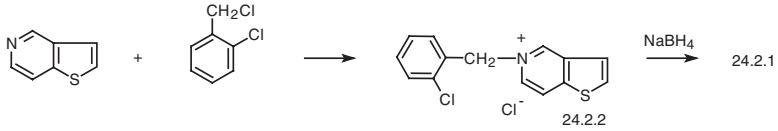
Dipiridamol is known as a coronary vasodilating agent, although it also possesses specific antiaggregant activity. It is used for preventing thrombo-formation after cardiac valve replacement in combination with warfarin. The mechanism of dipiridamol's antiaggregant action is not completely clear, and its efficacy is questionable.

Ticlopidine: Ticlopidine, 5-(*o*-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (24.2.1), is synthesized in many different ways [33–39]. The first way consists of N-alkylation of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine with 2-chlorobenzylchloride.



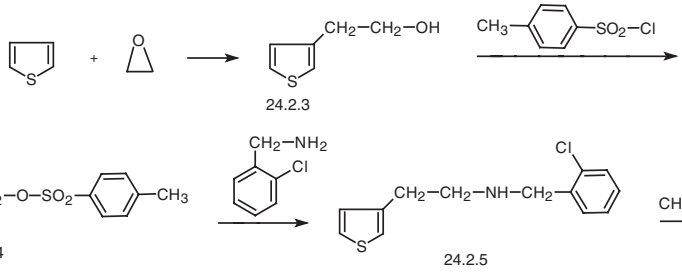
24.2.1

According to the second way, thieno[3,2-c]pyridine undergoes N-alkylation using 2-chlorobenzylchloride, and the resulting pyridinium salt (24.2.2) is further reduced by sodium borohydride to the desired ticlopidine.



24.2.2 24.2.1

Finally, the third way of making this drug consists of alkylating thiophene with ethylene oxide, forming 2-(2′-hydroxy)ethylthiophene (24.2.3), which reacts with *p*-toluenesulfonic acid chloride to give the corresponding tosylate (24.2.4). Substitution of the tosyl group using 2-chlorobenzylamine gives an amine (24.2.5), which under reaction conditions for chloromethylation cyclizes to the desired ticlopidine (24.2.1).



24.2.3 24.2.4 24.2.5 24.2.1

Ticlopidine suppresses aggregation of thrombocytes and possesses antiaggregant activity. It is believed that its action is connected to its effect on thrombocyte membranes and the reduction in quantity of released adenosine diphosphate and serotonin, which facilitate aggregation of thrombocytes. In wide-ranging clinical trials, ticlopidine presented a number of advantages compared to aspirin. Synonyms of this drug are ticlid, anagregal, ticlosan, and others.

24.3 FIBRINOLYTICS (THROMBOLYTICS)

Fibrinolytics are compounds capable of dissolving clots that have already formed. Their primary effect consists of either activation of the physiological system of fibrinolysis, activation of the fibronolytic enzyme plasmin (fibrionlysin), stimulatory lysis and secretion of existing blood clots, or by inflammation of missing fibrinolysin. (Heparin and oral anticoagulants are ineffective in terms of reducing the size of fibrin clots that have already formed.) Plasminogen activators are usually introduced in order to activate the endogenic

fibrinolytic mechanism. The most frequently used drugs are those such as streptokinase and urokinase. It is believed that streptokinase reacts with plasminogen, thus causing a change in the conformation of plasminogen, which results in a breaking of peptide bonds in plasminogen and forming plasmin. It is also believed that unlike streptokinase, urokinase directly breaks down plasminogen to plasmin, which causes breakdown of fibrin and other contents of blood clots. However, there is a certain risk in using these drugs, such as developing bleeding, because of the possible breakdown of fibrinogen and other coagulant factors in the plasma. A primarily new type of fibrinolytics is alteplas, an activator of tissue plasminogen.

Streptokinase: Streptokinase is a protein produced by certain strains of hemolytic group C streptococcus, and it was the first clinically useful fibrinolytic [40–45]. Unlike other plasminogen activators, streptokinase is not an enzyme and cannot break any bonds in a plasminogen molecule by itself. It forms an equimolecular compound with plasminogen, thus forming a streptokinase–plasminogen complex. In the plasminogenic region of the resulting complex, certain conformational changes lead to a break in a few peptide bonds, and transformation of this complex into a streptokinase–plasmin complex, or free plasmin, which also decomposes fibrin. This drug has a half-life in the plasma of 15–30 min, and is used intravenously to treat patients with severe, massive pulmonary embolism and thrombus of the veins; it is also used during myocardial infarctions. Recently, a number of streptokinase derivatives have been proposed, in particular acetylated derivatives, which are developed for use as fibrinolytics. Synonyms of this drug are kabikinase, streptase, and others.

Urokinase: Urokinase is an enzyme that is extracted from human urine or kidney cells [46–55], which directly cleaves specific peptide bonds, in particular the Arg-560–Val-561 bond in the plasminogen molecule, thus transforming it into plasmin. It is used for the same indications as streptokinase. Synonyms of this drug are abbokinase and others.

Alteplase: Alteplase is a drug that activates human tissue plasminogen (t-PA). It is a glycoprotein of molecular mass 68,000 that is synthesized by vascular endothelial cells. t-PA cells were first isolated from cultured human melanoma cells [56–58], but currently a genetically recombined form of rt-PA is genetically engineered.

As a main endogenic promoter of fibrinolysis, t-PA binds with fibrin and, like urokinase, breaks Arg-560–Val-561 peptide bond in the fibrin-binded plasminogen molecule, thus turning it into an active plasmin molecule that breaks apart fibrin clots. Its action is localized in thrombotic regions, and thus the likelihood of systemic fibrinolysis originating during its use is much lower than that which can originate while using streptokinase and urokinase.

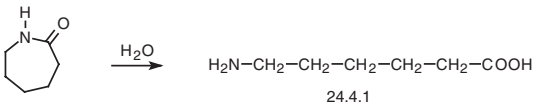
Both forms of t-PA and rt-PA have very short half-lives (about 3 min), and they are quickly removed from the organism, mainly by the liver. Therefore, they are used only by infusion methods. They can be prescribed for patients who cannot use streptokinase (for example, those patients that recently had a streptococcus infection). Synonyms of this drug are activase and others.

24.4 HEMOSTATICS (PROCOAGULANTS)

Hemostatics are drugs used to stop local bleeding, acting to arrest the flow of blood. Absorbable hemostatics arrest bleeding either by the formation of an artificial clot or by providing a mechanical matrix that facilitates clotting when applied directly to the bleeding surface. These agents function more at the capillary level and are not effective at stemming arterial or venous bleeding under any significant intravascular pressure. Sometimes after trauma, surgical interventions, uterine bleeding, cirrhosis of the liver, fibrinolytic overdose, and other reasons, activity of the fibrinolysis system in the organism can be elevated high enough to cause bleeding. Hemostatics, currently used in medicine, act either by replacing the debt of coagulation factors (antihemophylic factor), which are synthesized from human plasma, or by raising the concentration of endogenic coagulation factors in the plasma (desmopressin), or by inhibiting the natural mechanism of fibrinolysis (aminocapronic acid, tranexamic acid).

24.4.1 Systemic hemostatics

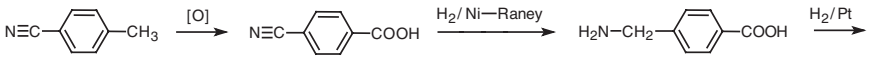
Aminocaproic acid: Aminocaproic acid (24.4.1) is synthesized by hydrolyzing ε-caprolactam at high temperature [56–62].



24.4.1

Because binding of plasminogen or plasmin to fibrinogen or fibrin is mediated by lysine groups that are part of the structures of fibrin and fibrinogen, aminocaproic acid, which is a structural analog of lysine that only differs in that it has one less amino group, acts as a competitive inhibitor for binding of plasmin(ogen) to fibrin. Aminocaproic acid shifts the homeostatic balance on the side of coagulation, thus restoring fibrinolytic mechanism activity. Aminocaproic acid, which is not a procoagulant, such as those used during surgical intervention and various pathological conditions, is accompanied by an elevation in fibrinolytic activity of blood and tissue. It is used to stop bleeding. Synonyms of this drug are afibrin, capracid, epsilamine, coflamin, and others.

Tranexamic acid*:* Tranexamic acid, *trans*-4-(aminomethyl)cyclohexane carboxylic acid (24.4.5), is synthesized from 4-methylbenzonitrile. Oxidation of the methyl group gives the mononitrile of terephthalic acid 24.4.2. The cyano group in this compound is reduced by hydrogen using Raney nickel as a catalyst. The benzene ring of the resulting 4-aminomethylbenzoic acid (24.4.3) is reduced to a cyclohexane moiety by hydrogen and a platinum catalyst, which forms an isomeric mixture of 4-aminomethylcyclohexane carboxylic acids (24.4.4), and the desired *trans*-isomer 24.4.5 is isolated by crystallization of the mixture of its sodium salts [63–68].



24.4.2 24.4.3

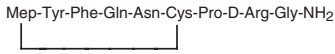


24.4.4 24.4.5

Tranexamic acid can also be viewed as a structural analog of lysine. It is presumed that it works by the same mechanism as aminocaproic acid; however, it is 6–10 times more active. It inhibits action of a plasmin and plasminogen inhibitor, and has a hemostatic effect. It is used for bleeding or risk of bleeding upon increased fibrinolysis (malignant neoplasms, post-operational bleeding, gastrointestinal bleeding, hematuria, and so on). Synonyms of this drug are ugurol, cyclocapron, amcacid, tranex, and others.

Antihemophilic factor: Antihemophilic factor is a protein that converts prothrombin to thrombin, and replaces a deficit of endogenic hemophilic factor. It is synthesized by processing human plasma [69–70]. It is used to treat classic hemophilia A and to stop bleeding. Synonyms of this drug are hemophil T, monoclate, cryoblin, and others.

Desmopressin: Desmopressin, 8-D-arginine vasopressin-1-(3-mercaptopropionic acid) (24.4.6), is a structural analog of vasopressin. It is synthesized by a multi-step synthesis by methods specific to peptide chemistry, and its synthesis will not be examined here [71–74].



24.4.6

Along with the primary use of this drug as an antidiuretic for treating diabetes, it is used to treat classic hemophilia A. A synonym of this drug is DDAVP.

24.4.2 Local procoagulants

Thrombin: In order to stop local bleeding, thrombin, a natural thrombin drug that catalyzes the transformation of fibrinogen to fibrin, is frequently used. Thrombin is synthesized from cow plasma [75–77], and it is used to stop bleeding from open vessels when it is not possible to use other methods. It is used to stop light bleeding. Synonyms of this drug are thrombin, thrombostat, and others.

Gelatine absorbable: Absorbable gelatine is used in the form of a sterile film, sponge, or powder for external use. Its use is very limited, yet it sometimes is used orally for gastric bleeding. Synonyms of this drug are gelfoam, gelfilm, and others.

Microfibrillar collagen hemostat: Microfibrillar collagen hemostat is synthesized from cow collagen. It is used for surgical intervention as an adjuvant drug for bleeding when other procedures are ineffective and impractical. A synonym of this drug is avitene.

Oxidized cellulose: Oxidized cellulose is a surgical gauze treated with nitrogen dioxide. Upon contact with tissue fluids, it forms artificial clots, which support mechanical hemostasis.

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– 25 –

Thyroid Hormone and Antithyroid Drugs

Endogenous iodine-containing thyroid hormones L-thyroxine and L-triiodothyronine are produced by the thyroid gland, which exhibits pronounced metabolic control over practically every cell in the body using the two mentioned iodine-containing hormones. By controlling the rate of oxidative cellular processes, these hormones take part in regulation of growth and development of the organism, formation of bone marrow and bone tissue; they affect activity of the CNS, cardiovascular system, gastrointestinal tract, metabolism of carbohydrates, fats, and proteins; they have an effect on regulation of body temperature, muscle activity, water–electrolyte balance, and reproduction, playing an extremely important role in normal physical and mental development. Unlike many other hormones, they exhibit a diffusive effect on the whole organism, not on individual organs.

Synthesis, storage, and release of thyroid hormones by the thyroid gland are primarily regulated by the thyrotropin hormone, while the iodides necessary for their synthesis are usually present in consumed foods.

Diseases associated with thyroid glands are the result of either excess production of thyroid hormone (hyperthyroidism), or its insufficiency (hypothyroidism). Both cases can result in a goiter.

Thyroid hormones are used clinically primarily to treat hypothyroidism.

This disease is characterized by a decrease or lack of endogenic thyroid hormone secretion. When originating in childhood, it can be clinically described as cretinism (infantile hypothyroidism), and in adults as myxedema (adult hypothyroidism), which is expressed in a loss of mental or physical ability to work, suppression of metabolic processes in the body, and edema. Since thyroid function cannot be restored, the clinical effect is only visible when using thyroid hormones. Using thyroid hormones in hypothyroidism is a replacement therapy that does not correct the disease itself.

Currently, a very small number of various drugs such as drugs of animal thyroid glands and synthetic drugs are used to treat hypothyroidism. They are: thyroidin-dried thyroid, which is made from cow, sheep, and pig thyroid glands; thyroglobulin (proloid), a purified extract of pig thyroid glands; synthetic drugs levothyroxine and lyothyronin, and also lotrix, a mixture of synthetic levothyroxine and lyothyronin in a 4:1 ratio.

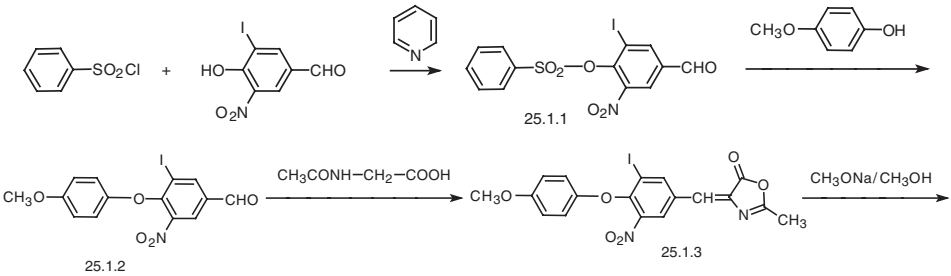
In a hyperfunctioning of the thyroid gland, secretion of an excess quantity of thyroid hormones leads to a hyperthyroid condition (Basedow's disease, goiter). In this condition, drugs are used that suppress production of thyrotropic hormones in the anterior lobe of the hypophysis (diiodotyrosine), in the thyroid gland (propylthiouracil, methylthiouracil,

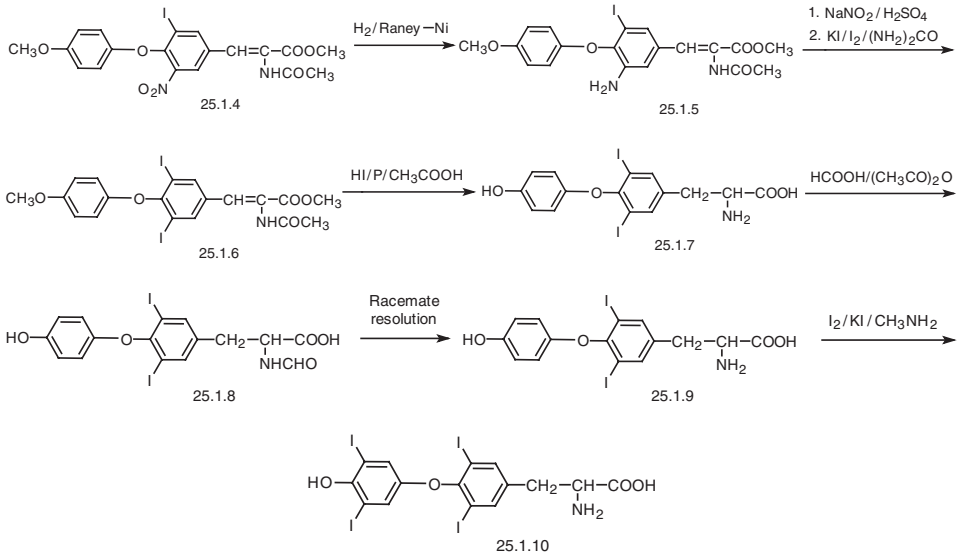
methimazole, and carbimazole), as well as drugs that destroy thyroid gland follicles (radioactive iodine).

25.1 DRUGS FOR TREATING HYPOTHYROIDISM

Hypothyroidism (myxedema) results when there is a breakdown of thyroid hormone production in the thyroid gland. Treatment consists of replacing this hormone with aforementioned drugs. Treatment with levothyroxine, 3,5,3′,5′-tetraiodothyronine, is preferred. Lyothyronin, L-3,5,5′-triiodothyronine, is also used, as is lotrix, a mixture of levothyroxine and levothyronine in a 4:1 ratio. Of the drugs of animal origin, thyroidin and thyroglobulin (proloid) are used.

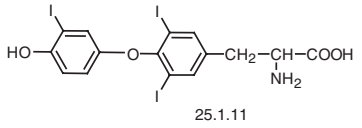
Levothyroxine: Levothyroxine, L-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl] alanine (25.1.10), is synthesized in a multi-stage synthesis from 4-hydroxy-3-iodo-5-nitrobenzaldehyde. Reacting this with benzenesulfochloride in pyridine gives the corresponding benzenesulfonate 25.1.1, the benzenesulfonyl group of which is easily replaced with a 4-methoxyphenyloxy- group upon reaction with 4-methoxyphenol. The resulting 3-iodo-4-(4-methoxyphenoxy)benzaldehyde (25.1.2) is reacted further with *N*-acetylglycine in the presence of sodium acetate in a Knoevenagel reaction, in which the resulting ylidene compound cyclizes to an oxazolone derivative 25.1.3. The oxazolone ring of this compound is opened upon reaction with sodium methoxide, forming the desired cinnamic acid derivative 25.1.4. The nitro group of this product is reduced to an amino group by hydrogen in the presence of a Raney nickel catalyst, forming the corresponding amine, and subsequent diazotation and replacement of the diazo group of which with iodine gives the methyl ester of α-acetamido-3,5-diiodo-4-(4-methoxyphenoxy)crotonic acid (25.1.6). The resulting compound undergoes simultaneous reaction with hydrogen iodide and phosphorous in acetic acid, in which the double bond in the crotonic acid is reduced, and the methoxy protection is removed from the phenol ring. During this, a simultaneous hydrolysis of the acetyl group on the nitrogen atom also takes place, forming D,L-3,5-diiodothyronine (25.1.7). The amino group in this product is once again protected by the reaction with formic acid in the presence of acetic anhydride, which gives D,L-*N*-formyl-3,5-diiodothyronine. Separation of isomers in the resulting racemic mixture is accomplished using brucine, giving D-(−)-*N*-formyl-3,5-diiodothyronine L-(+)-*N*-formyl-3,5-diiodothyronine (25.1.8). The protecting formyl group is hydrolyzed using hydrobromic acid, giving L-(+)-3,5-diiodothyronine (25.1.9), which undergoes direct iodination using iodine in the presence of potassium iodide in aqueous methylamine, to give the desired levothyroxine [1–4].





Effects of this drug depend heavily on dosage. In small doses, levothyroxine exhibits anabolic action. In medium doses, it stimulates growth and development of tissue, metabolism of protein, fats, and carbohydrates, increases functional activity of central nervous and cardiovascular systems, as well as kidneys and liver. In large doses, it slows the thyrotropic activity of the hypophysis and suppresses thyroid gland production. Levothyroxine is used for hypothyroidism, myxedema, thyrotoxicosis, erythyroid conditions, and cretinism. Synonyms of this drug are eltroxin, levoid, noroxin, syntroid, and others.

Levothyronine: Levothyronine, L-3-[4-(4-hydroxy-3-iodophenoxy)-3,5-diiodophenyl]alanine (25.1.11), is synthesized in the exact same manner using one equivalent of iodine during iodination of L-(+)-3,5-diiodothyronine (25.1.9) [5–9].



Levothyronine has properties of levothyroxine; however, it acts faster and binds less with blood proteins. Indications for using levothyronine are the same as with levothyroxine – hypothyroidism, euthyroid goiters, thyroiditis; however, its use is considered more appropriate in the first stage of treatment. Synonyms of this drug are tibon, cinomel, tertroxin, and others.

25.2 DRUGS FOR TREATING HYPERTHYROIDISM

Hyperthyroidism results from excess production of thyroid hormones due to various reasons. Treatment of the resulting thyrotoxicosis (Basedow's disease) consists of using

drugs that inhibit excess synthesis of hormones, as well as using radioactive iodide in order to disrupt or remove thyroid gland follicles with excess activity.

Drugs used for hyperthyroidism can be classified as drugs that suppress thyroid hormone synthesis in the anterior lobe of the hypophysis, and they consist of diiodotyrosine and iodine, as well as drugs that suppress thyroid hormone synthesis in thyroid glands (propylthiouracil, methylthiouracil, methimazole, and carbimazole).

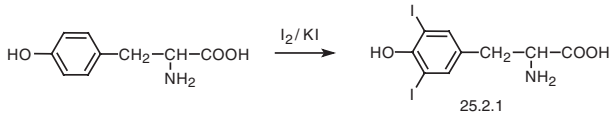
The most useful drugs used for this purpose are classified as thioamides. They are chemically similar and contain thiourea-like thioamide functional groups. The most preferred are propylthiouracil and methimazole, although methylthiouracil and carbimazole are widely used.

Thioamides are reducing agents. They inhibit thyroid hormone synthesis by inhibiting the peroxidase enzymatic system, which catalyzes oxidation of iodide ions and iodine that are consumed in food, which is necessary for iodination of tyrosine derivatives. Thus they reduce the concentration of free iodine necessary to react with tyrosine derivatives, and they can also block oxidative addition reactions of mono- and diiodtyrosines, which form L-thyroxine and L-triiodothyronin.

Drugs that inhibit absorption of iodine by the thyroid gland are sometimes used to treat thyrotoxicosis, in particular potassium chlorate.

In some cases it is recommended to take radioactive iodine drugs such as iodotop (NaI^{131}). It accumulates in the thyroid gland along with L-thyroxine and L-triiodothyronin, where radioactive decay takes place—weak β-radiation destroys thyroid gland follicle cells, which leads to a gradual decline in thyroid hormone secretion.

Diiodotyrosine: Diiodotyrosine, 3,5-diiodotyrosine (25.2.1), is synthesized by directly iodinating tyrosine with iodine in the presence of sodium iodide in aqueous ethylamine, or in a mixture of acetic and hydrochloric acids with the addition of hydrogen peroxide [10–12].

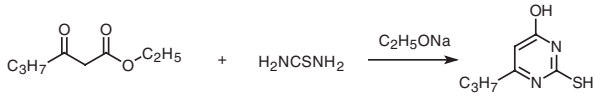


25.2.1

Diiodotyrosine does not possess pronounced hormonal activity. However, it stops production of thyrotropic hormone by the anterior lobe of the hypophysis, which activates thyroid gland activity.

It is used for hyperthyroid forms of endemic and sporadic goiters, diffuse, toxic goiters, and other illnesses accompanied by thyrotoxicity. Synonyms of this drug are ditirin, iodoglobin, and others.

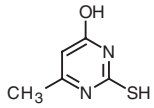
Propylthiouracil: Propylthiouracil, 6-propyl-2-thio-2,4-(1H,3H)-pyrimidindione (25.2.2), is synthesized by condensating ethyl butyroacetate with thiourea in the presence of sodium ethoxide [13].



25.2.2

This drug has a pronounced thyrostatic effect and causes reduced thyroxine synthesis in the thyroid gland. It inhibits the process of iodination of thyroglobulin, reduces formation of the active form of iodine in the thyroid gland, and blocks the peroxidase system. Propylthiouracil is used for hyperthyrosis, thyrotoxic crises, and on thyrodectomia. Synonyms of this drug are propycil and tireostat.

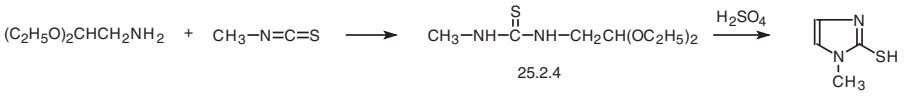
Methylthiouracil: Methylthiouracil, 6-methyl-2-thio-2,4-(1H,3H)-pyrimidindione (25.2.3), is synthesized in a completely analogous manner by condensing ethyl acetoacetate with thiourea in the presence of sodium ethoxide [14].



25.2.3

Methylthiouracil is used for the same indications as propylthiouracil. Synonyms of this drug are murcain and thiocyl.

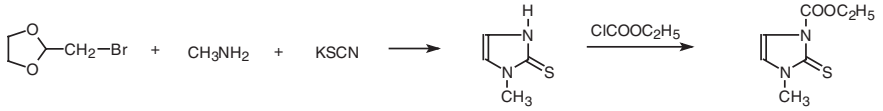
Methimazole: Methimazole, 1-methyl-2-imidazolthiol (25.2.5), is synthesized by reacting aminoacetic aldehyde diethylacetal with methylisothiocyanate and subsequent hydrolysis of the acetal group of the resulting disubstituted urea derivative 25.2.4 by a solution of sulfuric acid, during which a simultaneous cyclization reaction takes place, forming the imidazole ring of the desired methimazole [15,16].



25.2.4

Methimazole also directly disrupts thyroxine and triiodothyronin sysnthesis in the thyroid gland, and it is used for the same indications as propylthiouracil and methylthiouracil to treat hyperfunctioning thyroid glands in patients with Basedow's disease. Synonyms of this drug are merazolil, thiamazole, metothyrin, timidazol, and others.

Carbimazole: Carbimazole, the ethyl ester of 3-methyl-2-thioimidazolin-1-carboxylic acid (25.2.7), is synthesized by a simultaneous reaction of ethylenacetal of bromoacetaldehyde with methylamine and potassium isocyanate, forming 3-methyl-2-imidazolthione (25.2.6), which is further acylated at the nitrogen atom by ethyl chloroformiate, giving the desired product (25.2.7) [17–19].



25.2.6 25.2.7

Indications for using carbimazole are the same as those of the aforementioned drugs. Synonyms of this drug are carbotiroid and neomercazole.

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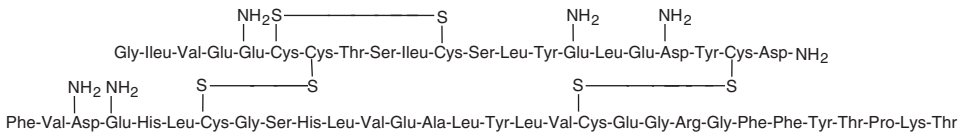
– 26 –

Insulin and Synthetic Hypoglycemic Agents

Drugs used for lowering the glucose level in the blood are called hypoglycemic agents. Likewise, substances that raise the level of glucose in the blood are called hyperglycemic agents. Changes in the level of glucose in the blood can be caused by various reasons, the primary cause being diabetes mellitus. Diabetes mellitus is a metabolic disease associated with a high level of blood sugar and as a rule, disturbance of carbohydrate, lipid, and protein metabolism. The most common biochemical condition in diabetes mellitus is ketoacidosis. Insulin and other hypoglycemic agents are used to treat diabetes mellitus. Depending on the condition of the organism, diabetes is classified into two types. Insulin-dependant (type I), in which there is suppression of endogenous insulin production by the organism itself, and insulin-independent (type II), which results either because of insufficient insulin production, or because of a breakdown of insulin receptors, which is usually a result of other problems in the organism, in particular, obesity.

26.1 INSULIN

Insulin, a pancreatic hormone, is a specific antidiabetic agent, especially for type I diabetes. Human insulin is a double-chain protein with molecular mass around 6000 that contains 51 amino acids (chain A—21 amino acids, chain B—30 amino acids), which are bound together by disulfide bridges.



Pig insulin differs from human insulin only in that it has a different amino acid at position 30, and bovine insulin has different amino acids at positions 8, 10, and 30. Insulin was discovered in 1921. It was isolated from pancreatic tissue of mammals [1–9]. Currently, human and some animal insulins (pigs and large oxen) can be synthesized [10–12], and there "are methods for" making it by genetic engineering [13–16]. Rather than relying on insulin extracted from animal sources, genetic technology has permitted the production of large quantities of essentially human insulin by bacterial cells.

In the body, insulin is synthesized by β-cells of Langerhans islets in the pancreas. The rate of formation changes depending on the type of food consumed, gastrointestinal hormones, and neuronal control. Insulin circulating in the body has a biological half-life of about 5 min. It is quickly broken down by enzymes and is removed from the blood by the liver or kidneys.

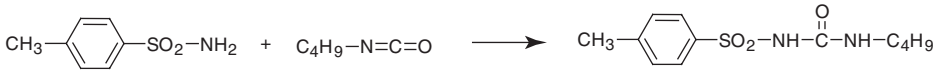
The mechanism of the hypoglycemic action of insulin is not completely understood. However, it has been proposed that insulin acts by binding with specific receptors on the surface of the insulin-sensitive tissues such as skeletal muscle, cardiac muscle, fatty tissue, and leukocytes. Insulin lowers the sugar content in the blood by turning glucose into glycogen. Using insulin in diabetes mellitus leads to lower levels of sugar in the blood, and a build up of glycogen in tissues. Lowering glucose in the blood stops glycosuria, thus lowering elevated diuresis and thirst, normalizing carbohydrate, protein, and fat volume, and reducing diabetic comas. Insulin is effective in insulin-requiring diabetes mellitus. Because insulin is degraded by digestive enzymes, the method of introduction is rarely parenteral. Usually it is hypodermic, and less often intravenous or intramuscular. There are prolonged-action insulin drugs, which are slowly absorbed from the introduction site. Insulin drugs lower the level of blood glucose. Insulin is used in insulin-dependent and non-insulin diabetes mellitus.

26.2 SYNTHETIC HYPOGLYCEMIC DRUGS

For patients with type II diabetes, in which endogenic secretion of insulin functions to some degree, a number of very effective hypoglycemic drugs are prescribed. Six of the most widely used drugs today are subdivided into two groups. First generation drugs—derivatives of sulfonylurea were the most popular in the early 1980s, and include tolbutamide, acetohexamide, tolazamide, and chlorpropamide. Second generation drugs—derivatives of guanidine, such as glyburide and glipizide, entered medical practice after 1984. All of these drugs have very similar chemical structures and mechanism of action, and they differ in the structure of their side chains, and accordingly, activity and pharmacokinetic characteristics.

It is believed that the sulfonylamide action consists of elevated insulin secretion. It is also presumed that the hypoglycemic effect of these drugs is also associated with the suppression of release of glucagon, a hormone produced by α-cells of Langerhans islets in pancreas, and which is a polypeptide made up of 29 amino acid residues. The effect of glucagon on carbohydrate volume is evident by hyperglycemia, which is associated with increased glycogenogenesis (synthesis of glucose from non-carbohydrate precursors) in the liver. An important ability of all of the examined drugs is the possibility of peroral introduction. Many of the medicinal drugs used in various diseases are antagonists of oral hypoglycemic drugs (corticosteroids, thyroid hormones, thiazide diuretics, furosemide, and oral contraceptives). At the same time phenyllantazone, clofibrate, dicumarol and salicyclates are potentiating the action of hypoglycemic drugs.

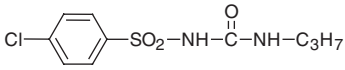
Tolbutamide: Tolbutamide, 1-butyl-3-*p*-toluenesulfonylurea (26.2.2), is made in a single step reaction by interaction of *p*-toluenesulfonylamide (in the form of sodium salt) with butylisocyanate [17–20].



26.2.2

Tolbutamide is one of the most widely used antidiabetic agents. Its action is preferably connected with stimulatory action of β-cells in the pancreas, which results in intensive insulin secretion. It is used for type II diabetes mellitus of medium severity with no expressed microvascular complications. Synonyms of this drug are mebenol, oramid, orabet, tolbuton, butamide, rastinon, and others.

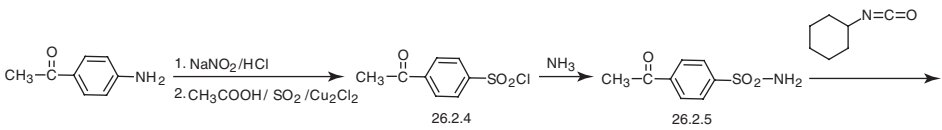
Chlorpropamide: Chlorpropamide, 1-(*p*-chlorophenylsulfonyl)-3-propylurea (26.2.3), is made in a completely analogous manner by reacting *p*-chlorobenzenesulfonylamide with propylisocyanate [21–26].



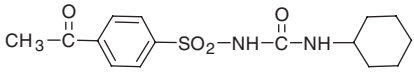
26.2.3

Indications for use and the mechanism of action are also similar to those of all of the examined compounds, i.e. stimulation of insulin secretion in the presence of functional pancreas tissue. It is used to treat non-insulin requiring, stable diabetes mellitus. Synonyms of this drug are diabinis, chloronas, and others.

Acetohexamide: Acetohexamide, 1-(*p*-acetyl phenylsulfonyl)-3-cyclohexylurea (26.2.6), is made in an analogous scheme by reacting *p*-chlorobenzenesulfonylamide with cyclohexylisocyanate. The necessary *p*-acetylbenzenesulfonylamide is made by diazotating of p-aminoacetophenone in the presence of sulfur dioxide and copper(II) chloride, forming the sulfonylchloride 26.2.4, which is reacted further with ammonia to give the sulfonamide (26.2.5). Reacting this with cyclohexylisocyanate gives acetohexamide (26.2.6) [27–31].



26.2.4 26.2.5

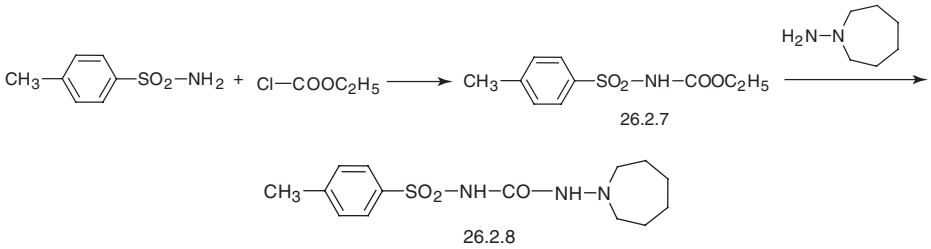


26.2.6

Indications for use and the mechanism of action of acetohexamide are analogous to those of the examined groups of compounds. Synonyms of this drug are cyclamide, agliral, and others.

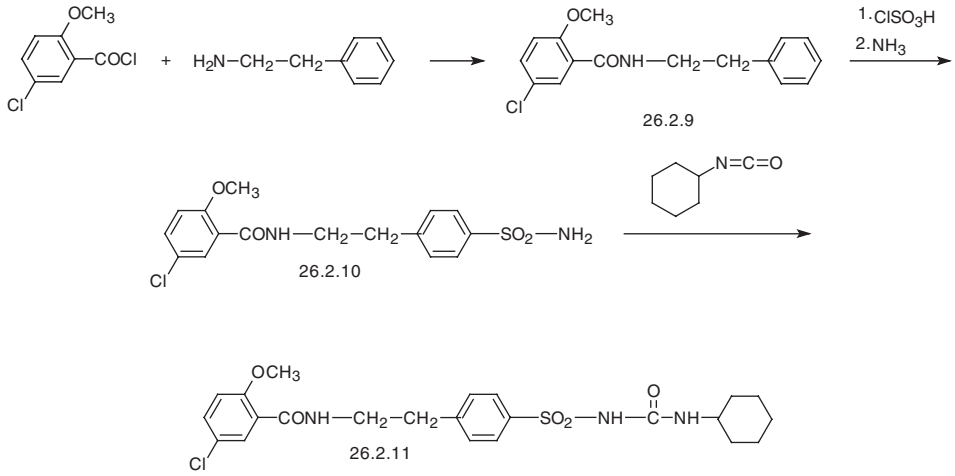
Tolazamide: Tolazamide is 1-hexahydro-1H-azepin-1-yl)-3-(*p*-toluenesulfonyl)urea (26.2.8). By maintaining structural similarities with first-generation drugs, this drug differs from the other drugs examined in that it has a semicarbazide group instead of a urea residue, and an azepine group instead of a cyclohexyl group. It is synthesized by reacting

with ethyl-(*p*-toluenesulfonyl)carbamate (26.2.7), which is made from p-toluenesulfonamide and ethylchloroformate, with 1-aminoazepine [32–35].



This drug is also a derivative of first generation of sulfonylurea, and it possesses stimulatory action on β-cells in pancreas, as well as the same range of action as all other drugs of the group of examined compounds. Tolazamide is used for non-insulin-dependent diabetes mellitus without expressed microvascular complications. Synonyms of this drug are norglycin, tolanase, and others.

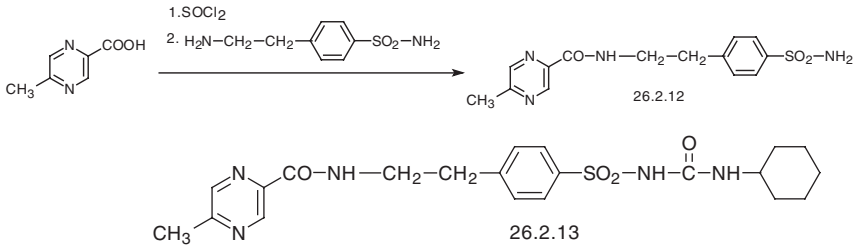
Glyburide: Glyburide, 1-[4-[2-(5-chloro-2-methoxybenzamido)ethyl]-phenylsulfonyl]-3-cyclohexylurea (26.2.11), is a second-generation drug that differs from those described above in that it has a more complex structure in the sulfonylamide region of the molecule into which an additional pharmacophore group is added. It is synthesized from 2-methoxy-5-chlorobenzoic acid chloride, which is transformed into an amide 26.2.9 by reacting it with 2-phenylethylamine. This undergoes subsequent sulfonylchlorination by chlorosulfonic acid, and then amination by ammonia, which gives sulfonamide 26.2.10. The resulting sulfonamide is reacted with cylclohexylisocyanate to give the desired glyburide (26.2.11) [36–39].



This drug belongs to the second-generation sulfonylurea derivatives. Like all of the other oral hypoglycemic drugs examined, it is a β-cell stimulant in pancreas; but on the other hand, it increases the sensitivity to insulin, the degree to which it binds with target cells. At the same time, it differs in that it is easier to tolerate. The hypoglycemic effect sets in

at significantly lower doses than with first-generation drugs. It is used for type II diabetes mellitus of medial severity with no expressed microvascular complications. Synonyms of this drug are glybenclamide, manilil, dihaben, daonil, and many others.

Glipizide: Glipizide, 1-cyclohexyl-3-[[*p*-[2-(5-methylpyrazincarboxamido)ethyl]phenyl] sulfonyl]urea (26.2.13), differs from glyburide in the structure of the amide region of the molecule, in which the 2-methoxy-5-chlorobenzoic acid part is replaced with 6-methylpyrazincarboxylic acid. It is also synthesized by a synthesis alternative to those described above. In the given scheme, 6-methylpyrazincarboxylic acid is initially reacted with thionyl chloride, resulting in the corresponding chloride, which undergoes further action with 4-(2-aminoethyl)benzenesulfonamide, forming the corresponding amide 26.2.12. The resulting sulfonamide is reacted in a traditional scheme with cyclohexylisocyanate, forming the desired glipizide (26.2.13) [40–42].



Indications for use and the mechanism of action are also similar to those of glyburide. Synonyms of this drug are glybinis, minidiab, glucotrol, and others.

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– 27 –

Corticosteroids

The term corticosteroids refers to steroid hormones secreted by the adrenal cortex. Corticosteroids are involved in a wide range of physiologic systems such as stress response, immune response, and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.

Drugs belonging to this class are: glucocorticoids (hydrocortisone, 11-dehydrocorticosterone, corticosterone), mineralocorticoids (aldeosterone, 11-deoxycorticosterone, 11-deoxy-17-oxycorticosterone), and sex hormons (androsterone, androstendion, estrone, progesterone).

Formation of these drugs is under the direct control of a polypeptide adrenocorticotropic hormone (ACTH, corticotropin), which is processed by the anterior lobe of the hypophysis. Human ACTH consists of 39 amino acids and has a molecular weight of about 4500. It differs from animal ACTH in the amino acid compositions at positions 29–33.

Glucocorticoids are endogenous compounds that have an effect on carbohydrate, lipid, and protein metabolism, and which exhibit anti-inflammatory, desensitizing, and anti-allergy action. They are immunodepressants, and they also possess anti-shock and anti-toxic action.

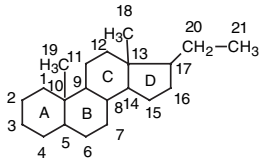
Mineralocorticoids are endogenous compounds that have an effect on fluid and electrolytic balance in the body, mainly by promoting sodium retention in the kidney.

Sex hormones are hormones that affect the reproductive system.

However, the spectrum of biological properties of many corticosteroids, as a rule, is much broader than the spectrum of properties present in ‘clean’ glucocorticoids, as well as ‘clean’ mineralocorticoids by definition.

In the body, natural steroid hormones are synthesized from cholesterol. The rate-determining step is the oxidation of the cholesterol side chain, which forms pregnenolone and isocaproic aldehyde.

All corticosteroids are derivatives of cyclopentanophenanthrene with keto-groups at C_3 and C_{20} and an unsaturated bond between C_4 and C_5 (indicated as Δ^4), and the presence of an axial β-CO-CH_2OH side chain at C_{17}, which is absolutely necessary. They differ from one another in the presence of a keto- or β-hydroxyl group at C_{11}, as well as on C_{17} and/or C_{18}. These differences determine the major pharmacological properties of these drugs and their precursors.



Steroids reversibly bind with two proteins in the plasma: corticosteroid-binding globulin, which is a specific α_2-globulin; and albumin, which has nonspecific activity and a weakly expressed affinity to steroids.

Free steroids that do not bind with plasma proteins enter target cells by passive diffusion and bind with cytoplasmic soluble-binding proteins (acceptor region), forming a steroid–protein complex. This enters the nucleus, where it interacts with steroid receptors on chromatin.

Corticosteroids do not heal illnesses, but they are widely used in various conditions when it is necessary to utilize their anti-inflammatory, immunosuppressant, and mineralocorticoid properties. In addition, they are used in replacement therapy for patients who have adrenal insufficiency. Corticosteroids can be used in vital situations for asthma, severe allergic reactions, and transplant rejections. They are effective in noninfectious granulomatous diseases such as sarcoidosis, collagen vascular disease, rheumatoid arthritis, and leukemia. Steroids are used as lotions, ointments, etc. in treating a number of dermatological and ophthalmologic diseases.

Corticosteroids are very powerful drugs whose side effects are practically impossible to avoid. Therefore, they should be used in the smallest effective doses, and for a very short time. It is recommended that use of these drugs should not be stopped abruptly, but rather they should be stopped gradually.

27.1 GLUCOCORTICOIDS

Glucocorticoids are compounds that act first and foremost on the metabolism of carbohydrates, proteins, and fats, and to some degree on the electrolytic and water balance in the body. They have effects on practically all tissues and organs, and can change the immune response of the body to various types of influences. The end result of using them is induction (anabolism), or suppression (catabolism) of protein synthesis. They have an effect on the cardiovascular system, the gastrointestinal tract, the skeletal musculature, skin, connective tissue, blood, and the endocrine system. The direct indication for using them is severe and chronic adrenal insufficiency. They are used for collagenosis, rheumatoid arthritis, rheumatism, eczema, neurodermatitis, and other skin diseases, allergies, tissue transplants, bronchial asthma, and many other diseases.

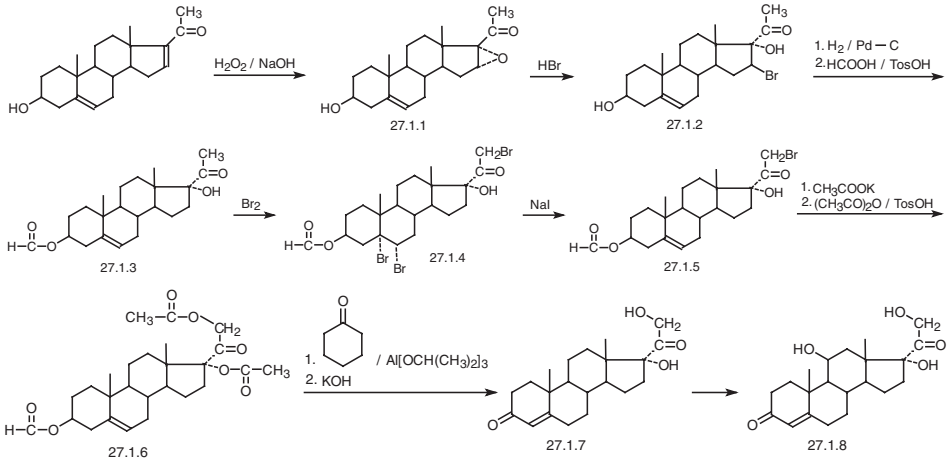
The connection between chemical structure and biological action of corticosteroids is extremely complex. However, it is possible to make a number of generalizations.

In order for glucocorticoid activity to be expressed, the presence of a hydroxyl group at position $C_{11}\beta$ and $C_{17}\alpha$ in the structure of the pregnane system is very important. At the same time, in order for adequate mineralocorticoid activity to be expressed, an oxygen functional group is needed at C_{11} and C_{18}, or else an absence of a hydroxyl functional groups are simultaneously needed at C_{11} and C_{17}. In general, it is likely that the glucocorticoid binding with receptor sites should take place only in the simultaneous presence of the $C_{11}\beta$-hydroxyl group and a $C_{17}\beta$-CO-CH_2OH side chain of the steroid system. The presence of other bulky axially oriented β-substituents in the molecule, as a rule, inhibits binding of steroid molecules with receptors, while analogs with equatorial α-substituents do not cause large problems.

The primary endogenic glucocorticoids are hydrocortisone and cortisone. Numerous synthetic analogs of natural glucocorticoids have been made and used, and they have turned out to be more effective, and currently they have almost completely replaced cortisone (prednisolon, prednisone, dexamethasone, and others).

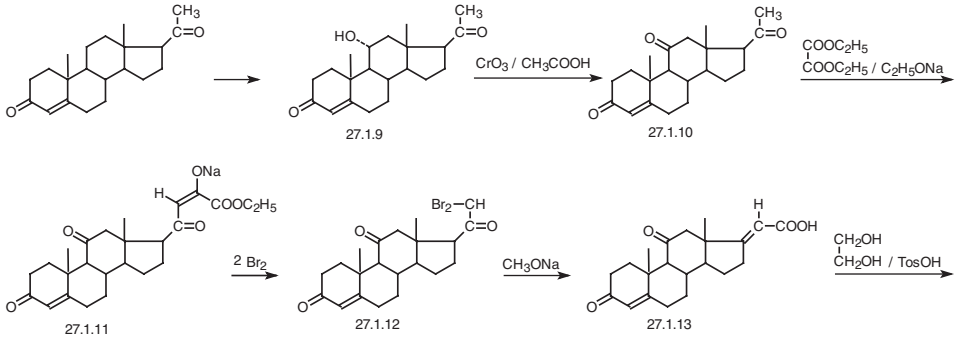
Glucocorticoids are used orally, intravenously, intramuscularly, as inhalants, and in the form of ointments, creams, and so on.

Hydrocortisone: Hydrocortisone, 11β,17α,21-trihydroxypregn-4-en-3,20-dione (27.1.8), is synthesized in various ways and from various compounds containing a steroid skeleton. According to one of them, hydrocortisone is synthesized from dextropregnenolone. The double bond between C_{16} and C_{17} of dextropregnenolone is oxidized using hydrogen peroxide in a base, forming an epoxide 27.1.1. Interacting this with hydrobromic acid opens the epoxide ring, forming 16-bromo-17-hydroxydextropregnenolone (27.1.2). The resulting bromo derivative undergoes debromination by hydrogen using a palladium on carbon catalyst, and then the secondary hydroxyl group undergoes esterification using formic acid in the presence of *p*-toluenesulfonic acid, giving 3-formyloxy-17-hydroxydextropregnenolone (27.1.3). The resulting 3-formyloxy-17-hydroxydextropregnenolone undergoes bromination by bromine, which results in bromination of the C_4–C_5 double bond and the methyl group of acetyl moiety, which forms a tribromo derivative 27.1.4. Reacting the product with sodium iodide results in dehalogenation of the resulting vicinal dibromide, during which the double bond is simultaneously shifted into the position between carbon atoms C_5 and C_6 that gives the bromoketone 27.1.5. This is reacted with potassium acetate and then with acetic anhydride in the presence of *p*-toluenesulfonic acid, forming a diacetate 27.1.6. Taking into account that unlike acetates, formates are easily oxidized and give exactly the same products as do the corresponding alcohols, the resulting diacetate is oxidized in an Oppenauer oxidation reaction, using aluminum isopropoxide and cyclohexanone as a hydrogen acceptor. During this, isomerization of the double bond into the primary position between C_4 and C_5 simultaneously takes place, forming a stable, conjugated vinylketone, after which the acetyl protection of both hydroxyl groups is hydrolyzed using potassium hydroxide, giving 17-hydroxy-11-deoxycorticosterone (27.1.7). This undergoes microbiological oxidation at position C_1, forming the desired hydrocortisone (27.1.8). Side reactions of microbiological oxidation using the very same microorganisms can cause hydroxylation of steroids in different positions, using easily accessible progesterone [1–5] as an initial substance [1–5].

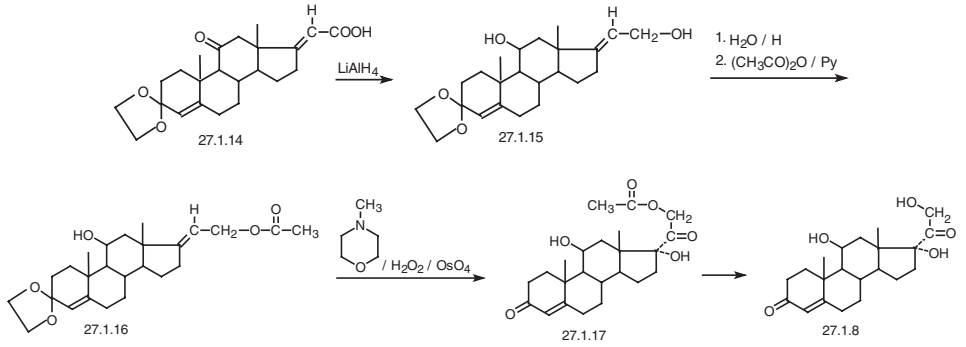


27.1.1 27.1.2 27.1.3 27.1.4 27.1.5 27.1.6 27.1.7 27.1.8

From the synthetic chemist's point of view, another interesting way of making hydrocortisone consists of using progesterone as the starting substance. In the first stage of the synthesis, progesterone undergoes microbiological oxidation analogous to that described above, which forms 11α-hydroxyprogesterone (27.1.9). The resulting hydroxyl group is oxidized by chromium (VI) oxide in acetic acid, giving 11-ketoprogesterone (27.1.10). This is reacted with diethyloxalate in the presence of sodium ethoxide, forming the corresponding α-ketoester in the form of the sodium enolate 27.1.11, which undergoes bromination by two equivalents of bromine, giving the dibromoketone 27.1.12. The resulting dibromoketone undergoes Favorskii rearrangement and is further hydrolyzed, giving an unsaturated acid 27.1.13. Then the carbonyl group at position C_3 is ketalized using ethylenglycol in the presence of *p*-toluenesulfonic acid, during which a migration of the double bond between carbon atoms C_5 and C_6 takes place, forming a ketal 27.1.14. The resulting product is reduced by lithium aluminum hydride. During this, the carboxyl and ketogroups at C_{11} are reduced to alcohol groups, forming a diol 27.1.15. The ketal protecting group is subsequently removed in acidic conditions, during which the double bond again migrates back to the initial position between C_4 and C_5, and the primary hydroxyl group is acylated by acetic anhydride in pyridine forming the product 27.1.16. The double bond in this compound is oxidized using hydrogen peroxide in the presence of osmium tetroxide in *N*-methylmorpholine, forming hydrocortisone acetate (27.1.17). Hydrolysis of the acetyl group with potassium hydroxide gives hydrocortisone (27.1.8) [6,7].



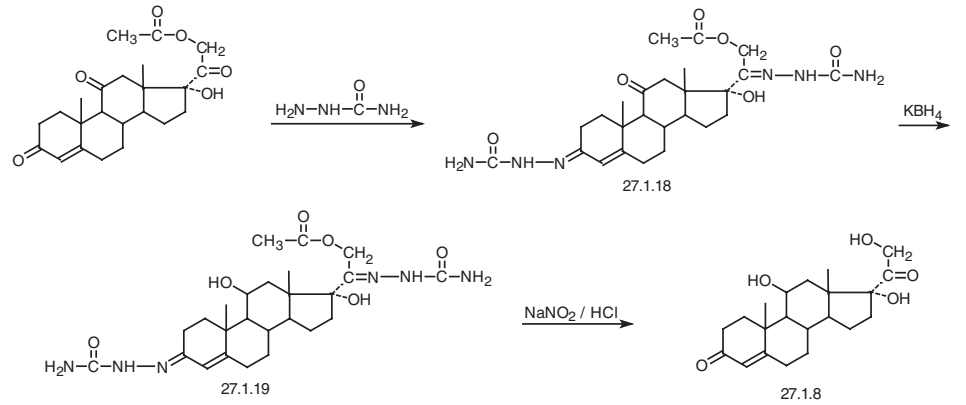
27.1.9 27.1.10 27.1.11 27.1.12 27.1.13



27.1.14 27.1.15 27.1.16 27.1.17 27.1.8

Hydrocortisone can also be synthesized from cortisone acetate. It is treated with semicarbazide, during which the disemicarbazone 27.1.18 is formed as a result of a reaction at both carbonyl groups at C_3 and C_{20}. The carbonyl group at C_{11} is reduced by potassium borohydride to an alcohol group, during which the acetyl group on the hydroxyl at C_{21} is simultaneously removed, giving semicarbazone 27.1.19. By removing the semicarbazide protection using nitric acid, hydrocortisone (27.1.8) is formed.

Hydrocortisone is used in the form of a free alcohol (speaking of the hydroxyl group at C_{21}), as well as in the form of an acetate, succinate, or phosphate [8].



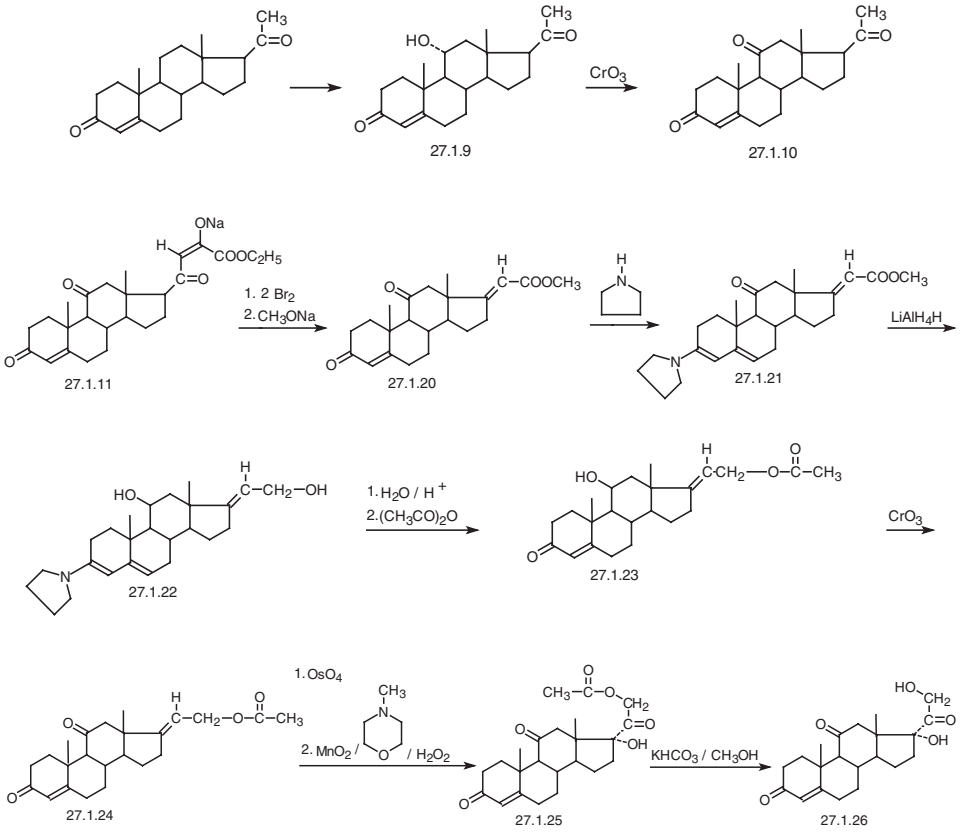
27.1.18 27.1.19 27.1.8

Hydrocortisone exhibits anti-shock, anti-allergy, and anti-inflammatory action. It raises sugar content in the blood, increases potassium secretion, and lowers sodium excretion from the body. It exhibits anti-metabolic action and reduces histamine synthesis in the body.

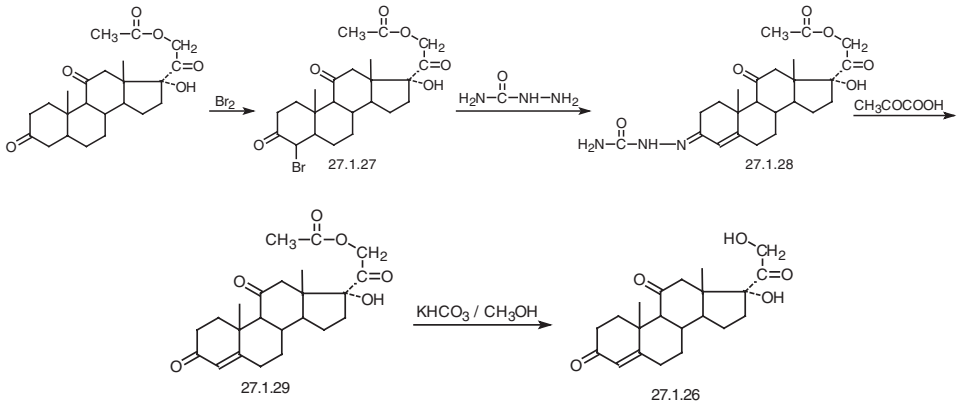
Hydrocortisone drugs are used for severe inflammation, shock, primary or secondary renal insufficiency, adrenal insufficiency, ulcerative colitis, and rheumatoid, gouty, and psoriatic arthritis, collagen and dermatological diseases, allergic conditions, ophthalmologic and gastrointestinal diseases, and respiratory tract diseases. Synonyms of this drug are cortef, hydrocorton, and others.

Cortisone: Cortisone, 17α,21-dihydroxypregn-4-en-3,11,20-trione (27.1.26), is also synthesized in various ways from compounds already having the steroid skeleton. One of

them is very similar to a method of making hydrocortisone described above, in which it is synthesized from progesterone, which undergoes microbiological oxidation, forming 11α-hydroxyprogesterone (27.1.9). The hydroxyl group of the last is oxidized by chromium(VI) oxide in acetic acid, giving 11-ketoprogesterone (27.1.10). This is reacted with diethyloxalate in the presence of sodium ethoxide, forming the corresponding α-ketoester in the form of a sodium enolate 27.1.11, which undergoes bromination with two equivalents of bromine, giving a dibromoketone 27.1.12. The resulting dibromoketone undergoes a Favorskii rearrangement, but the product is not hydrolyzed, and the unsaturated acid is isolated in the form of a methyl ester 27.1.20. Reacting this with pyrrolidine gives a dienamine 27.1.21, which undergoes reduction by lithium aluminum hydride, which results in that, the keto-group on C_{11} transforms into a hydroxyl group, and the carbmethoxy group to a primary alcohol, forming the compound 27.1.22. Acidic hydrolysis of the product and subsequent acetylation gives an acetate 27.1.23, and the hydroxyl group at C_{11} in which it is oxidized with chromium(VI) oxide to a ketone, forming the compound 27.1.24. This undergoes a reaction with osmium tetroxide, and the resulting osmate is oxidized by magnesium dioxide in *N*-methylmorpholine, giving cortisone acetate 27.1.25. Hydrolysis of the acetyl group using sodium bicarbonate leads to the formation of cortisone (27.1.26) [6,9,10].

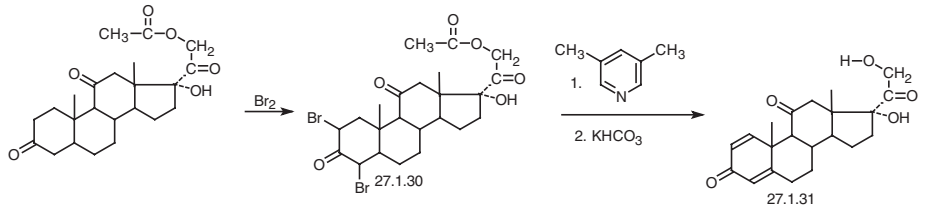


Another way of making cortisone is from dihydrocortisone acetate. This undergoes monobromination by bromine, giving the 4-bromo derivative of dihydrocortisone acetate (27.1.27). This is reacted with semicarbazide, which results in removal of hydrobromic acid and simultaneously making the semicarbazone at the keto-group on C_3, forming the product 27.1.28. Next, 21-*O*-acetylcortizone (27.1.29) is isolated from semicarbazone using pyruvic acid. Hydrolysis of the acetyl group using potassium bicarbonate gives the desired cortisone (27.1.26) [11–13].



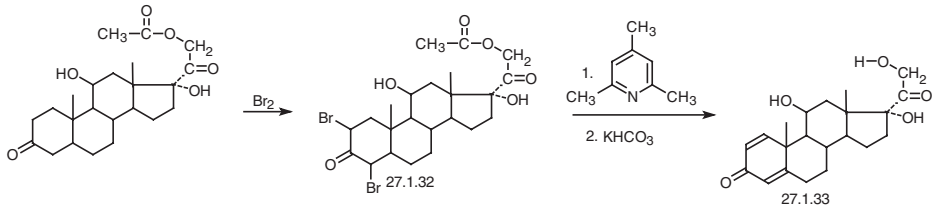
Cortisone is used for inflammatory processes, allergies, and adrenal insufficiency. Synonyms of this drug are cortisan, cortol, adreson, cortadren, and others.

Prednisone: Prednisone is 17α,21-dihydroxypregna-1,4-dien-3,11-20-trione (27.1.31). Prednisone differs from cortisone in the presence of an additional double bond between C_1 and C_2. There are various ways of synthesizing it. In one of these, as is in the case when synthesizing cortisone, it is synthesized from dihydrocortisone acetate. However, in the given example, this compound undergoes dibromination by molecular bromine, giving 2,4-dibromo-derivative of dihydrocortisone 27.1.30. Dehydrobromination with 3,5-lutidine, followed by subsequent hydrolysis of the acetyl group using potassium bicarbonate gives the desired prednisone (27.1.31) [14,15]. Prednisone is also synthesized by microbiological dehydrogenation of cortisone [16,17].



Prednisone is used for the same indications as cortisone for inflammatory processes, allergies, and adrenal gland insufficiency; however, it is somewhat more active than cortisone and has less of an effect on mineral volume. Synonyms of this drug are cortancyl, decortisil, paracort, and others.

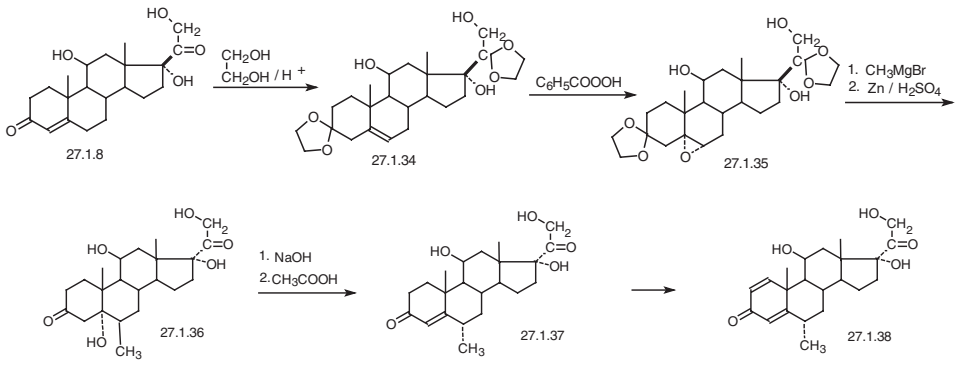
Prednisolone: Prednisolone is 11β,17α,21-trihydroxypregna-1,4-dien-3,20-dione (27.1.33). Structurally, prednisolone differs from prednisone in that the keto-group at C_{11} of prednisone is replaced by a hydroxyl group. Prednisolone is synthesized either by microbiological dehydrogenation of C_1–C_2 bond in hydrocortisone [16–19], or from 21-acetoxy-11β,17α-dihydroxy-5α-pregnan-3,20-dione, which undergoes dibromination by molecular bromine in acetic acid at positions C_2 and C_4, and then the resulting dibromide 27.1.32 is dehydrobrominated by heating it in collidine, which gives prednisolone as an acetate at position C_{21}. Hydrolyzing this compound leads to formation of prednisolone (27.1.33) [14].



Prednisolone also exhibits anti-shock, anti-allergy, anti-inflammatory, and immunosuppressive action. It raises glucose levels in the blood, increases potassium secretion, and reduces sodium secretion from the organism.

Prednisolone is used for the same indications as all corticosteroids: rheumatism, polyarthritis, bronchial asthma, neurodermatitis, and eczema. Synonyms of this drug are antisolon, decortin, cortolon, precortilon, and many others.

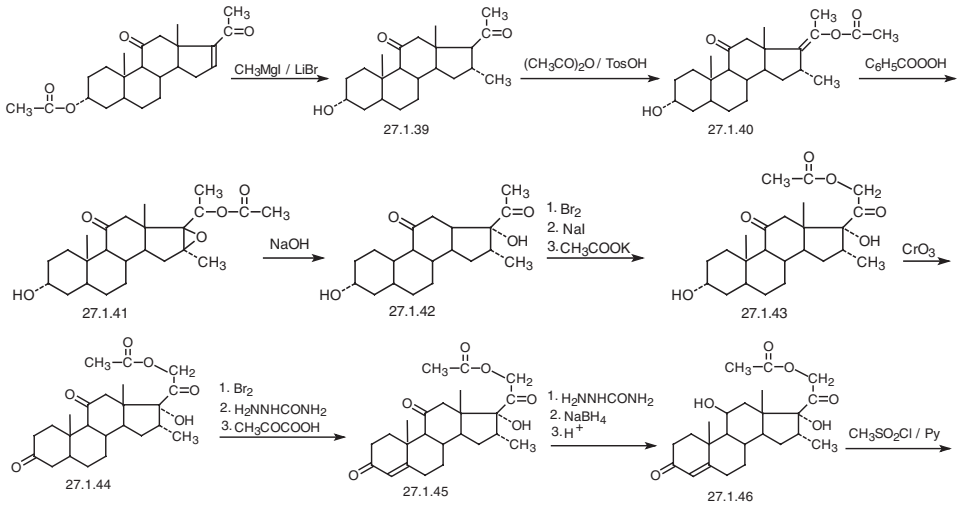
Methylprednisolone: Methylprednisolone, 11β,17α,21-trihydroxy-6α-methylpregna-1, 4-dien-3,20-dione (27.1.38), differs from prednisolone in the presence of a methyl group at position C_6 of the steroid skeleton of the molecule. This seemingly simple difference in structure requires a different approach to synthesis. It is synthesized from hydrocortisone (27.1.8), the carbonyl group of which initially undergoes ketalization by ethylene glycol in the presence of traces of acid, during which the double bond at position C_4– C_5 is shifted to position C_5– C_6, giving the diethyleneketal 27.1.34. The product is oxidized to an epoxide (27.1.35) using perbenzoic acid. Next, the resulting epoxide is reacted with methylmagnesium bromide, and subsequent removal of the ketal protection by hydrogen reduction gives the 5-hydroxy-6-methyl derivative of dihydrocortisone 27.1.36. The resulting β-hydroxyketone is dehydrated using an alkaline, and then the resulting 6α-methylcortisone (27.1.37) undergoes microbiological dehydration at position C_1–C_2, giving the desired methylprednisolone (27.1.38) [20–25].

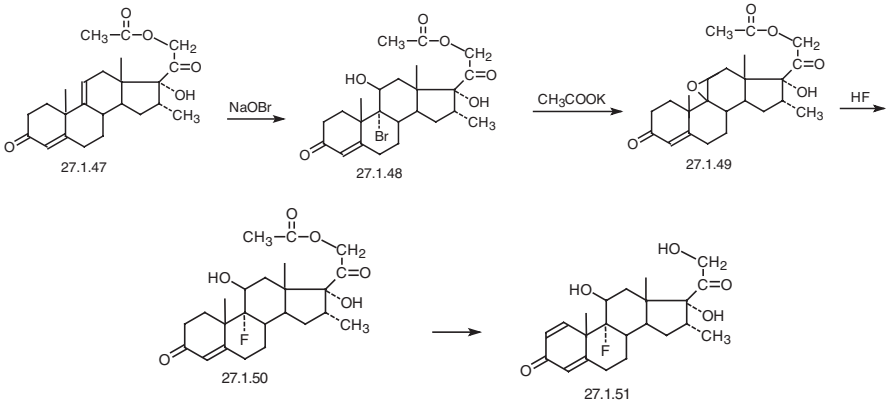


Methylprednisolone is an analog of prednisolone that exhibits a more prolonged effect than prednisolone and cortisone; it has practically no mineralocorticosteroid activity and is better tolerated. Synonyms of this drug are metipred, medron metrisone, and others.

Dexamethasone: Dexamethasone, 9α-fluoro-16α-methyl-11β,17,21-trihydroxypregna-1,4-dien-3,20-dione (27.1.51), or simply 9α-fluoro-16α-methylprednisolone. The distinctive characteristic of dexamethasone is the presence of a fluorine atom at C_9 of the steroid ring.

Dexamethasone is synthesized in a multistage process from 3α-acetoxy-16-pregnen-11,20-dione, which is reacted with methylmagnesium bromide in the presence of lithium bromide to give 3α-hydroxy-16α-methylpregnan-11,20-dione (27.1.39), after which a 17α-hydroxyl group is added. This is done by a reaction with acetic anhydride in the presence of *p*-toluenesulfonic acid, forming the 3-acetoxy-17-enolacetate 27.1.40, which is epoxidized by perbenzoic acid 27.1.41, and the product is hydrolyzed by an alkali to give an oxyketone 27.1.42. Addition of another hydroxyl group at C_{21} is accomplished by subsequent bromination of a methyl group with molecular bromine, replacing the bromine atom with iodine, and reacting iodide with potassium acetate, which forms the corresponding acetoxyketone 27.1.43. The hydroxyl group at C_3 is oxidized to a carbonyl by chromium(VI) oxide in pyridine, giving the 3,11,20-triketone 27.1.44, which again undergoes bromination by molecular bromine, but at position C_4. Dehydrogenation of this compound is accomplished using semicarbazide, which results in the formation of an unsaturated triketone 27.1.45. In order to avoid formation of semicarbazones at the keto-groups at C_3 and C_{20}, the final product is treated with pyruvic acid. Semicarbazones are then specially formed at the keto-groups of C_3 and C_{20}, and the keto-group at C_{11} that does not take part in semicarbazone formation is reduced to hydroxyl group using sodium borohydride. After removing the protective semicarbzone groups, 21-*O*-acetoxy-16β-methylhydrocortisone (27.1.46) is formed. This is reacted with potassium acetate and transformed to the epoxide 27.1.49. Reacting this with hydrofluoric acid results in an opening of the epoxide ring, during which the fluorohydrin 27.1.50 is formed. Finally, microbiological dehydrogenation of this compound at C_1–C_2 and simultaneous deacetylation gives dexamethasone (27.1.51) [26–28].



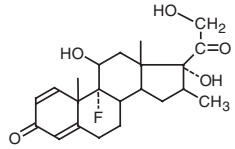


27.1.47 27.1.48 27.1.49 27.1.50 27.1.51

Dexamethasone is used for the same indications as all corticosteroids; however, it exhibits a significantly more powerful anti-inflammatory and anti-allergic action.

It is used for circulatory collapse—shock during or after surgical operations, trauma, blood loss, myocardial infarction, and burns. It is also used in severe infections—toxemia, vascular collapse in meningococcosis, septicemia, diphtheria, typhoid fever, and peritonitis. It is used in severe allergic conditions—asthmatic status, laryngeal edema, severe anaphylactic reactions to medicinal drugs, and pyrogenic reactions. Synonyms of this drug are decacort, decardan, hexadrol, novometazon, and others.

Betamethasone: Betamethasone is 9α-fluoro-16β-methyl-11 β,17,21-trihydroxypregna-1,4-dien-3,20-dione, or simply 9α-fluoro-16β-methylprednisolone (27.1.52). As seen from the chemical name of the drug, betamethasone only differs from dexamethasone in the orientation of the methyl group at C_{16}. The proposed method of synthesis differs from the other method in a number of details and successive reactions besides the first stage, in particular concerning the addition of the methyl group at C_{16} of the steroid ring. Betamethasone, like dexamethasone, is synthesized from 3α-acetoxy-16-pregnen-11,20-dione; however, the methyl group at C_{16} of the steroid ring is not reacted with methylbromide, but rather is reacted with diazomethane followed by hydrogenation of the double bond between carbon atoms $C_{16}-C_{17}$ of the steroid ring using a palladium on carbon catalyst, which results in the corresponding β-orientation of the introduced methyl group [29].

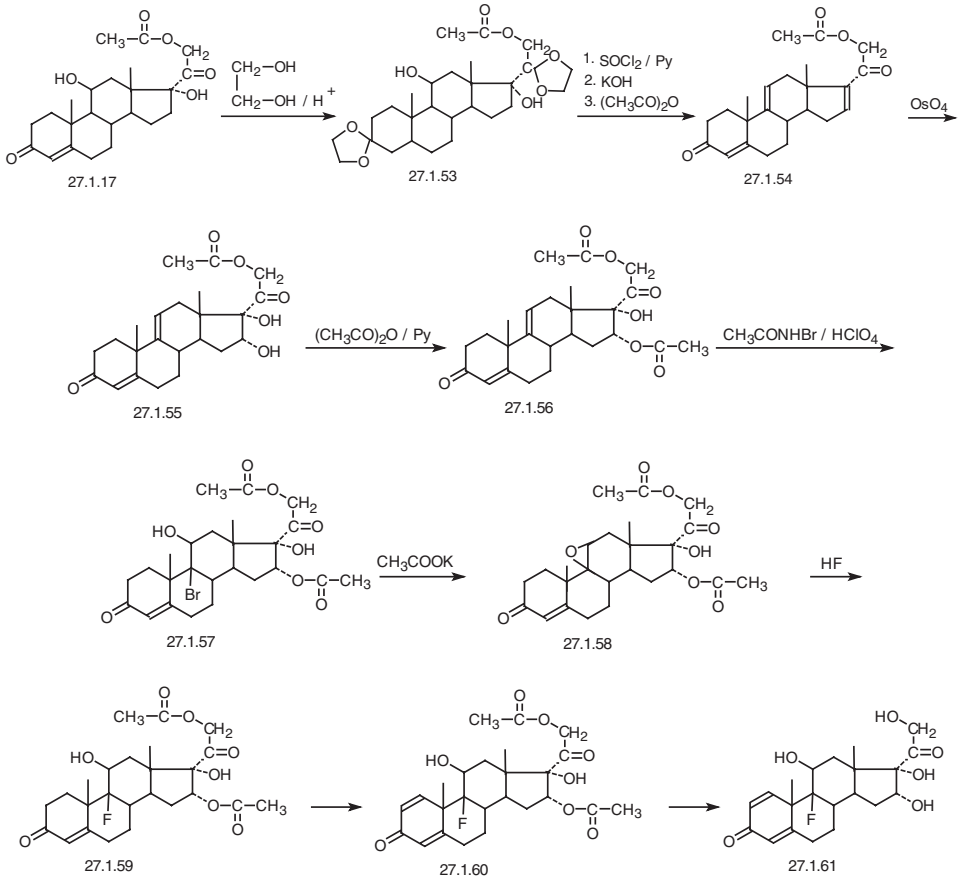


27.1.52

As an isomer of dexamethasone, betamethasone is primarily used locally to treat dermatitis and eczema, and also as an anti-itch agent. Synonyms of this drug are betacor, celestan, supercortene, and others.

Triamcinolone: Triamcinolone, 9a-fluoro-11b,16a,17,21-tetrahydroxypregna-1, 4-dien-3,20-dione (27.1.61), differs from dexamethsone in terms of chemical structure in

that the a methyl group at C_{16} is replaced with a hydroxyl group. It is synthesized from the 21-O-acetate of hydrocortisone 27.1.17. In the first stage, both carbonyl groups of this compound undergo ketalization by ethylene glycol. Next, the hydroxyl group in the resulting diketal 27.1.53 is replaced with chlorine using thionyl chloride, and the product undergoes dehydrochlorination using an alkaline, during which the 21-O-acetyl group also is hydrolyzed. Acetylating the hydroxyl group once again with acetic anhydride gives a triene 27.1.54. Reacting this with osmium tetroxide gives the vicinal diol 27.1.55. The secondary hydroxyl group at C_{16} of this product undergoes acetylation by acetic anhydride in pyridine, which forms the diacetate 27.1.56. Treating the product with N-bromoacetamide in chloric acid gives a bromohydrin (27.1.57), which upon reaction with potassium acetate is transformed to an epoxide (27.1.58). Opening of the epoxide ring, using hydrofluoric acid, gives the corresponding 9-fluoro-11-hydroxy derivative 27.1.59. Upon microbiological dehydrogenation, the C_1–C_2 bond is oxidized to a double bond, forming triamcinolone acetate (27.1.60), the acetyl group of which is hydrolyzed, forming the desired triamcinolone (27.1.61) [30–32].



Triamcinolone is similar to dexamethasone in terms of pharmacological action, and it is better tolerated in some cases. Synonyms of this drug are ledercort, cenocort, delsolon, and others.

27.2 MINERALOCORTICOIDS

Mineralocorticoids play a major role in regulating the balance of electrolytes and water, especially in the kidneys, where they facilitate reabsorption of sodium ions and water from urine.

The main endogenic mineralocorticoid is aldosterone, which is not used in clinical medicine, however. Deoxycorticosterone is widely used.

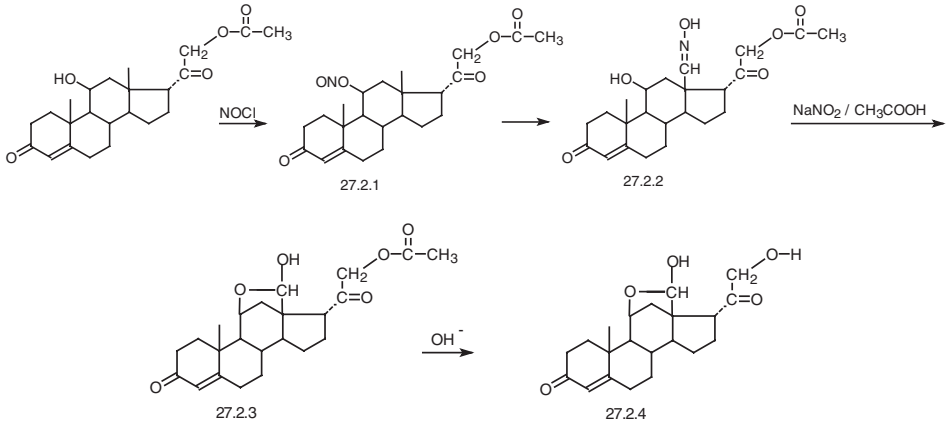
Unlike glucocorticoids, mineralocorticoids have an insignificant effect on carbohydrate volume. They do not exhibit any anti-inflammatory or anti-allergy properties. They are used for chronic adrenal insufficiency, as well as for raising tonicity and work capacity of muscles.

The correlation between chemical structure and action of mineralocorticoids is extremely complex; however, a number of partial conclusions can be synthesized.

In particular, it should be noted that since 11-deoxycorticosterone does not exhibit glucocorticoid activity; yet, it is a powerful mineralocorticoid and has only two potentially reactive substituents capable of reacting with a receptor, and the interaction should occur by way of a C_3-keto and/or a $C_{17}\beta$-CO-CH_2OH groups. The necessity of either a simultaneous presence of acidic functions at C_{11} and C_{18}, or the necessity of simultaneous absence of acidic functions at C_{11} and C_{17} in the structure of the pregnane system is also apparent.

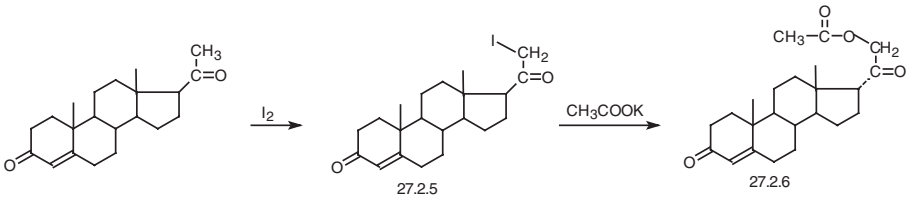
Fluorination at $C_9\alpha$-position increases the mineralocorticoid activity of both C_{11}-hydroxy (hydrocortisone) and C_{11}-deoxy (deoxycorticosterone) compounds.

Aldosterone: Aldosterone, 11β,21-dihydroxypregn-4-en-2,18,20-trione (27.2.4), is synthesized from 21-*O*-acetylcorticosterone, which when reacted with nitrosyl chloride in pyridine gives the nitrite 27.2.1. When photochemically irradiated, this compound is transformed to the oxime 27.2.2, which is hydrolyzed by nitrous acid and forms the semiacetal 27.2.3, which is an acetate of the desired aldosterone. Alkaline hydrolysis of the acetyl group of this compound leads to the desired aldosterone (27.2.4) [33].



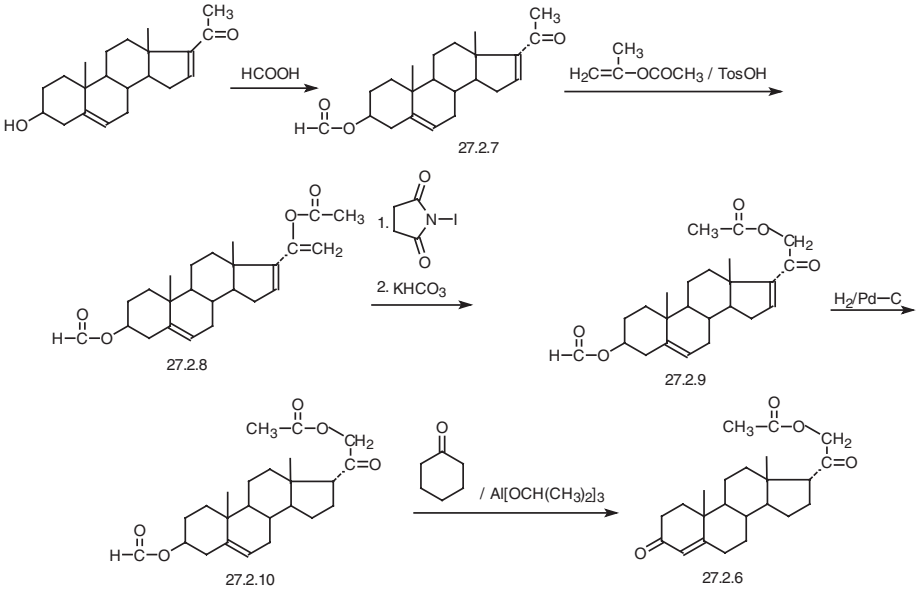
For a number of reasons, aldosterone is practically never used as a therapeutic agent for correcting electrolytic irregularities in adrenal insufficiency, for which deoxycorticosterone and fludrocortisone are more frequently used.

Deoxycorticosterone: Desoxycorticosterone, 21-hydroxypregn-4-en-3,20-dione acetate (27.2.6), is synthesized in a number of ways, the easiest of which being iodination of progesterone at C_{21} in the methyl group, and subsequent reaction of the resulting iodo-derivative 27.2.5 with potassium acetate, which leads to formation of the desired desoxycorticosterone in the form of the acetate (27.2.6) [34].



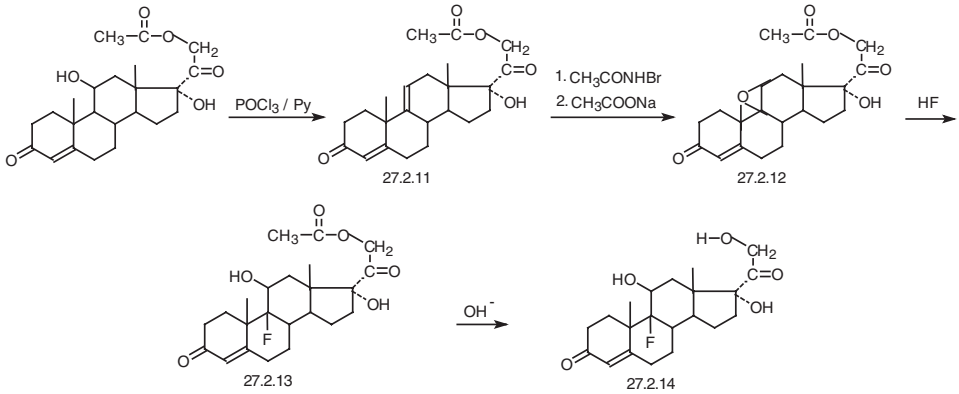
Another method of synthesizing desoxycorticosterone acetate (27.2.6) is from 3-hydroxy-5,16-pregnadien-20-one. First, the hydroxyl group at C_3 must be protected. It undergoes formylation by formic acid, which gives the formate 27.2.7. Reacting this with isopropenylacetate in the presence of *p*-toluenesulfonic acid gives the enolacetate 27.2.8. Treating the resulting enolacetate with iodosuccinimide, which reacts exclusively with the enolacetate double bond, an iodoketone is formed, which is reacted with potassium acetate to form the acetate 27.2.9. The double bond at C_{16}–C_{17} is reduced by hydrogen using a palladium on carbon catalyst, forming the product 27.2.10.

Oxidizing this product with aluminum, isopropylate in the presence of cyclohexanone gives desoxycorticosterone acetate (27.2.6) [35,36].



Desoxycorticosterone causes an increase in reabsorption of sodium ions and excretion of potassium ions from the renal tubules, which leads to increased tissue hydrophilicity. This facilitates an elevated volume of plasma and increased arterial pressure. Muscle tonicity and work capability are increased. It is used for an insufficiency of function of the adrenal cortex, myasthenia, asthenia, adynamia, and overall muscle weakness. Synonyms of this drug are percorten, docabolin, cortitron, and others.

Fludrocortisone: Fludrocortisone, 9α-fluoro-11β,17α,21-trihydroxypregn-4-en-3,20-dione (27.2.14), is synthesized from hydrocortisone acetate (27.1.17). In the first stage of synthesis, dehydration of the hydrocortisone molecules is accomplished using phosphorous chloride in pyridine, which forms a product with a double bond at C_9–C_{11} 27.2.11. The resulting double bond is synthesized into an epoxide by an initial transformation to a bromohydrine using *N*-bromoacetamide and subsequent dehydrobromination using sodium acetate, which forms 21-*O*-acetoxy-9d-11β-epoxy-17α-hydroxy-4-pregnen-3,20-dione (27.2.12). As described above, the epoxide ring is opened by hydrofluoric acid, which results in the formation of the 21-*O*-acetate of fludrocortisone 27.2.13. Hydrolysis of the acetyl group of this compound using potassium acetate gives fludrocortisone (27.2.14) [37–42].



This drug has practically the exact same activity as desoxycorticosterone, and it is even forcing it out of medicinal use. The primary synonym of this drug is florinef.

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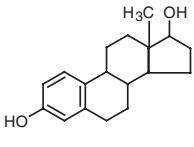
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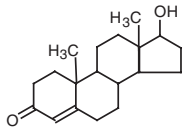
– 28 –

Female Sex Hormones

Of the numerous hormones that regulate body function, two steroid hormones are extremely important: estradiol, a female sex hormone and testosterone, a male sex hormone. Present in the body in insignificant amounts, they regulate sexual differentiation and reproduction as well as affect the performance of many other physiological systems. Despite the great similarity in chemical structure, they are very different in terms of physiological action.



estradiol



testosterone

The two primary classes of female sexual hormones are estrogens and progestins, which are formed in the ovaries, to a lesser degree in the adrenal cortex, and in the placenta during pregnancy. Together they carry out a very important function in the development of secondary female sex organs, controlling pregnancy, controlling ovulation and menstrual cycles, and modulating a large number of metabolic processes.

One of the most important areas of synthetic estrogens and progestins are their use as oral contraceptives, for hormone replacement therapy, and as drugs for menstrual disorders.

These drugs can be a fixed composition containing a constant amount of estrogen (for example, ethinyl estradiol) and progestin (for example, norethindrone), a composition that contains a constant amount of estrogen with varying doses of progestin, or pills that contain only progestin in constant doses.

28.1 ESTROGENS

Natural or synthetic compounds that coordinate systemic regulation during the ovulatory cycle, including the reproductive tract, breasts, mucous membranes, and other tissues are called estrogens. They also play an important role in the development of some tumors, estrogen in particular, and antiestrogens are also used to treat breast and

prostate tumors. Estrogen is a general term used to describe compounds that possesses estrogenic activity. However, they in turn can be subdivided into two groups: estrogens, which are functionalized derivatives of a steroid structure, and compounds that do not contain a steroid ring.

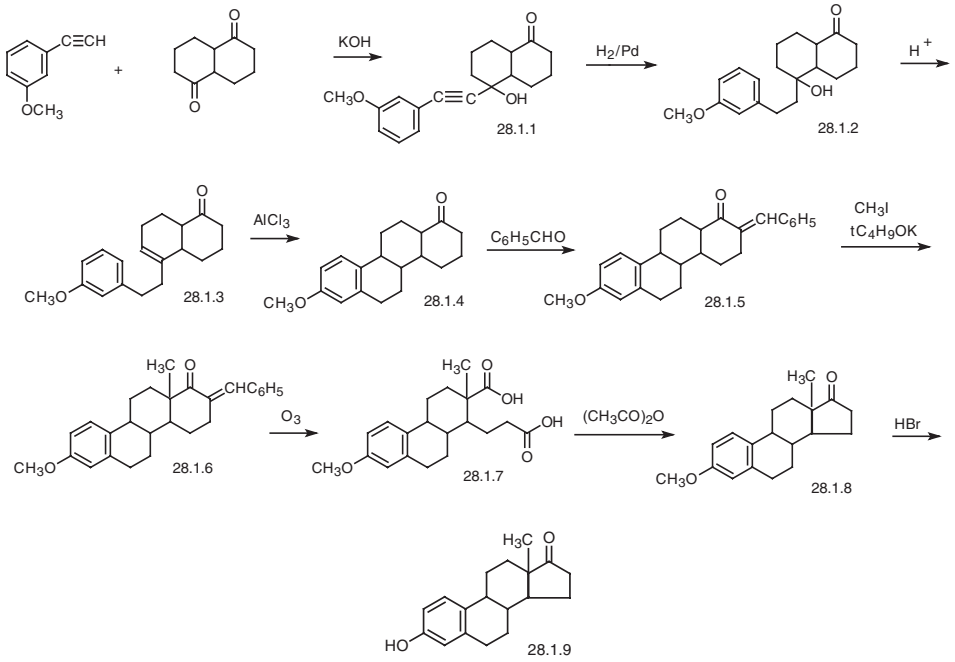
There are three natural human estrogens: 17β-estradiol, the most powerful estrogen that transforms into a weaker metabolite estron, and which in turn is metabolized to estriol.

17β-Estradiol is the main estrogen synthesized and secreted by normal female ovaries. Its oxidized analog, estrone, is secreted to a significantly lesser degree by premenopausal ovaries. The hormonal effect of estrogens on target tissues is based on a complex mechanism that includes their reaction with specific estrogenic cytoplasmic receptors. After binding with these receptors, a conformational change occurs, which results in the estrogen–receptor complex penetrating into the nucleus, where it disassociates and returns to its native condition. Estrogens are used for insufficient ovary function. Estrogen replacement therapy is used in agonadal, menopausal, hypothalamic, and amenorrheal conditions (i.e. in cases of primary hypogonadism and hormone therapy in postmenopausal women). Estrogens are also recommended for other clinical endocrine diseases if hypoestrogenism has been established. Estrogens are most widely used in combination with progestins in a number of oral contraceptive drugs. They are frequently used to prevent and treat osteoporosis, and as replacement therapy drugs for relieving a number of symptoms upon entering menopause. Estrogens are also used as antagonists of androgen in cases of androgen-sensitive forms of cancer.

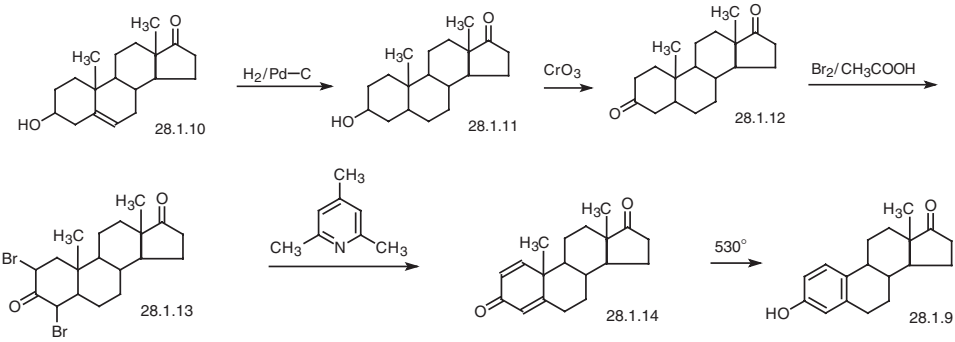
Of the drugs that have steroid structures, estrone, estradiol, estriol, and ethinyl estradiol are used in medicine. Of the drugs with nonsteroid structures, sin-estrol, diethylstilbestrol, and chlortrianisene are used. Many drugs used for research purposes can be obtained from urine of pregnant females of pregnant animals. Synthetic drugs are often made from plant sterols—saponin, ergosterin, stigmasterin, and others, or from cholesterol or bile acids, by preliminary cleavage of their side chains to form the corresponding precursors for further syntheses. The synthesis of all main steroid hormones were realized. As an illustration, only the relatively simple full synthesis of estrone is shown below.

Estrone: Estrone, 3-hydroxyestra-1,3,5(10)-trien-17-one (28.1.9), has been made synthetically in various ways. According to one of the first and most simple schemes, synthesis was carried out in the following manner. Condensation of 3-methoxyphenylacetylene with bicyclohexane-1,5-dione in a Favorskii reaction conditions lead to the corresponding carbinol (28.1.1). The triple bond was reduced by hydrogen over a palladium catalyst, forming the tertiary alcohol (28.1.2), which was then dehydrated in acidic conditions to give the compound (28.1.3). Intramolecular alkylation of this compound in the presence of anhydrous aluminum chloride formed a tetracyclic ketone (28.1.4), which during condensation with benzaldehyde was transformed into an eneone (28.1.5). This was methylated at the β-position relative to the keto-group by methyl iodide in the presence of potassium tert-butylate, and the resulting compound (28.1.6) underwent ozonolysis, forming the dicarboxylic acid (28.1.7). Cyclization of this compound to a cyclopentanone derivative lead to the formation of methyl ester of the desired estrone (28.1.8), and demethylation of

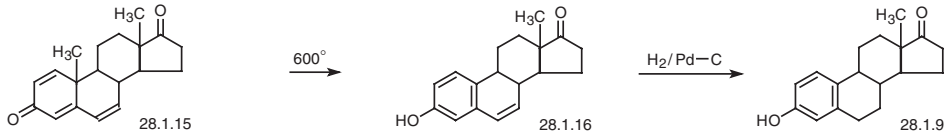
the phenolic hydroxyl group by hydrobromic acid formed the desired estrone (28.1.9) [1,2].



Another way is to synthesize it from available androstenolone (dihydroepiandrosterone) (28.1.10), which in turn is made from dibromocholesterol acetate. Reduction of the double bond in androstenolone by hydrogen using a palladium on carbon catalyst gives a keto-alcohol (28.1.11), which is further oxidized by chromium (VI) oxide to the diketone (28.1.12). This undergoes bromination by molecular bromine in acetic acid, giving a dibromide (28.1.13). The product undergoes dehydrobromination by heating it in collidine, which forms the dieneone (28.1.14). Upon heating this compound at a temperature of about 530 °, methane molecule detached from position 10 to form aromatic ring A and the desired estrone (28.1.9) is formed.



An analogous way of making estrone is demonstrated by starting from 1,4,6-androstatrien-3,17-dione (28.1.15), which when heated to 600 °C is also aromatized and releases methane molecule, forming 8,9-dihydroequilenin. The double bond in this molecule at $C_6 - C_7$ is reduced by hydrogen over a palladium catalyst, giving the desired estrone (28.1.9).



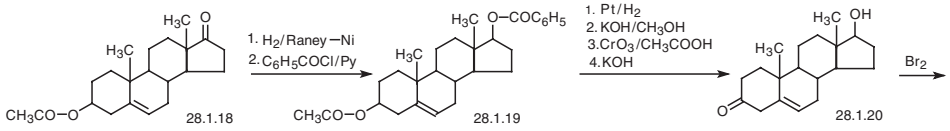
Other methods of synthesizing estrone have been suggested using other available functionalized derivatives of steroids isolated from natural sources as starting material, which are then modified [3–22].

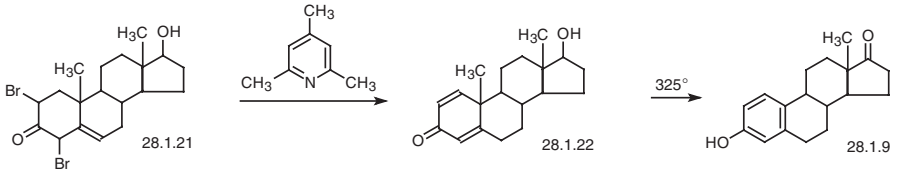
As was already noted, estrone is a follicular hormone necessary for the development of the female body from the time of pubescence to menopause. It is used for insufficient ovary function, for postmenopausal or postcastration disorders, infertility, postmature pregnancies, weak uterine contractions, and after gynecological operations. Synonyms of this drug are foliculin, detoxyestrin, telestrin, bestrone, and many others.

Estradiol: Estradiol, estra-1,3,5(10)-trien-3,17β-diol (28.1.17), is most easily made by reducing the keto-group of estrone by various reducing agents, in particular potassium borohydride [23,24].



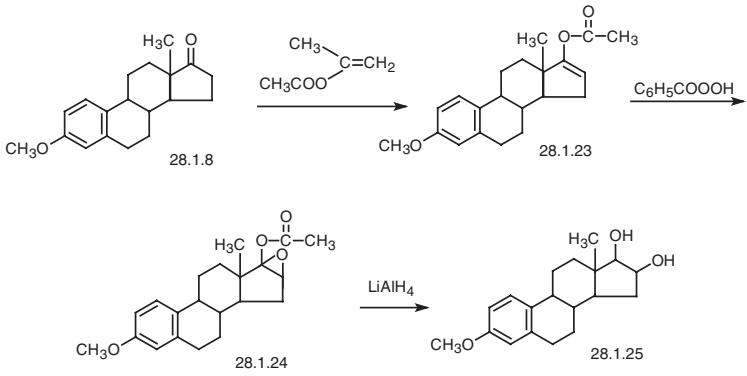
An alternative way of making estradiol is based on using androstenolon acetate (3-acetoxy-5-androsten-17-one) (28.1.18). Reduction of the keto-group in this molecule by hydrogen using a Raney nickel catalyst and subsequent acylation of the resulting hydroxyl group with benzoyl chloride forms a diester (28.1.19). This undergoes a number of transformations, in particular reduction of the double bond at $C_5 - C_6$ with hydrogen over a platinum catalyst, and then mild alkaline hydrolysis in methanol of the acetyl protecting group at C_3, oxidation of the resulting hydroxyl group to a ketone using chromium (VI) oxide, and then the benzoyl protecting group of the hydroxyl at C_{17} is hydrolyzed by an aqueous base, giving the keto-alcohol (28.1.20). This compound undergoes bromination with molecular bromine, just as in the method described for making estrone, which results in the formation of a dibromide (28.1.21). This product undergoes dehydrobromination when heated in collidine, giving a dienone (28.1.22). When heated in tetraline to a temperature about 325 °C, methane molecule cleaves off the position 10 followed by aromatization of the ring A, and the desired estradiol (28.1.17) is formed [25,26]. Estradiol is also made in other ways [27,28].





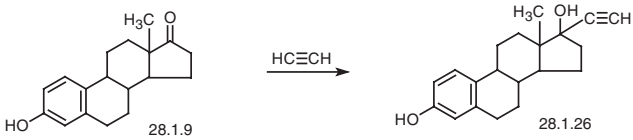
Estradiol is produced in female organisms together with estrone, and if taken in the form of acid ester derivatives it exhibits strong and prolonged estrogenic action. It is used for the same indications as estradiol. Synonyms of this drug are delestrogen, estraval, retestin, deladiol, and others.

Estriol: Estriol, estra-1,3,5(10)-trien-3,16α,17β-*triol* (28.1.25), is proposed to be synthesized from the methyl ester of estrone (28.1.8). Methyl ester of estrone is reacted with isopropenylacetate in the presence of *p*-toluenesulfonic acid, forming the corresponding enolacetate (28.1.23). The resulting enolacetate is oxidized to an epoxide using perbenzoic acid. The resulting epoxide (28.1.24) undergoes reduction by lithium aluminum hydride to



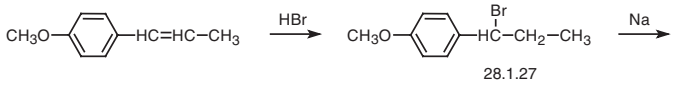
Estriol is significantly less active than estradiol; however, it has a selective ability to stimulate blood flow and restoration of genital epithelium. In addition, using this drug reduces mental symptoms of menopausal syndrome. It is used in the premenopausal and menopausal periods, for skin atrophy and signs of genital degeneration, and so on. Synonyms of this drug are ovestin, hormonin, and others.

Ethinyl estradiol: Ethinyl estradiol, 17α-ethinyl-1,3,5(10)-estratrien-3-17β-diol (28.1.26), is made either by condensing estrone with acetylene in the presence of potassium hydroxide (Favorskii reaction), or by reacting sodium acetylenide in liquid ammonia with estrone [34–36].

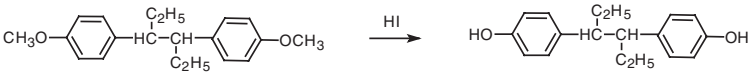


As a matter of fact, ethinylestradiol differs structurally from estradiol in the presence of an ethynyl group at C_{17}. However, this difference in structure leads to a significant increase in estrogenic activity of the drug. Synonyms of this drug are progynon, binordin, gestrol, ovranet, oural, and many others.

Hexestrol: Hexestrol, 4,4′-(1,2-diethylethylene)diphenol (28.1.29), is a derivative of α,β-diphenylethane, and it is a synthetic estrogen. Hexestrol is made in a Wurtz dimerization reaction of 1-bromo-1-(4-methoxyphenyl)propane (28.1.27) in the presence of sodium, magnesium, aluminum, or iron. The initial 1-bromo-1-(4-methoxyphenyl)propane (28.1.27) is made in turn by addition reaction of hydrogen bromide to 4-methoxy-1-propenylbenzene. Subsequent removal of the methoxy protective groups from the resulting dimerization product (28.1.28) using hydroiodic acid gives hexestrol (28.1.29) [37–43].



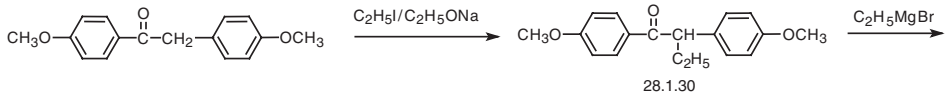
28.1.27



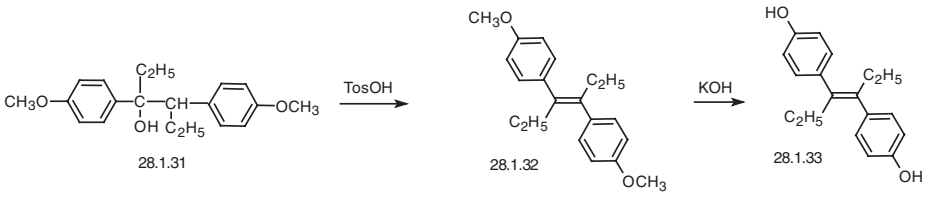
28.1.28 28.1.29

While differing significantly from steroid estrogenic hormones in terms of structure, this drug exhibits all of the characteristic biological properties as these hormones. Hexestrol is used for the same indications as estrone. It is also used for prostate cancer or its hypertrophy in men. Synonyms of this drug are sin-estrol, cycloestrol, and others.

Diethylstilbestrol: Diethylstilbestrol, trans-α,β-diethyl-4,4′-stilbendiol (28.1.34), is proposed to be synthesized in various ways. According to one of them, desoxyansoine is alkylated by ethyl iodide in the presence of sodium ethoxide, and the resulting ketone (28.1.30) is reacted in a Grignard reaction with ethylmagnesium bromide, which forms the carbinol (28.1.31). Dehydration of this compound by distillation in the presence of *p*-toluenesulfonic acid gives dimethyl ether of stilbestrol (28.1.32), methyl groups of which are removed by heating it at high temperatures with potassium hydroxide, thus forming diethylstilbestrol (28.1.33) [44].

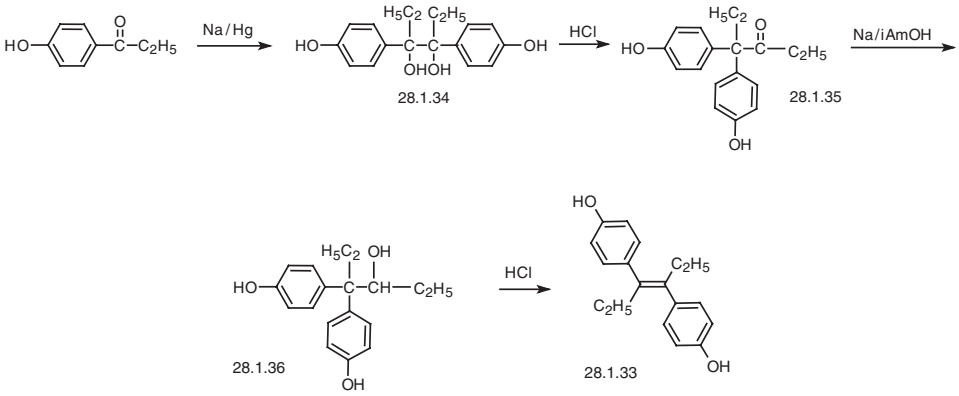


28.1.30



28.1.31 28.1.32 28.1.33

Diethylstilbestrol is also made in the following manner: 4-hydroxypropiophenone undergoes pinacone reduction using sodium amalgam, which gives the corresponding pinacone (28.1.34). Next, the resulting pinacone undergoes a pinacone rearrangement by a reaction with hydrochloric acid, forming ketone (28.1.35). The keto-group in this compound is reduced using sodium in isoamyl alcohol, which gives the corresponding carbinol (28.1.36). The resulting carbinol is treated with hydrochloric acid, which is simultaneously dehydrated and the rearranges into diethylstilbestrol (28.1.33) [45,46].



Diethylstilbestrol is a derivative of stilbene, and it differs from sin-estrol by the presence of a double bond with trans-configuration of the two phenyl groups. In terms of estrogenic activity, this drug surpasses both estrone and hexestrol. Synonyms of this drug are distilben, menopax, stilphostrol, tilosteron, antigestil, and many others.

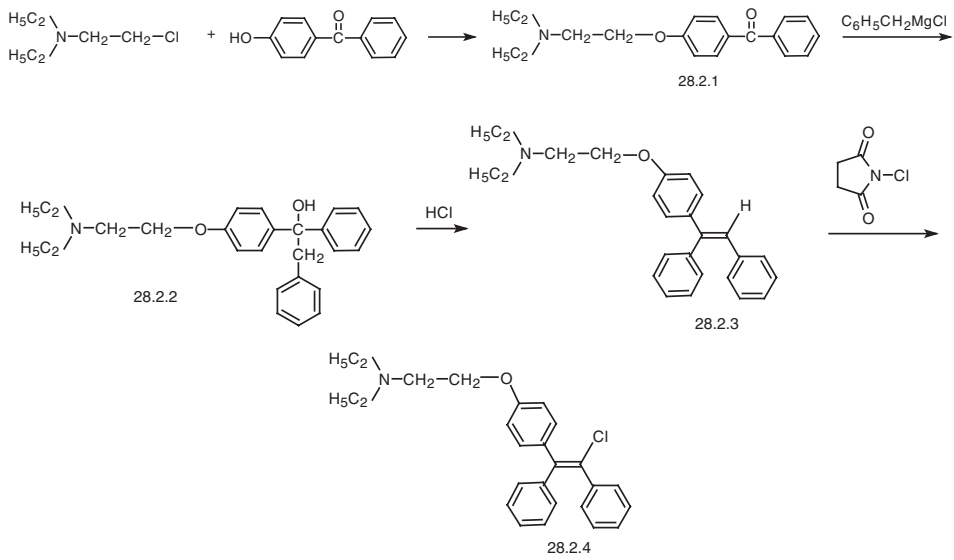
28.2 ANTIESTROGENS

As is evident from the name, antiestrogens are compounds that suppress the effects of estrogens. These are synthetic, nonsteroid substances that likely act by blocking estrogenic receptors, thus suppressing them and the effects of estrogen. By binding with these same receptors in small doses, they exhibit a moderate estrogenic effect, and only in large doses do they exhibit antiestrogenic action. They are used as drugs that enhance functional activity of ovaries typically in female infertility, but also for treating estrogen-receptors positive breast cancer. They are also used for androgenic insufficiency and oligospermia in men.

The main antiestrogenic drugs are used in medical practice as synthetic drugs of clomifene and tamoxifen, which belong to the diethylstilbestrol group.

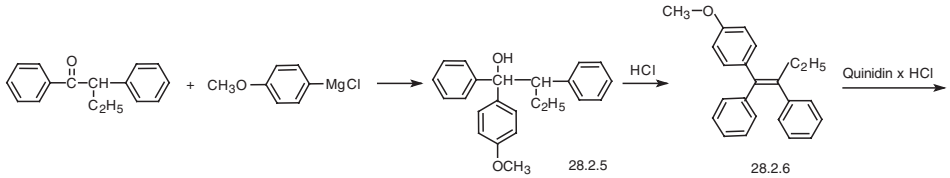
Clomifene: Clomifene, 2-[*p*-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine (28.2.4), is synthesized from 4-hydroxybenzophenone by reacting it with 2-diethylaminoethylchloride in the presence of an alkali, which gives 4-(2-diethylaminoethoxy)benzophenone (28.2.1). This is reacted with benzylmagnesium chloride in a Grignard reaction, forming as a result the corresponding carbinol (28.2.2). Dehydrating this with hydrogen

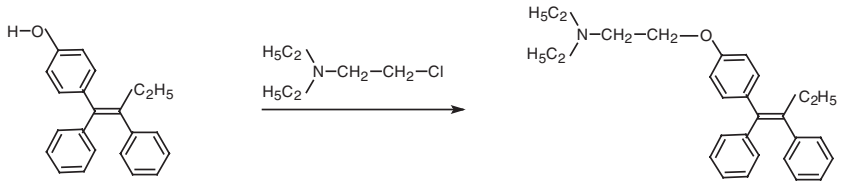
chloride gives 2-[p-(1,2-diphenylvinyl) phenoxy]triethylamine (28.2.4), the vinylic hydrogen atom of which is replaced with a chlorine atom using *N*-chlorosuccinimide, giving clomifene (28.2.4) [47,48].



Clomifene acts by enhancing follicular growth caused by ovulation. The primary indication for using clomifene is induction of ovulation in non-ovulating women who still have some estrogen production. Clomifene is used for infertility in order to increase reproductive properties of oligoovulatory women who have three or four ovulatory cycles per year, leading to normal monthly ovulation. Synonyms of this drug are clomid, serophene, clostibegit, and others.

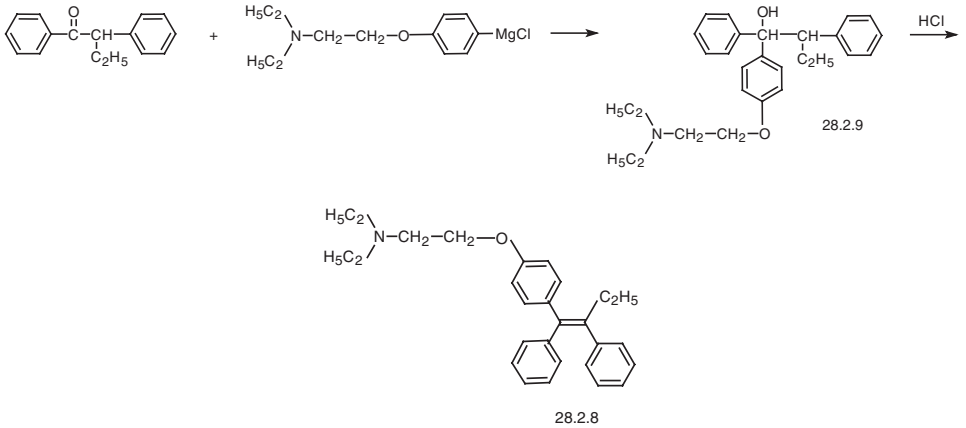
Tamoxifen: Tamoxifen, (*Z*)-2-[*p*-(1,2-diphenyl-1-butenyl)phenoxy]*N*,*N*-dimethylethylamine (28.2.8), is synthesized from α-ethyldezoxybenzoin. Interaction of this with 4-methoxyphenylmagnesium bromide gives the corresponding carbinol (28.2.5). Its dehydration in acidic conditions gives a derivative of stilbene (28.2.6), and further heating of which with quinidine hydrochloride as a demethylating agent gives 2-[*p*-(1,2-diphenyl-1-butenyl)phenol] (28.2.7). The phenolic hydroxyl is further alkylated by dimethylaminoethylchoride using sodium ethoxide as a base, which forms a mixture of *E* and *Z* isomers of the final product. The desired *Z* isomer, tamoxifen (28.2.8) is isolated by fractional crystallization from petroleum ester.





28.2.7 28.2.8

An alternative way of making tamoxifen is the direct interaction in the Grignard reaction of the α-ethyldeoxybenzoin and the 4-(2-dimethylaminoethoxy)phenylmagnesium bromide, and further dehydration of the resulting carbinol (28.2.9) followed by subsequent separation of the mixture of E and Z isomers [49–56].



28.2.9 28.2.8

Tamoxifen is a competitive inhibitor of estradiol. It is used for palliative treatment of estrogen-receptor positive breast cancer. It is used in combination with other chemotherapeutic agents. Synonyms of this drug are nolvadex, cessar, and others.

28.3 PROGESTINS

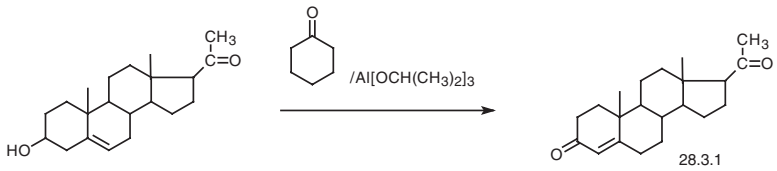
The term progestin includes progesterone and other natural or synthetic compounds with physiological actions analogous to progesterone. Progesterone is a hormone produced by steroidogenic tissues—the corpus luteum and the placenta. Progesterone prepares the endometrium for implantation of the oocyte, prevents ovulation, and facilitates increased glandular tissue in the mammary glands. Its structure is more similar to the structure of the male sex hormone testosterone, differing only in the substituent on C_{17} (acetyl group instead of a hydroxyl group), than to female sex hormones estrone or estrols. Progesterone is considered as a pregnancy hormone since it is made during the entire pregnancy, and it increases excitability and contractability of the uterus while simultaneously preventing new oocytes from maturing. The result of its action is prevention of forming oocytes equal to that of temporarily sterile women. This led to the creation of a

new method of preventing pregnancy by maintaining an artificial hormonal state of pseudopregnancy.

Progestins are used for various menstrual cycle disorders, for functional uterine bleeding of various origins, and as a contraceptive. Progestin therapy is also used to treat endometriosis and endometrial carcinomas. Progesterone is not effective when taken orally due to intensive metabolism, and therefore it is used by either parenteral or transvaginal introduction.

A number of active, synthetic progestins have been made for the use as oral contraceptives that have more activity and more prolonged action than progesterone. Moreover, various conclusions have been made relative to the modification of progesterone structures for making new progestins. It has been shown that progesterone significantly loses its characteristic biological activity when a hydroxyl group is added at position C_{17}. At the same time, esterification of the hydroxyl group by long-chained fatty acids, such as caproic acid, leads to formation of long-lasting, parenterally introduced progestin, oxyprogesterone caproate. Extremely effective progestins are C_{17} ethynyl derivatives linestrenol, norgestrel, and norethindrone, which provide highly effective contraception.

Progesterone: Progesterone, pregn-4-en-3,20-dione (28.3.1), is made by oxidizing pregnenolon with aluminum isopropylate in the presence of cyclohexanone as a proton acceptor (Oppenauer oxidation) [57–63]. Pregnenolon itself is made by subsequent oxidation and further cleavage of the side chain of stigmasterin, a sterin of plant origin that is isolated from soybeans.

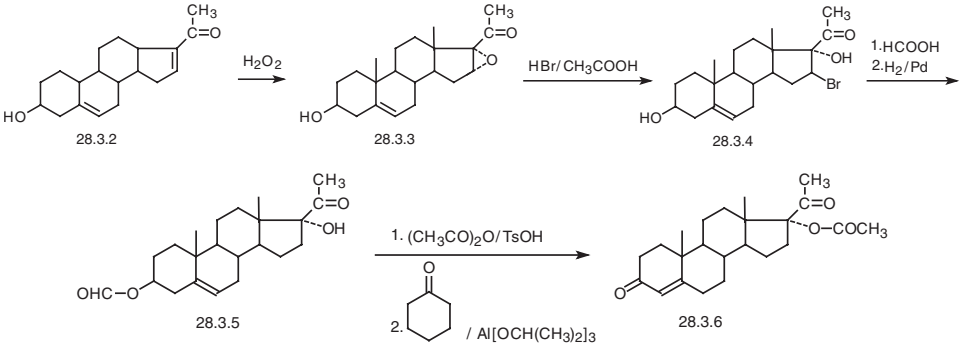


28.3.1

Progesterone is used as a contraceptive, for amenorrhea, for premenopausal syndrome, infertility, incomplete pregnancies, and anovulatory uterine bleeding. Synonyms of this drug are progestasert, sinergon, cyclogest, progestol, proluton, and many others.

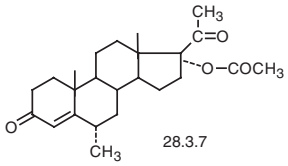
Hydroxyprogesterone: Hydroxyprogesterone, 17α-hydroxypregn-4-en-3,20-dione (28.3.6), is synthesized from dehydropregnenolon (28.3.2). Dehydropregnenolon itself is made by successive decomposition and oxidation of the side spiroketal group of diosgenin—the aglycone of one of the saponins of plant origin isolated from Discorea. The double bond at C_{16}–C_{17} or dehydropregnenolon is oxidized by hydrogen peroxide in the presence of a base to give an epoxide (28.3.3). Interaction of the resulting epoxide with hydrogen bromide in acetic acid forms a bromohydrin (28.3.4). The hydroxyl group of C_3 of the steroid system is formylated by formic acid, and reduction by hydrogen over a palladium catalyst removes the bromine atom at C_{16}, forming the product (28.3.5). The hydroxyl group at C_{17} of this product is acylated by acetic acid anhydride and then the formyl group at C_3 is oxidized by aluminum isopropylate in the presence of cyclohexanone, during which simultaneous isomerization takes place at the double bond, isomerizes from C_5–C_6 to position C_4–C_5, forming the desired hydroprogesterone ester, in the given case an acetate (28.3.6), in which

form it is used in medical practice [64,65]. Other alternative ways of synthesis have been proposed [66–72].



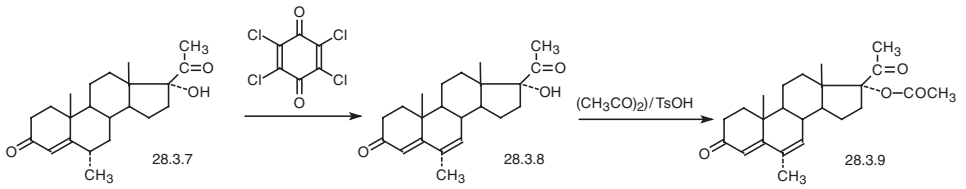
In terms of biological properties, this drug is similar to progesterone; however, it is more stable in the organism and acts slower, producing a prolonged effect. It is used for menstrual disorders, amenorrhea, threatening miscarriage, and other pathological processes associated with corpus luteum insufficiency. Synonyms of this drug are neolutin, singinon, caprosterone, and others.

Medroxyprogesterone: Medroxyprogesterone, 17α-hydroxy-6α-methylpregn-4-en-3,20-dione (28.3.7), differs from hydroxyprogesterone in the presence of an additional methyl group at C_6, which was inserted in different ways [73–77].



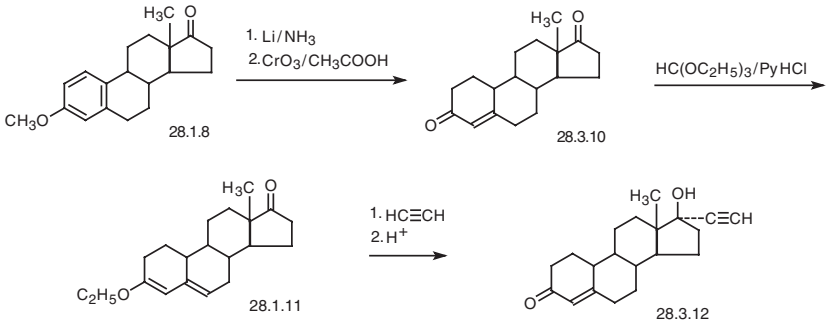
It is used for the same indications as the drugs described above. Synonyms of this drug are amen, curretab, provera, and others.

Megestrol: Megestrol, 17α-hydroxy-6α-methylpregna-4,6-dien-3,20-dione acetate (28.3.9), is a product of dehydrogenation medroxyprogesterone (28.3.7) with chloranil (tetrachloro-*p*-benzoquinone) in the presence of *p*-toluenesulfonic acid, which results in the formation of an additional double bond at position C_6–C_7, and subsequent acetylation of the product (28.3.8) leads to the desired megestrol (28.3.9) by acetic anhydride in the presence of *p*-toluenesulfonic acid [78,79].



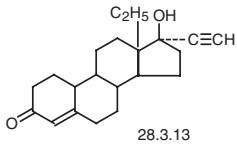
As a representitive of the compounds of the class of progestins, this drug is used for various forms of cancer, in particular cancer of the breast, kidneys, and others. Synonyms of this drug are megestat, niagestin, megeis, and others.

Norethindrone: Norethindrone, 17α-ethynyl-17β-hydroxyestra-4-en-4-one (28.3.12), is made from 19-nor-4-androsten-3,17-dione (28.3.10), which is in turn synthesized by partial reduction of the aromatic region of the 3-O-methyl ether of estrone with lithium in liquid ammonia, and simultaneously of the keto-group at C_{17} to and hydroxyl group, which is then oxidized back to a keto-group by chromium (VI) oxide in acetic acid. The conjugated with the double bond carbonyl group at C_3 is then transformed to dienol ethyl ether (28.3.11) using ethyl orthoformate. The obtained product is ethynylated by acetylene in the presence of potassium *tert*-butoxide. After hydrochloric acid hydrolysis, of the formed O-potassium derivative, during which the enol ether is also hydrolyzed, and the remaining double bond is shifted, the desired norethindrone (28.3.12) is obtained [80–85].



This drug can be used as a carboxylic acid ester, in particular, as an acetate. It causes the mucous membranes of the uterus to move into the secretory phase, which facilitates development of impregnated oocytes. It reduces the excitability and contractility of uterine musculature. It is used for amenorrhea, uterine bleeding, infertility, miscarriage, myoma, mastopathy, endometrial cancer, and other pathologies. Synonyms of this drug are conceplan, norfor, brevinor, and many others.

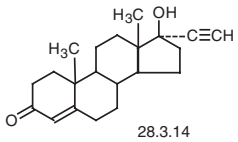
Norgestrel: Norgestrel, (±)-13-ethyl-17α-17β-hydroxyestr-4-en-3-one (28.3.13), differs from norethindrone in the presence of an ethyl group at C_{13} of the steroid system. It is synthesized by ethynylating 18-Methylestr-4-ene-3,17-dione [86–92].



The presence of an ethyl group at C_{13} of the steroid system makes it less active than progesterone; however, it retains activity when taken orally, which provides effective

contraception. Synonyms of this drug are anovlar, norlest, milligynon, loestrin, and others.

Ethisterone: Ethisterone, 17-ethynyl-17-hydroxyandrosten-4-en-3-one (28.4.14), is made by ethynylation of the androstenolon with acetylene and successive oxidation of the hydroxyl group at C_3 of the steroid system [93,94].



28.3.14

Ethisterone differs from norethindrone in the presence of two methyl groups at C_{10} and C_{13} of the steroid system. It makes it less active than progesterone; however, this drug retains its activity when taken orally, which provides highly effective contraception. Synonyms of this drug are pranone, oraluton, pregnoral, and others.

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– 29 –

Male Sex Hormones and Anabolic Steroids

The term androgens includes a number of natural and synthetic compounds that exhibit the masculinizing and anabolic action of testosterone, the main physiological, endogenic, and androgenic hormone.

Androgens, commonly referred to as male sex hormones or anabolic steroids, in particular, testosterone, are produced by male sex glands in the male body. Androgens have masculinizing, anabolic, and growth-stimulating effects. They are responsible for the development of sex organs, secondary sex characteristics, and they control spermatogenesis. Testosterone also facilitates synthesis of proteins in the body (anabolic action), and increases reabsorption of water and a number of ions in the kidneys. The physiological effect of testosterone and other androgens is exhibited over the course of a man's whole life, beginning prenatally, in particular, with the masculinization of the urogenital tract. The male body produces 2.5–10 mg of testosterone daily, mostly in the early morning. Androgens play an extremely important role in spermatogenesis and maturation of sperm, the growth process of muscle mass, tone of voice, and so on. It should be noted that the female body also produces androgens, but in a significantly smaller amount than in males.

Androgenic steroids are used in medicine for replacement therapy in men with insufficient function of the male sex glands, for maturation arrest, impotency, climacteric, and other irregularities, and in women for breast and ovarian cancer and climacteric disorders. Like all steroid drugs, androgens are functionalized derivatives of cyclopentanophenanthrene.

A number of studies were conducted in order to try and create a drug with high-androgenic and low-anabolic potential; however, most attempts were unsuccessful. Because they are structurally similar to testosterone, they exhibit both androgenic and anabolic activity, and are frequently used by athletes for building up muscle mass. At the same time, all of the anabolics currently used have androgenic activity.

29.1 ANDROGENS

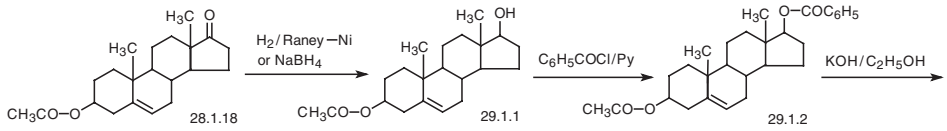
In applied medicine, testosterone esters (propionate, cypionate, and enantate) and a synthetic analog, methyltestosterone, are widely used. In many tissues, testosterone's androgenic

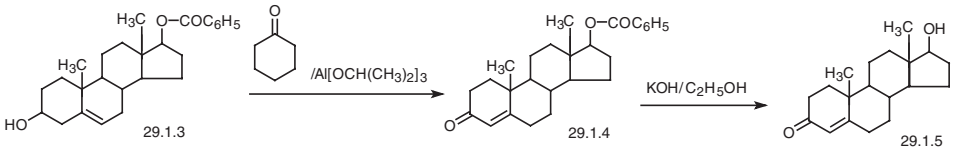
effect depends on the degree to which it is turned into dihydrotestosterone by the enzyme 5-α-reductase in the target tissues. It is believed that all steroids, including testosterone, exhibit their effect by binding with corresponding receptors in target tissues. It has been shown that the affinity to androgenic receptors of the 5-α-dihydrotestosterone is approximately 10 times stronger than that of testosterone. It has also been shown that the binding of androgens with corresponding receptors leads to the synthesis of a few specific proteins in the body, i.e. their use is always accompanied by anabolic action.

A number of synthetic analogs of androgen were made for various reasons, including the goal of prolonging the androgenic effect and for increasing drug absorbance when used via different methods of introduction. Modifying testosterone included esterification of the 17-β-hydroxyl group, and in particular, making testosterone esters, methylation (methyltestosterone, dromstanolone), demethylation (nandrolone), and adding halogens to the steroid skeleton (fluoximesterone), replacing the cyclohexane ring A of the steroid structure with a tetrahydropyrane ring (oxandrolone), and adding an additional heterocyclic ring to the steroid structure (stanozolol).

Androgens are used for therapy of androgen-deficient conditions such as hypofunctioning testicles, eunuchism and eunuchoidism, castration, impotence, climacteric conditions, and also for breast and ovarian cancer in women under 60 years.

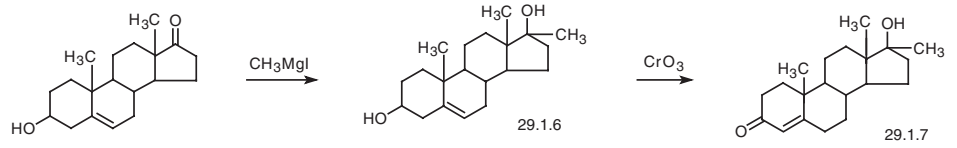
Testosterone: Testosterone, 17β-hydroxyandrost-4-ene-3-one (29.1.5), is made in a number of ways from different substances, including cholesterol, although it is most often made from androstenolone acetate. In order to do this, the keto-group at C_{17} of the steroid system of androstenolone acetate is reduced to a hydroxyl group by either sodium borohydride, lithium aluminum hydride, or hydrogen over Raney nickel, all of which result in a 17β-hydroxy compound. In the given example, reduction by sodium borohydride or hydrogen over Raney nickel leads to the formation of 3β-acetoxy-5-androsten-17β-ol (29.1.1). The hydroxyl group resulting from reduction then undergoes acylation by benzoyl chloride in pyridine, which forms a diester (29.1.2). After that, taking into consideration the differences in the acidic region of the two ester groups present in the molecule as well as the long-known fact that 17-hydroxy-group ester derivatives are harder to hydrolyze than 3-hydroxy-group ester derivatives, the acetyl protection of the hydroxyl group at C_3 is removed by selective hydrolysis using potassium hydroxide in ethanol, and the resulting alcohol (29.1.3) is oxidized to a ketone (29.1.4) by aluminum isopropylate in the presence of cyclohexanone as a hydrogen acceptor, during which isomerization of the double bond from position C_5–C_6 to C_4–C_5 simultaneously takes place. Subsequent hydrolysis of the remaining ester region of the molecule using an alkali gives the desired testosterone (29.1.5) [1–6]. When necessary to convert this into the corresponding ester (propionate, enantate, cypionate, and a few other testosterone esters), the necessary acylation can be accomplished.





Testosterone (esters) are used medicinally for maturation arrest, functional problems in the reproductive system, hypertrophy of the prostate gland, climacteric disorders in men, a few forms of infertility caused by abnormal spermatogenesis, post-castration syndrome, and endocrine impotence. Testosterone is sometimes used to treat women with reproductive organ and breast tumors, climacteric disorders, and when estrogen drugs are counterproductive. When taken orally, testosterone itself is inactive, and therefore it is generally used in the form of carboxylic acid esters (propionate, enantate, cypionate, and a few forms of testosterone esters). Synonyms of this drug are histerone, malogen, menopax, testoral, and others, while synonyms of testosterone esters include andronate, depotest, everon, and many others.

Methyltestosterone: Methyltestosterone, 17β-hydroxy-17α-methylandrost-4-en-3-one (29.1.7), is also synthesized from androstenolone by reacting it with methylmagnesiumiodide, forming the corresponding tertiary alcohol (29.1.6), and subsequent oxidation of the hydroxyl group at C_3 to a ketone using chromium (VI) oxide. Simultaneous isomerization of the double bond takes place under the reaction conditions, giving the desired methyltestosterone (29.1.7) [7–10].

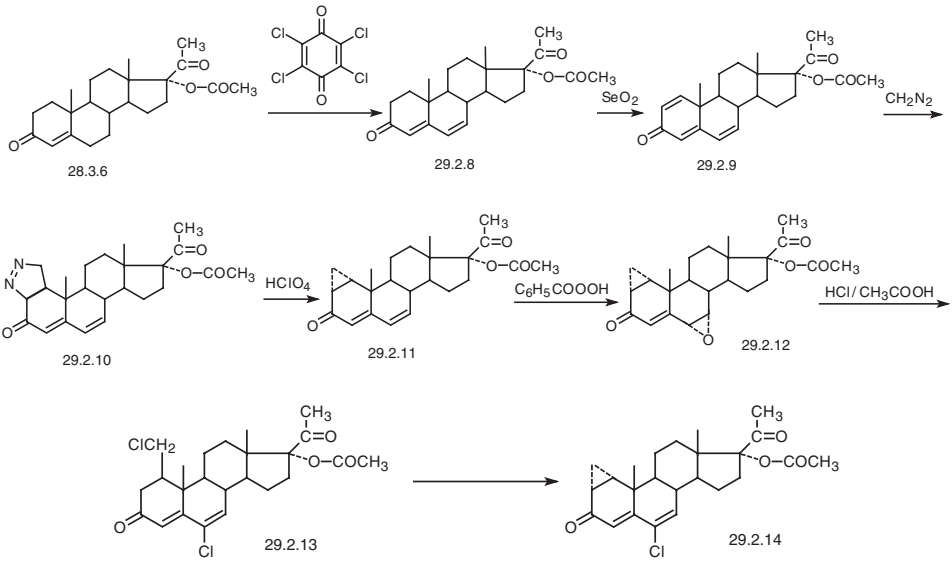


Methyltestosterone is a synthetic analog of testosterone that possesses all of the properties of testosterone, exhibiting stimulatory action on the development of male sex organs and secondary sex characteristics, although it is not degraded by enzymes in the gastrointestinal tract, and therefore it can only be taken orally. It is used for the same indications as testosterone for sexual underdevelopment, functional problems of the reproductive system, and the vascular nerve disorders associated with climacteric problems in men. It is also used for dysfunctional uterine bleeding in premenopausal and menopausal women as well as for breast and ovarian cancer. Synonyms of this drug are androral, testoral, oraviron, and others.

29.2 ANDROGEN ANTAGONISTS

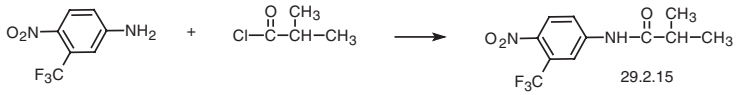
There are also androgen antagonists—drugs that lower production of androgens by male sex glands and that suppress spermatogenesis by blocking androgen receptors. These drugs include cyproterone and flutamide.

Cyproterone: Cyproterone, 6-chloro-17α-hydroxy-1α,2α-methylenpregna-4,6-dien-3,20-dione acetate (29.2.14), is made from 17α-hydroxyprogesterone acetate (28.3.36). Dehydrating this using chloranyl (tetrachloro-*p*-benzoquinone) results in formation of an additional double bond at position C_6–C_7 (29.2.8), and subsequent dehydration using selenium dioxide to form the corresponding divinyl ketone, 17α-acetoxy-1,4,6-pregnatrien-3,20-dione (29.2.9). Reacting this with diazomethane results in a 1,3-dipolar addition reaction at C_1–C_2 of the double bond of the steroid system, which forms a derivative of dihydropyrazole (29.2.10). This compound cleaves when reacted with chloric acid, releasing nitrogen molecules and forming a cyclopropane derivative (29.1.11). Next, the double bond at C_6–C_7 is selectively oxidized by benzoyl peroxide, and the resulting epoxide (29.2.12) undergoes a reaction with hydrochloric acid in acetic acid, resulting in the formation of chlorine and its subsequent dehydration, and a simultaneous opening of the cyclopropane ring, forming the compound (29.2.13). Heating this in collidine results in intramolecular alkylation, causing cyclization into a cyclopropane ring, which forms cyproterone (29.2.14) [11,12].



Cyproterone is used to control sexual attraction in men in cases of sexual deviations, as well as for inoperable prostate gland carcinoma. In women, it is used for severe cases of androgenization, and in children with idiopathic premature sexual maturity. Synonyms of this drug are cyprostat, androcur, daian, and others.

Flutamide: Flutamide, 4′-nitro-3′-trifluoromethylisobutyranilide (29.2.15), a nonsteroid antagonist of androgens, is made by acylating 4-nitro-3-trifluoromethylaniline with isobutyric acid chloride [13–15].

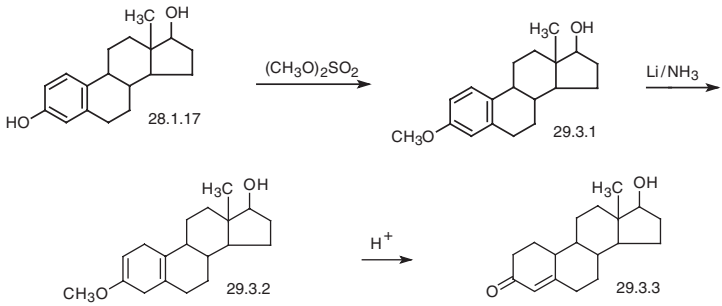


Flutamide is a nonsteroid drug that possesses antiandrogenic action. It blocks androgens from binding with target tissues, thus preventing androgen action. The mechanism of action is possibly also linked with a halt in dihydrotestosterone transport. It facilitates a reduction in size and density of the prostate gland, and it reduces the amount of metastases in such cancer, for which it is used in palliative treatment of prostate gland cancer. Synonyms of this drug are fugerel, eulexin, and others.

29.3 ANABOLICS

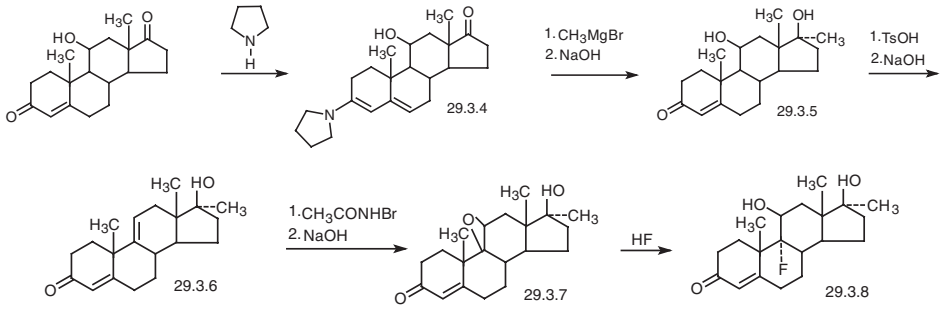
In searching for new androgenic compounds, substances very similar in structure to testosterone were made that have more pronounced, and even selective anabolic activity. Their most characteristic property is the ability to stimulate protein synthesis in the body, increase nitrogen exchange, slow down removal of nitrogen, phosphorous, potassium, and calcium from the body, which results in increased muscle mass, development of osseous tissue, the general condition of the body, and increased appetite. Anabolic steroids are used for cachexy, asthenia, after radiation therapy, osteoporosis, and for stimulating the regeneration processes.

Nandrolone: Nandrolone, 17β-hydroxyester-4-en-3-one (29.1.7), is made from estradiol (28.1.17). The phenol hydroxyl group undergoes methylation by dimethylsulfate in the presence of sodium hydroxide, forming the corresponding methyl ether (29.3.1), and then the aromatic ring is reduced by lithium in liquid ammonia, which forms an enol ether (29.3.2). Hydrolyzing this compound with a mixture of hydrochloric and acetic acids leads to the formation of a keto group, and simultaneous isomerization of the double bond from C_5–C_{10} to position C_4–C_5 gives the desired nandrolone (29.3.3) [16–19]. Upon necessity of using it in the form of acid esters, the product is acylated by corresponding acid derivatives [20].



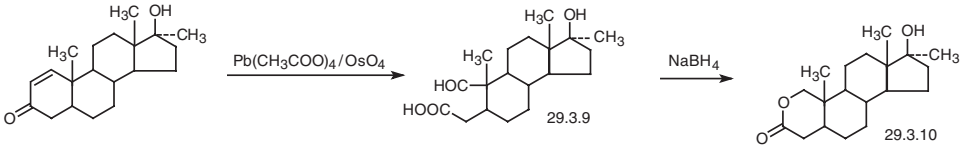
Nandrolone facilitates formation of body muscle mass and strengthens the process of osseous tissue development. The main indications for using nandrolone, as well as other anabolic steroids, are abnormal protein anabolism, asthenia, diseases accompanied by protein loss, adrenal insufficiency, steroid diabetes, and prolonged condition of sluggishness. Synonyms of this drug used in the form of acid esters are retabolil, fenobolin, eubolin, and many others.

Fluoxymesterone: Fluoxymesterone, 9-fluoro-11β,17β-dihydroxy-17α-methylandrost-4-en-3-one (29.3.8), is made from 11β-hydroxy-4-androsten-3,17-dione, which is reacted with pyrrolidine to give a dieneamine (29.3.4). This undergoes a reaction with methylmagnesiumiodide, which after hydrolysis forms 11β,17β-dihydroxy-17α-methylandrost-4-en-3-one (29.3.5). Dehydration of this compound by selective tosylation of the secondary hydroxyl group at C_{11} using *p*-toluenesulfonyl chloride and subsequent reaction with a base gives the diene (29.3.6), and the double bond at C_9–C_{11} is transformed to an epoxide (29.3.7) by subsequent reaction with *N*-bromoacetamide in a wet solvent (source of HOBr), and a base. Further reaction with hydrogen fluoride results in an opening of the epoxide ring and the formation of the desired fluoxymesterone (29.3.8) [21–30].



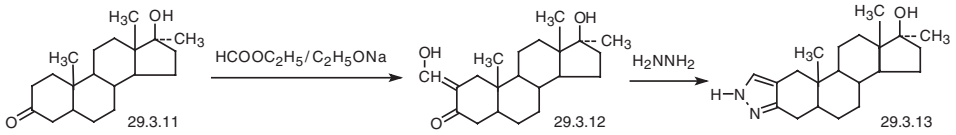
Fluoxymesterone is used for the same indications as nandrolone. Synonyms of this drug are ultandren, halosterin, halotestin, and others.

Oxandrolone: Oxandrolone, 17β-hydroxy-17α-methyl-2-oxa-5-androstan-3-one (29.3.10), is made by oxidation of the C_1–C_2 double bond of 17β-hydroxy-17α-methyl-1-androsten-3-one by a mixture of lead tetraacetate and osmium tetroxide with an opening of the A ring of the steroid system, which forms an aldehyde acid (29.3.9). Upon reducing the aldehyde group with sodium borohydride, intramolecular cyclization takes place, directly forming a lactone (29.3.10), which is the desired oxandrolone [31,32].



Oxandrolone is used for the same indications as nandrolone. Synonyms of this drug are vasorome, anavar, and others.

Stanozol: Stanozol, 17α-methyl-5α-androstano[3,2-c]pyrazol-17β-ol (29.3.13), is made by reducing the double bond at C_4–C_5 in methyltestosterone, which has independent interest as an anabolic drug of mestanolone (29.3.11). Mestanolone undergoes formylation with ethylformate in the presence of sodium ethoxide, forming a 2-formyl (oxymethylene) derivative (29.3.12), which upon reaction with hydrazine easily cyclizes to the desired stanazole (29.3.13), which is a pyrazol-condensed steroid system [33,34].



Stanzol is used for the same indications as nandrolone. Synonyms of this drug are stromba, vinstrol, and others.

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– 30 –

Antineoplastics

Cancer is a disease present in people and animals in which the structure and normal function of body tissues are disrupted. The exact etiology of most types of cancer is unknown. However, it is well known that infections, environmental factors (chemical substances, foreign particles, radiation), and genetic factors can induce transformation of normal cells to neoplastic cells, i.e. those that multiply and function abnormally.

Cancer can be characterized by the following parameters: Cells begin to divide uncontrollably because the mechanisms that control growth are disrupted. Cells cease to differentiate. Cells begin to exhibit invasiveness and gain the ability to metastasize, i.e. to appear in tissues separate from the place of initial localization. Cells begin to intensely synthesize macromolecules from nucleosides and amino acids.

Treatment of cancer includes surgical intervention, radiation, immunotherapy, and chemotherapy using neoplastic drugs. Chemotherapy is currently used in addition to surgical intervention in order to remove possible metastatic cells that still remain. Moreover, some types of tumors are currently treated first with chemotherapeutic agents.

As already noted, treatment of patients with cancer depends on the success of removing or destroying all cancerous cells in the body. Even with the best detection, only a certain percent of diagnosed patients are cured.

The reason is not because of bad diagnostic equipment, but because cancer frequently spreads beyond the area of initial localization, making local treatment inadequate. Thus, surgical intervention, chemotherapy, and radiation are the three composite ways to treat cancer; however, only chemotherapy effectively cures systemic disease.

Cancer chemotherapy is generally nonspecific. This means that drugs kill not only cancerous cells, but also normal cells. Because of the fact that it is nonspecific, special strategies are developed to increase the potential of destroying cancerous cells and lessening toxic effects on normal tissue. A decade of experience showed that the growth of tumor cells is much more intensive than that of cells of the tissue from which they were formed. The paradox, however, lies in the fact that contrary to expectation, normal tissues are often regenerated faster than cancer cells. Therefore, after the cytoinhibitory action of certain drugs, normal tissues can be restored after chemotherapy.

Drugs used to treat cancer are subdivided into six groups: antimetabolites, alkylating agents, antibiotics, drugs isolated from plants, hormones, and a group of substances not included in the classifications listed above, which are examined in another section.

30.1 ANTIMETABOLITES

Antimetabolites are structural analogs of ordinary cellular metabolites such as folic acid, pyrimidines and pyrines, which after being introduced in the body, begin to imitate the structure of ordinary metabolites. They compete with metabolites to block important reactions leading to formation of DNA/RNA.

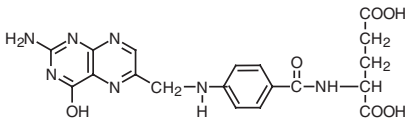
So, by competing with natural pyrines and pyrimidines in metabolic schemes, they interfere with the synthesis of nucleic acids, thus being included in place of ordinary metabolites. This leads to the formation of cellular products, which cannot function normally. Thus, cellular processes of division and multiplication are disrupted.

In addition, because they are structural analogs of natural substances, antimetabolites can act not only by being introduced into the metabolic process and form "false" nonfunctional metabolites, but also by inhibiting catalytic functions of certain enzymes or enzyme systems.

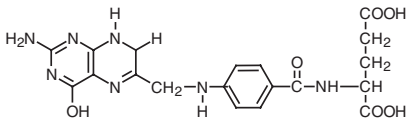
Antimetabolites are subdivided into three groups: folic acid antagonists (methotrexate), purine antagonists (mercaptopurine, thioguanidine), and pyrimidine antagonists (fluorouracil, floxuridine, cytarabine).

30.1.1 Folic acid antagonists

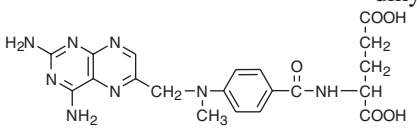
Folic acid antagonists, in particular methotrexate, act by competitively binding with the enzyme dehydrofolate reductase in place of folic acid. This is the general starting compound for enzyme-catalyzed reactions of transferring a methyl group. Folates are carriers of a single carbon group (methylating group) necessary during purine and pyrimidinethimidylate synthesis, and in particular for methylating deoxyuridine monophosphate to deoxythimidine monophosphate. Dihydrofolate reductase's affinity with antimetabolics is much higher than with usual substrates—folic acid and its reduced forms. Because of the pronounced affinity of dehydrofolatereductase to methotrexate, even large doses of folic acid introduced simultaneously turn out to be useless in preventing the effects of methotrexate.



folic acid



dihydrofolic acid

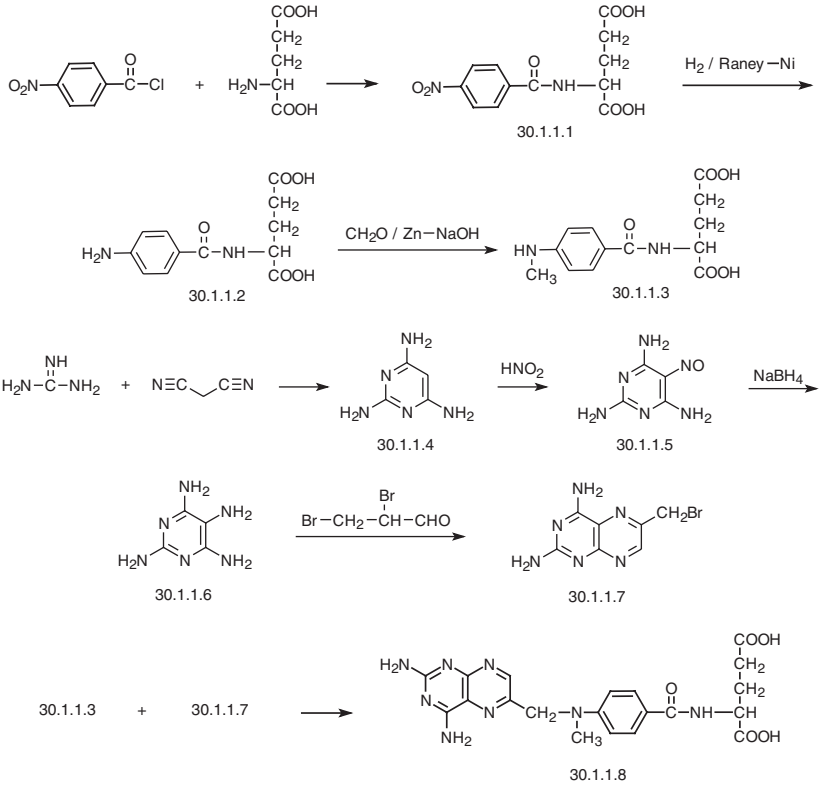


methotrexate

Methotrexate: Methotrexate, *N*-[*p*-[[2,4-diamino-6-piperidinyl)methyl]methylamino]-benzoyl]-L-(±)-glutamic acid (30.1.1.8), is made by reacting *N*-(4-methylaminobenzoyl)glutaminic acid (30.1.1.3) with 2-amino-4-hydroxyl-6-bromomethylpteridine

(30.1.1.7). In order to do this, *N*-(4-methylaminobenzoyl)glutaminic acid (30.1.1.3) is synthesized from 4-nitrobenzoyl chloride, which is reacted with L-glutamic acid, forming *N*-(4-nitrobenzoyl)glutamic acid (30.1.1.1), the nitro group of which is reduced to an amino group using hydrogen over Raney nickel, which gives *N*-(4-aminobenzoyl)glutamic acid (30.1.1.2). This undergoes reductive methylation using formaldehyde and hydrogen, which forms *N*-(4-methylaminobenzoyl)glutamic acid (30.1.1.3).

The second part of the methotrexate molecule, 2-amino-4-hydroxy-6-bromomethylpteridine (30.1.1.7), is made from 2,4,6-triaminopyrimidine (30.1.1.4), which is easily synthesized by reacting malonic acid dinitrile with guanidine. This is nitrosylated by anhydrous nitrous acid to 2,4,6-triamino-5-nitrosopyrimidine (30.1.1.5), and then it is reduced by sodium borohydride to 2,4,5,6-tetraaminopyrimidine (30.1.1.6). Upon reacting this with 1,2-dibromopropionic aldehyde, the product of attaching bromine to acrolein, 2-amino-4-hydroxy-6- bromomethyl-pteridine (30.1.1.7) is formed. Alkylating the amine nitrogen atom of *N*-(4-methylaminbenzoyl)glutamic acid (30.1.1.3) with resulting bromide (30.1.1.7) gives methotrexate (30.1.1.8) [1–8].



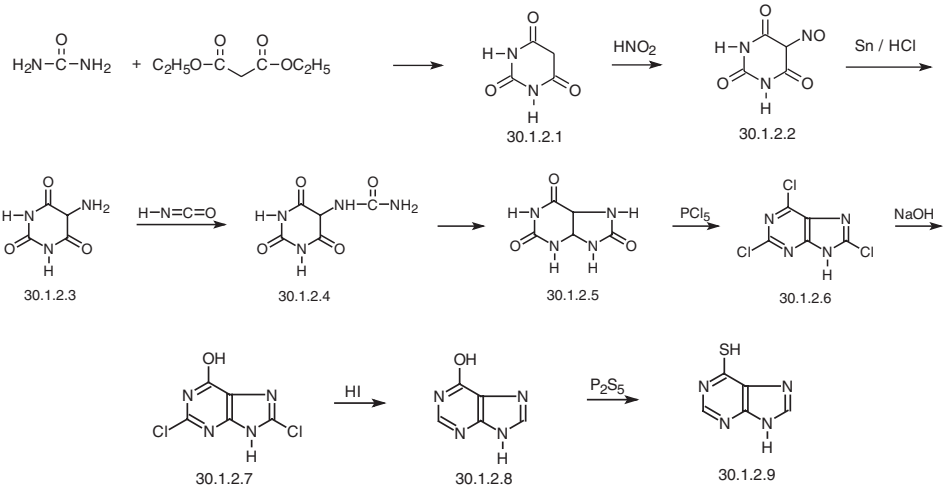
Methotrexate is used to treat severe lymphatic leukemia, choriocarcinoma, non-Hodgkin's lymphoma, bone carcinoma, as well as head, neck, breast, and lung tumors. Synonyms of this drug are farmitrexate, ledertrexate, ematexate, maxtrex, folex, mexate, and others.

30.1.2 Purine derivatives

Of the many synthetic analogs of purine, mercaptopurine and thioguanine turned out to be the most effective in chemotherapy for cancer.

These compounds inhibit synthesis of purine nucleotides, which are made up of purine bases and phosphorylated ribose. Both compounds must be transformed into nucleotides by adding a phosphoribosyl fragment.

Mercaptopurine: Mercaptopurine, 6-purinthiol, is made from uric acid (30.1.2.5), which is synthesized from barbituric acid (30.1.2.1). Barbituric acid (30.1.2.1) is easily made by condensing urea with malonic ester and then nitrosylating it with nitrous acid. The nitrosoderivative (30.1.2.2) is reduced by hydrogen (obtained *in situ* by reacting tin with hydrochloric acid) to an amine (uramil) (30.1.2.3), and then reacted with isocyanic acid, which forms pseudouric acid (30.1.2.4). This undergoes cyclization to uric acid (30.1.2.5) when heated in the presence of hydrochloric acid. Upon reacting phosphorous pentachloride with uric acid, 2,6,8-trichloropurine (30.1.2.6) is formed. The three chlorine atoms in trichloropurine differ significantly in terms of reactivity for nucleophilic substitution. The chlorine atom at C_6 is much more active than the chlorine atom at C_2, and this is more active than the chlorine atom at C_8, which allows subsequent manipulation by them. Interaction of 2,6,8-trichloropurine (30.1.2.6) with sodium hydroxide allows to replace the chlorine atom at C_6, forming the dichloro-derivative (30.1.2.7), which is then reduced by hydriodic acid to hypoxanthine (30.1.2.8). Upon reaction with phosphorous pentasulfide, hypoxanthine is transformed into mercaptopurine (30.1.2.9) [9–15].

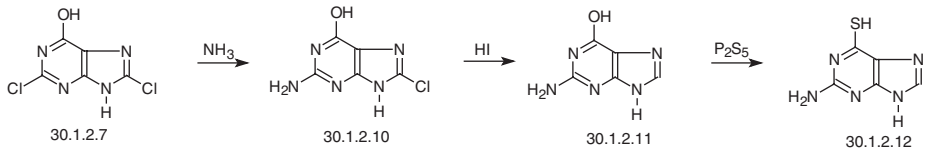


In the body, mercaptopurine is converted into an active form of the drug, nucleotide 6-thioinosin-5-phosphate. Nucleotide 6-thioinosin-5-phosphate inhibits the first step in the synthesis of inosin-5-phosphate by negative feedback, preventing its transformation to adenosine or guanine nucleotides, which are necessary for synthesizing DNA. Thus,

mercaptopurine inhibits synthesis and interconversion of purine nucleotides, which leads to a halt in DNA synthesis in proliferating cells during the cell cycle.

Mercaptopurine is used for treatment of lymphobastomas, myeloblastoma leucosis, and to treat neuroleukemia. Synonyms of this drug are isimpur, classen, purinethol, and others.

Thioguanine: Thioguanine, 2-aminopurin-6-thiol (30.1.2.12), is made from 2,8-dichloro-6-hydroxypurine (30.1.2.7), in which the second chlorine atom at C_2 is replaced with an amino group when reacted with ammonia, forming 2-amino-8-chloro-6-hydroxy-purine (30.1.2.7), which is then reduced by hydrogen iodide to 2-aminopurin-6-ol (30.1.2.11). Replacement of the hydroxyl group with a mercapto group at C_6 is carried out by reacting it with phosphorous pentasulfide, which forms thioguanine (30.1.2.12) [14, 16–20].



30.1.2.7 30.1.2.10 30.1.2.11 30.1.2.12

In the body, thioguanine is converted into an active form, 6-thioguanin-5-phosphate. The main mechanism of its action consists of including its triphosphate form into DNA, replacing the guanine nucleotide, and inhibiting DNA synthesis.

Mercaptopurine is important as a drug of supportive therapy in treatment of both adults and children. Thioguanine may have specific clinical use, or may be used in combination with other drugs in severe myelogenous therapy. Synonyms of this drug are lanvis and others.

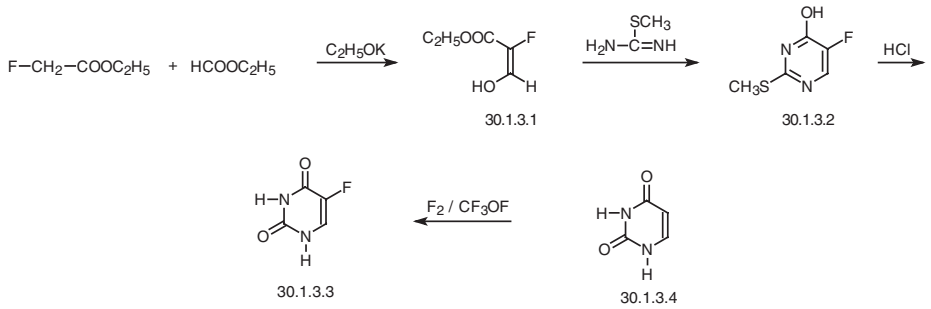
30.1.3 Pyrimidine derivatives

A large number of fluorinated analogs of pyrimidine are synthesized as potential anticancer drugs. Fluorouracil and fluoxuridine have been studied the most. It is possible that the most important mechanism of action of fluorinated pyrimidines is the inhibition of thymidylate synthetase synthesis, thus affecting the process of DNA production. This action is accompanied by formation of an active metabolite, 5-fluorodeoxyuridinomonophosphate from both fluorouracil and fluoxuridine. 5-fluorodeoxyuridinomonophosphate forms a complex with reduced folate N^5,N^{10}-methylentetrahydrofolate. This complex inhibits thymidylate sythetase and reduces methylation of 2-deoxyuridine acid for formation of thymidylic acid. The resulting thymidine deficit causes damage and death of cells.

It is also believed that the triphosphorylated form of fluorinated analogs of pyrimidine can be included in RNA, and can have an effect on protein synthesis.

Fluorouracil: Fluorouracil, 4-fluorouracil (30.1.3.3), is made by condensing the ethyl ester of fluoroacetic acid with ethylformate in the presence of potassium ethoxide, forming hydroxy-methylenfluoroacetic ester (30.3.1), which cyclizes by reacting it with *S*-methyl-isothiourea to 2-methylthio-4-hydroxy-5-fluoropyrimidine, which is subsequently hydrolyzed by hydrochloric acid to fluorouracil (30.1.3.3) [21,22]. An alternative method of synthesizing

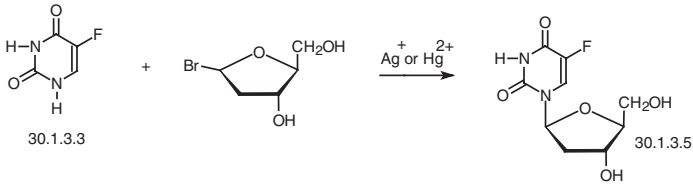
5-fluorouracid is direct fluorination of uracil with fluorine or trifluoromethylhypofluoride [23–28].



Fluorouracil acts by inhibiting synthesis of pyrimidine, and thus the formation of DNA.

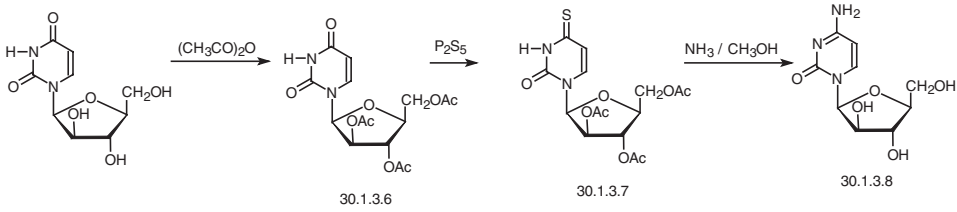
Fluorouracil is used to treat carcinomas of the head, neck, colon, rectum, breast, stomach, bladder, pancreas, and for actinic and solar creatitis. Synonyms of this drug are effluderm, fludix, fluoroblastin, arumel, benton, lifril, and others.

Fluoxuridine: Fluoxuridine, 5-fluoro-1-(2-deoxyribofuranosyl)-pyrimidin-2,4-(1*H*,3*H*)-dione (30.1.3.5), is a pyrimidine nucleotide made by reacting fluorouracil (30.1.3.3) with 2-deoxyribofuranosylbromide in the presence of silver or mercury salts [29–33].



Fluoxuridine is administered by infusive introduction into the hepatic artery for metastases in the liver. Synonyms of this drug are FUDR and others.

Cytarabine: Cytarabine, 4-amino-1-β-arabinofuranosyl-2(1*H*)pyrimidone (30.1.3.8), is made from 1-β-D-arabinofuranosyluracil by preliminary acylation of the hydroxyl group, forming a triacetyl derivative (30.1.3.6), and subsequent replacement of the carbonyl group at position 4 of the pyrimidine ring with a thiocarbonyl group using phosphorous pentachloride, and finally replacing the mercapto group of 30.1.3.7 with an amino group using ammonia and simultaneous hydrolysis of the acetyl-substituted groups, giving cytarabine (30.1.3.8) [34–38].



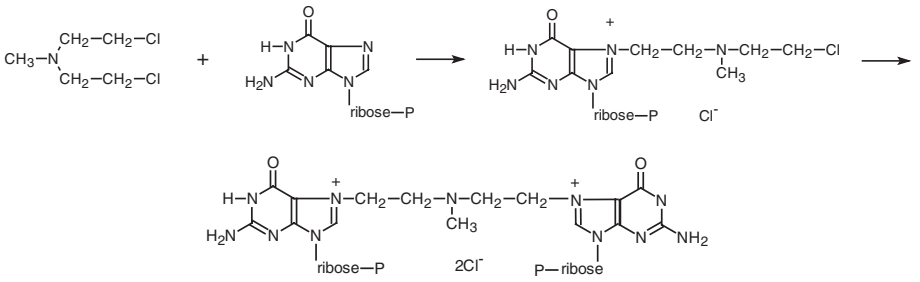
Cytarabine, like the drugs described above, also acts by inhibiting synthesis of pyrimidines and thus DNA in cells.

Cytarabine is an effective antimetabolite in treating leukemia. Like other pyrimidine antimetabolites, cytarabine must be "activated" by initially transforming into the corresponding nucleotide. The active form of the drug is cytarabine triphosphate. Cytarabine is used for all types of leukemia. Synonyms of this drug are cytosine, arabinoside, and ara-C.

30.2 ALKYLATING AGENTS

Alkylating agents are highly reactive compounds capable of forming covalent bonds with nucleofile regions of intracellular macromoleculs, containing amino-, hydroxy-, sulfhydril-, and carboxy- groups, as well as nitrogen heterocycles, such as nucleic acids, phosphates, aminoacids, and proteins. As a rule, alkylating drugs used in medicine alkylate position N_7 of guanine. In principle, however, alkylation can occur and occurs at O_6 or N_3 of guanine, at N_1, N_3, or N_7 of adenine, or at N_3 of cytosine. During this process, many parts of cells, including DNA, RNA, proteins, membrane components, and so on, are also alkylated. However, according to a working hypothesis, the main cytotoxic effect of these compounds can be explained by their ability to bind with DNA nucleotides themselves causing not only alkylation, but also ring cleavage, abnormal base-pairing. This leads to an incorrect reading of information from DNA, and as a rule, cells die because of intervention in replication and mitosis. Bifunctional alkylating agents have the possibility of forming inter-chain bonds in DNA, causing cross-linking of two chains of DNA, and are considered more toxic than monofunctional alkylating agents.

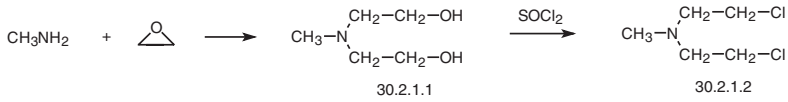
The schematic mechanism of the action of alkylating drugs, mechlorethamine for example, the most simple of them all, can be explained by the following scheme.



Despite the fact that alkylating agents exhibit a common mechanism of action, their clinical use varies depending on differences in pharmacokinetics, metabolism, lipid solubility, ability to penetrate membranes, and toxicity. They can be classified as nitrogen-containing mustard derivatives (mechorethamine, chlorambucil, melfalan, cyclophosphamide, ifosfamide), derivatives of ethylenimine (thiotepa), nitrosoureas (carmustine, lomustine, streptozocin), alkylsulfonates (busulfan), and derivatives of platinum (*cis*platin, carboplatin).

30.2.1 Nitro-containing mustard derivatives

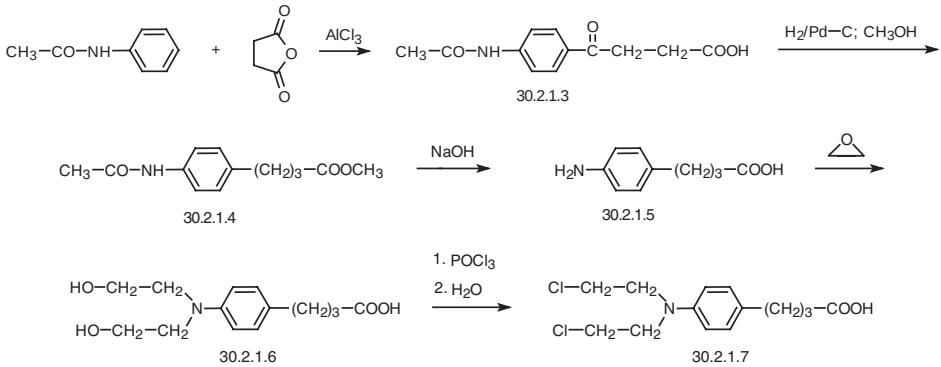
Mechlorethamine: Mechlorethamine, bis-(2-chloroethyl)methylamine (30.2.1.2), is made by reacting methylamine with ethylene oxide, forming bis-(2-hydroxyethyl)methylamine (30.2.1.1), which upon reaction with thionyl chloride turns into the desired mechlorethamine [39–41].



30.2.1.1 30.2.1.2

Mechlorethamine is widely used intravenously in combination with other drugs to treat Hodgkin's disease, lymphosarcoma, leukemia, and bronchogenic carcinoma. Synonyms of this drug are azotoyperit, chlorethamine, chlorethazide, mustine, and many others.

Chlorambucil: Chlorambucil, 4-[*p*-[bis-(2-chloroethyl)amino]phenyl]butyric acid (30.2.1.7), is made from acetanilide and succinic anhydride. In the first stage of synthesis, acetanilide is acylated by succinic anhydride, giving 4-(4-acetaminophenyl)-4-ketobutyric acid (30.2.1.3). The keto group in this compound is reduced by hydrogen in a methanol solution using palladium on carbon as a catalyst. This results in the formation of the methyl ester of 4-(4-acetaminophenyl)-butyric acid (30.2.1.4). This is treated with an alkali in order to hydrolyze both the amide and ester parts of the molecule, which forms 4-(4-aminophenyl)butyric acid (30.2.1.5), which upon reaction with ethylene oxide gives 4-[*p*-[bis(2-hydroxyethyl) amino]phenyl]butyric acid (30.2.1.7). Replacing all of the hydroxyl groups in this compound using phosphoryl chloride and subsequent treatment with water to hydrolyze the resulting intermediate acid chloride to an acid gives chlorambucil (30.2.1.7) [42–46].

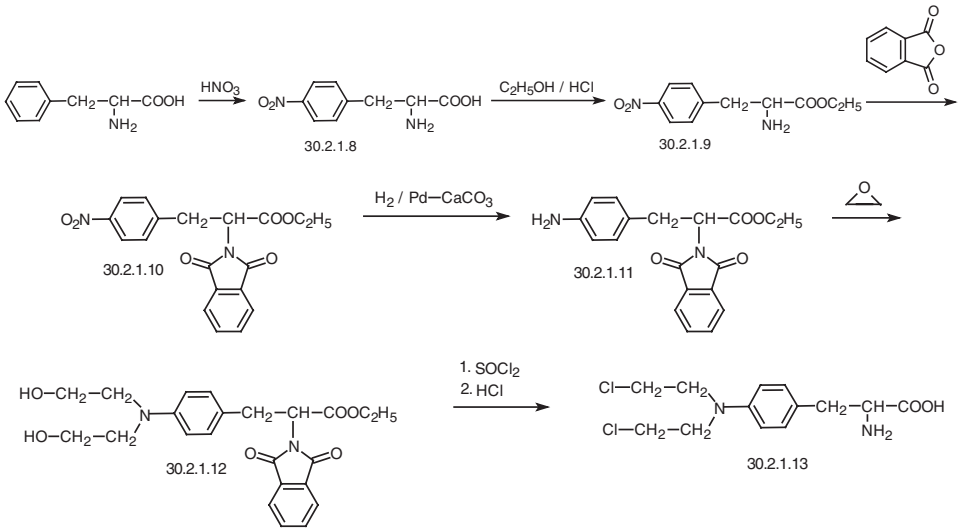


30.2.1.3 30.2.1.4 30.2.1.5 30.2.1.6 30.2.1.7

Chlorambucil is well adsorbed when administered orally. It is used for chronic lymphatic leukemia and for multiple myelomas. Synonyms of this drug are leukeran, amboclorin, and others.

Melphalan: Melphalan, L-3-[*p*-[bis-(2-chloroethyl)amino]phenyl]alanine (30.2.1.13), is a structural analog of chlorambucil in which the butyric acid fragment is replaced with an aminoacid fragment, alanine. This drug is synthesized from L-phenylalanine, the nitration of

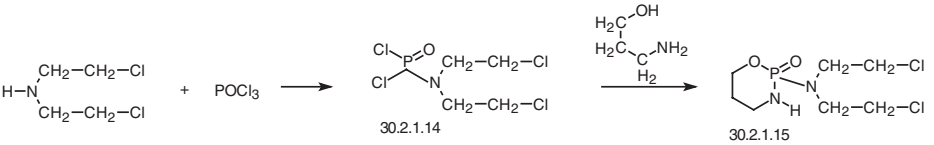
which with nitric acid gives 4-nitro-L-phenylalanine (30.2.1.8). Reacting this with an ethanol in the presence of hydrogen chloride gives the hydrochloride of 4-nitro-L-phenylalanine ethyl ester (30.2.1.9), the amino group of which is protected by changing it to phthalamide by a reaction with succinic anhydride to give 30.2.1.10. The nitro group in this molecule is reduced to an amino group using palladium on calcium carbonate as a catalyst. The resulting aromatic amine (30.2.1.11) is then reacted with ethylene oxide, which forms a bis-(2-hydroxyethyl)-amino derivative (30.2.1.12). The hydroxy groups in this molecule are replaced with chlorine atoms upon reaction with thionyl chloride, after which treatment with hydrochloric acid removes the phthalamide protection, giving melphalan (30.2.1.13) [47–50].



Melaphalan is used intravenously and orally to treat multiple myeloma and cancers of the breast, neck, and ovaries. A synonym of this drug is alkeran.

The racemic form of this drug, D,L-3-[*p*-[bis-(2-chloroethyl)amino]phenyl]alanine, is also widely used under the name sarcolysine or racemelfalan.

Cyclophosphamide: Cyclophosphamide, 2-[bis-(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorin-2-oxide (30.2.1.15), is made by reacting bis(2-chloroethyl)amine with phosphorous oxychloride, giving *N*,*N*-bis-(2-chloroethyl)dichlorophosphoramide (30.2.1.14), which upon subsequent reaction with 3-aminopropanol is transformed into cyclophosphamide (30.2.1.15) [51–59].



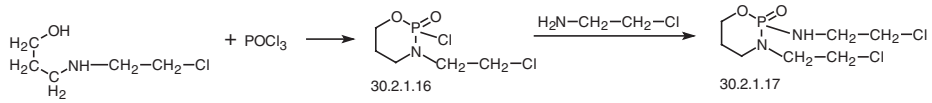
The distinctive chemical structure of this drug gives it selective antineoplastic activity. Present in the blood, it is practically inactive, although upon penetrating cancerous cells

and reacting with a relatively large number of phosphamidases, it cleaves, essentially releasing a cytostatic substance, bis-(2-chloroethyl)amine.

This means that the alkylating action of this drug is specifically directed toward cancerous cells. Cyclophosphamide is one of the most frequently used chemotherapeutic agents.

Cyclophosphamide is used both intravenously and orally. It is used for chronic lymphatic leukemia, Hodgkin's disease, Burkitt's lymphoma, multiple myeloma, and cancer of the breast, neck, ovaries, and so on. Synonyms of this drug are endoxan, cyclostin, cytoxan, cyclophosphane, and others.

Ifosfamide: Ifosfamide, 3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorin-2-oxide (30.2.1.17), which is viewed as an isomeric compound of cyclophosphamide (30.2.1.15) and which is analogous in terms of action, is made by reacting *N*-(2-chloroethyl)-*N*-(3-hydroxypropyl)amine with phosphorous oxychloride, giving 3-(2-chloroethyl)-2-chlorotetrahydro-2*H*-1,3,2-oxazaphosphorin-2-oxide (30.2.1.16), which is reacted with *N*-(2-chloroethyl)amine, forming the desired ifosfamide (30.2.1.17) [60–62].



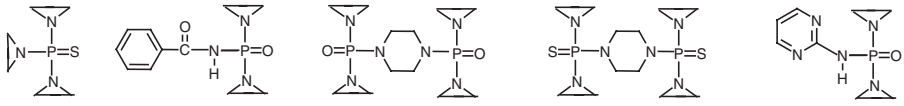
30.2.1.16 30.2.1.17

Ifosfamide is an experimental drug that is analogous to cyclophosphamide. Synonyms of this drug are goloxan and mitoxan.

30.2.2 Ethylenimine derivatives

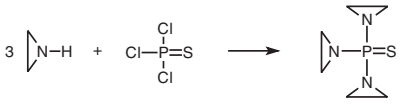
Ethylenimines are highly reactive alkylating reagents. They alkylate DNA at position N_7 of guanine, analogous to mechlorethamine. Ethyenimines exhibit cytostatic action and suppress development of proliferating, as well as malignant tissues. They disrupt the metabolism of nucleic acids and block mitotic cell division.

They are used for breast and ovarian cancer, nonoperable tumors, and other reoccurrences and metastases. In medicine, triethylenphosphortriamide, or thiotepa (30.2.2.1) is generally used; however, other drugs are also used, including benzotef (30.2.2.2), dipin (30.2.2.3), thiodipin (30.2.2.4), fosphemide (30.2.2.5), and others.



30.2.2.1 30.2.2.2 30.2.2.3 30.2.2.4 30.2.2.5

Thiotepa: Thiotepa, tris(1-aziridinyl)phosphine sulfate (30.2.2.1), is made by reacting ethylenimine with phosphorous sulfochloride [63,64].



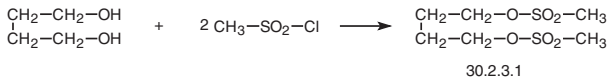
30.2.2.1

Triethylenthiophosphoramide is used intravenously in early stages of liver, uterine, and breast carcinomas. It is used for chronic lymphatic leukemia, lymphogranulomatosis, and lymphosarcomatosis. It is used for reducing the number of reoccurances and metastases, and in complex treatment of various forms of cancer. Synonyms of this drug are tespamin, tilphophamid, thiophosil, and others.

30.2.3 Alkyl sulfonates

Busulfan is the one drug in the alkylsulfonate series used in medicine.

Busulfan: Busulfan, 1,4-butandioldimethansulfonate (30.2.3.1), is made by reacting butandiol with methanesulfonyl chloride [65,66].



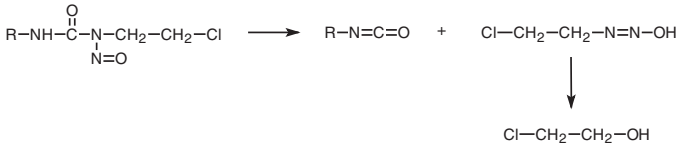
30.2.3.1

Busulfan is a bifunctional alkylating agent that weakly binds to DNA; however, it has the ability to cross-linking. Busulfan selectively alkylates position N_7 of guanine, and also alkylates the sulfhydryl group of glutathione and cysteine. Unlike other alkylating agents, it has little effect on lymphocytes and exhibits much less immunosuppressive ability. It has strong cytotoxic properties and the ability to kill stem cells. It can be taken orally. It is generally used for chronic myelogenic leukemia and polycythemia. Unlike other alkylating agents, it does not increase cases of secondary leukemia. Synonyms of this drug are cytosulfan, leukosulfan, myelosan, mytostan, and others.

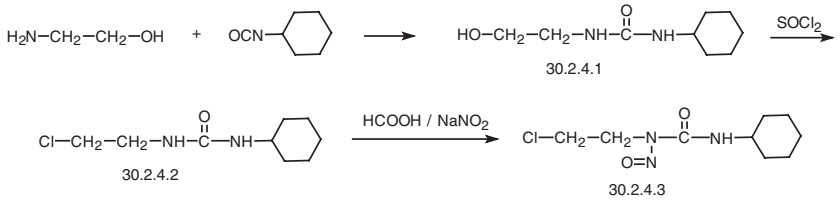
30.2.4 Nitrosoureas

The next group of antineoplastic drugs used in medicine is made up of nitrosoureas (lomustine, carbustine, streptozocin). There are also other drugs of this group (nimustine, semustine, and others), and they differ only in the presence of a different R group, which is shown in the scheme below. It is believed that in the body, nitrosoureas break down to β-chloroethanol and alkylisocyanate. The resulting β-chloroethanol is a highly reactive alkylating agent, and the alkylisocyanates are carbamoylating agents for proteins, which also exhibit certain cytotoxic activity.

The probable scheme of decomposition of nitrosourea in the body into active components is shown below.

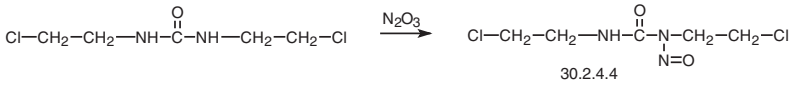


Lomustine: Lomustine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (30.2.4.3), is made by reacting ethanolamine with cyclohexylisocyanate, which forms 1-(2-hydroxyethyl)-3-cyclohexylurea (30.2.4.1). Upon reaction with thionyl chloride, the hydroxyl group in it is replaced with a chlorine atom, giving 1-(2-chloroethyl)-3-cyclohexylurea (30.2.4.2). This is nitrated in non-aqueous conditions with formic acid and sodium nitrite to give lomustine (30.2.4.3) [67,68].



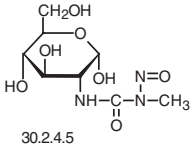
Like other nitrosoureas, lomustine acts as a DNA-alkylating agent, and it also inhibits various key enzymatic reactions by carbamoylating proteins. Lomustine is used only orally. It is used for central nervous system tumors, brain, throat, and larynx tumors, lymphogranulomatosis, non-Hodgkin's lymphoma, and lung and gastrointestinal tract cancer. Synonyms of this drug are belustine, CCNU, and others.

Carmustin: Carmustin, 1,3-bis-(2-chloroethyl)-1-nitrosourea (30.2.4.4), is made by nitrating 1,3-bis(2-chloroethyl)urea with nitrogen trioxide [68,69].



The mechanism of action of this drug is analogous to the mechanism of action of lomustine. Carmustine is only used intravenously. It is used for non-Hodgkin's lymphoma, multiple myeloma, and brain tumors. Synonyms of this drug are carmubris, nitrumon, and BICNU.

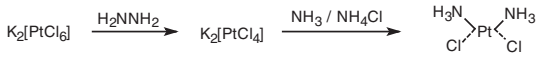
Streptozocin: Streptozocin, 2-deoxy-2-[[(methylnitrosoamino)carbonyl]amino]-D-glucose (30.2.4.5), is an antibiotic isolated from live *Streptomyces achromaogenes* [70–72].



Despite the fact that this drug is an antibiotic, it only formally belongs to the nitrosourea series, and the absence of the characteristic chloroethyl group makes it properties distinct from others of the nitroso-compounds. It exhibits alkylting (methylating) properties, although it is not able to cross-linking with DNA chains. It also does not have carbamoylating activity, which is present in other nitrosoureas, as a result of quickly occurring intramolecular reactions of cyclization of glycosylisocyanate, which is made during the transformation of streptozocin in the body; however, it inhibits synthesis of amino acids necessary for making proteins in cancer cells.

Streptozocin is only used intravenously. It is generally used for pancreatic cancer and carcinoids. Synonyms of this drug are zanosar and others.

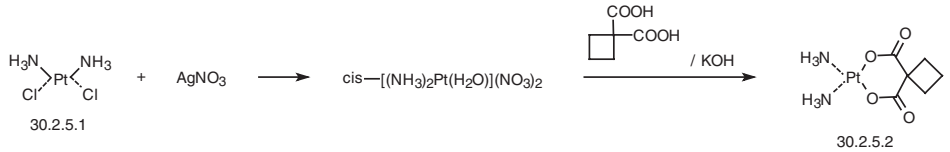
Cisplatin: Cisplatin, *cis*-diaminodichloroplatinum (30.2.5.1), is made by reducing potassium hexachloroplatinate by hydrazine to potassium tetrachloroplatinate, which reacts with ammonia to give cisplatin (30.2.5.1) [73–77].



30.2.5.1

Cisplastin is an non-organic platinum-containing drug with alkylating properties. It causes cross-linking of DNA and RNA chains. In particular, it has been shown, that cisplastin, like other alkylating agents, bind primarily at N_7 of two neighboring deoxyguanylates to DNA, which inhibits its replication. It is only used intravenously. It is highly reactive with carcinomas of the testicles, ovaries, heat, neck, spleen, lungs, and so on. Synonyms of this drug are platinol, platiblastin, platinex, neoplatin, and others.

Carboplatin: Carboplatin, *cis*-diamino-(1,1-cyclobutandicarboxylate)platinum(II), is made from cisplatin by reacting it with a solution of silver nitrate, and then with cyclobutan-1,1-dicarboxylic acid to form the desired carboplatin (30.2.5.2) [78,79].



30.2.5.1 30.2.5.2

Of the wide array of platinum derivatives, carboplatin is the only compound except cisplatin that is used in medical practice, and it differs from cisplatin in the replacement of two chlorine atoms with a cyclobutan-1,1-dicarboxylic acid fragment. Like cisplatin, carboplatin also reacts with DNA to form both internal and external cross-bonds. The range and indications of use are practically analogous to cisplatin. Synonyms of this drug are paraplatin and others.

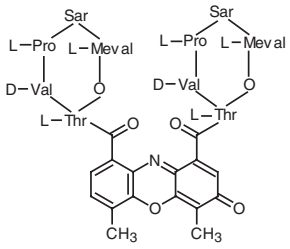
30.3 ANTIBIOTICS

A number of antibiotics possess pronounced cytostatic properties, and they are extremely effective in treating certain tumors. Included in this group are actinomycin, anthracyclins (daunorubicin and doxorubicin), bleomycin, and others.

A few of them, not including mitoxanthrone, which is a purely synthetic drug, are made microbiologically, and a few of them, whose syntheses are included in the reference literature, have also been developed synthetically. In this chapter, only their structure and indications for use will be examined.

30.3.1 Dactinomycines

Dactinomycin: Dactinomycin, 2-amino-1,9-bis-(2,9-diisopropyl-6,10,13-trimethyl-1,4,8,11,14-pentaoxo-7-oxa-3,10,13-17a-tetraaza-5-bicyclo[14.3.0]nonadecylcarbamoyl)-4,6-dimethyl-3*H*-phenoxazin-3-one (30.3.1), is one of the first antibiotics isolated from a liquid culture of microorganisms of the family *Streptomyces parvulus* [80–87]. It is a chromonopeptide with a phenoxazine ring and two cyclic polypeptides joined to the carboxyl group at position 2 and 9 of the phenoxazine ring.



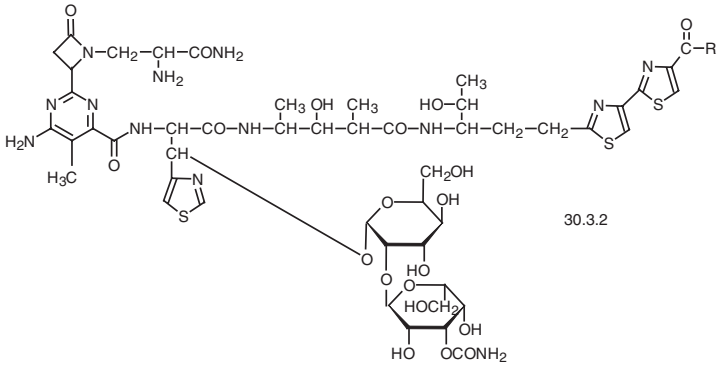
30.3.1

Actinomycines basically exhibit an inhibitory effect on both gram-positive and -negative bacteria, as well as on fungi. However, dactinomycin exhibits pronounced neoplastic action. It forms a complex with DNA due to binding with guanine–cytosine segments, and as a result, DNA-requiring synthesis of RNA is blocked. The other cytotoxic effect of actinomycin is that it prevents DNA from spiraling. In addition, actinomycin inhibits topoisomerase II. In can be used intravenously. It is used to treat Wilms' tumors, Kaposi's and Edwin's sarcomas, lymphomas, and so on. Synonyms of this drug are actinomycin D, cosmegen, and others.

30.3.2 Bleomycins

Bleomycin: Bleomycin is a stereoisomer of 6-amino-*N*-[[2-[[4-[[1-[[[2-[4-(aminocarbonyl)[2,4^1-bintiazol]-2^1-yl]ethyl]amino]carbonyl]-2-hydroxypropylamino-2-hydroxy-1,3-dimethyl-4-oxobutyl]amino-1-[[2-*O*-[3-O-(aminocarbonyl)-α-D-

mannopyranosyl-α-L-glucopyranosyl]oxy]-1*H*-imidazol-4-ylmethyl]-2-oxoethyl]-2-[1-(2,3-diamino-3-oxopropyl)-4-oxo-azethidinyl]-5-methyl-4-pyrimidincarboxamide (30.3.2)].



30.3.2

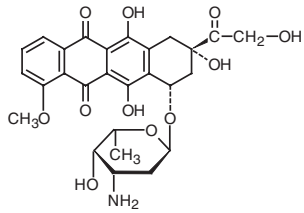
Bleomycin is a complex of no less than 16 glycopeptide antibiotics made from the family *Streptomyces verticilus*, which have different R groups [88–94]. Bleomycines exhibit antitumor, antiviral, and antibacterial activity. When bound to DNA, they disturb the spiraling of both single and double strands of DNA. To a lesser degree, they inhibit RNA and protein synthesis. It is administered both intravenously and intramuscularly.

It is used for lymphomas, carcinomas, and sarcomas. Synonyms of this drug are blenoxane, bleocin, and others.

30.3.3 Anthracyclines

Doxorubicin and daunorubicin are antibiotics made from microorganisms of the family *Streptomyces peucetius.* The structure of these anthracyclines contains an aminosaccarhide residue daunozamine attached to a naphthacenequinone nucleus. Doxorubicin differs from daunorubicin in the presence of a hydroxyl group at C_{14}. A number of mechanisms have been suggested in which anthracyclines exhibit cytotoxicity. They cause DNA to denature, are involved in oxidation–reduction reactions, chelate bivalent cations and react with cell membranes, changing their function. They are used for severe leukemia, lymphoma, breast and ovarian cancer, and other solid tumors.

Doxorubicin: Doxorubicin, 7,8,9,10-tetrahydro-6,7,9,11-tetrahydroxy-9-hydroxyacetyl-4-methoxy-5,12-naphthacenequinon-7-(3-amino-5-methyl-2,3-dideoxy-L-lixopyranozide) (30.3.3), was isolated from a cultured fluid of *S. peucetius* var. *caesuis* [95,96], and later synthesized [97–100].



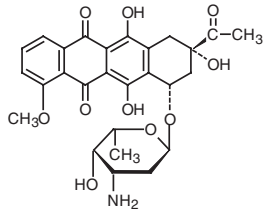
30.3.3

Doxorubicin is one of the most effective neoplastic drugs, and is mainly used in combination with other drugs for treating solid tumors.

This drug is used for leukemia, various sarcomas, practically every type of cancer, neuroblastomas, leukoses, and lymphomas. Synonyms of this drug are adriacin, adriablastin, and others.

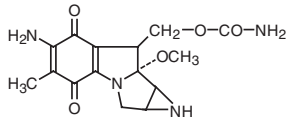
Daunorubicin: Daunorubicin, 9-acetyl-7,8,9,10-tetrahydro-6,7,9,11-tetrahdroxy-4-methoxy-5,12-naphthacenequinon-7-(3-amino-5-methyl-2,3-dideoxy-L-lixopyranozide) (30.3.4), was isolated from a cultured fluid of *S. peucetius* [101–104], and was later synthesized [105–108].

The mechanism of action of daunorubicin and the indications for use are exactly the same as those of doxorubicin. Synonyms of this drug are daunoblastina, rubomycin, and cerubidine.



30.3.4

Mitomycin: Mitomycin is 6-amino-1,1a,2,8,8a,8b-hyxahydro-8-hydroxymethyl)-8a-methoxy-5-methylazirino [2′,3′:3,4] pyrrolo [1,2-a]indol-4,7-dione carbamate (30.3.6).



30.3.6

Mitomycin is an antibiotic isolated from the products of living microorganisms of the family *Streptomyces caepitosus* and contains quinone, urethane, and aziridine fragments [109–114], and it was later synthesized [115,116].

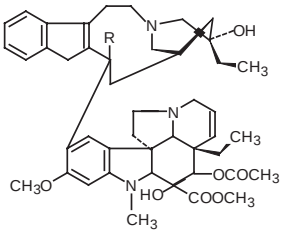
It is also alkylating agent and inhibits DNA synthesis. It is administered intravenously in combinations with other chemotherapeutic drugs for treating carcinomas of the pancreas, breast, lungs, prostate, head, neck, and so on. Synonyms of this drug are ametycin and others.

30.4 COMPOUNDS ISOLATED FROM PLANTS

Vinblastine and vincristine are alkaloids isolated from plants of the periwinkle family (*Vinca rosea*). These compounds cause cells to stop at metaphase and inhibit assembly of microtubules, and likewise, failure of mitotic spindle formations. They inhibit synthesis of nucleic acids and proteins.

Vinblastine and vincristine differ only in the substituent on the nitrogen atom of the indol fragment of the molecule, and are used in combination with other chemotherapeutic agents. They are mainly used for leukoses, myelomas, sarcomas, cancer of various organs, and for lymphomas.

Vinblastine: Vinblastine, [3aR-[3aα,4β,5β,5aβ,9(3R*,5S*,7R*,9S*),10bR*,13aα]]methyl-4-(acetyloxy)-9-[5-ethyl1,4,5,6,7,8,9,10-octahydro-5-hydroxy-9-(methoxycarbonyl)-2*H*-3,7-methanoazacycloundecino-[5,4=b]indol-9-yl]-3a-ethyl-,4,5,5a,6,11,12,13a-octahydro-5-hydroxy-8-methoxy-6-methyl-1*H*-indolizino [8,1-cd]-carbozol-5-carboxylate (30.4.1), is isolated from *V. rosea* [117–120].



30.4.1

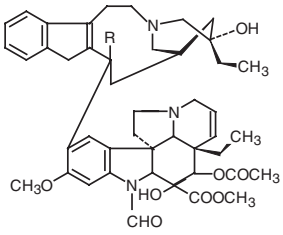
R = —COOCH$_3$

Vinblastine suppresses cell growth during metaphase, affects amino acid metabolism, in particular at the level of including glutamine acid into the citric acid cycle and preventing it from transformation into urea, and it also inhibits protein and nucleic acid synthesis.

Vinblastine is used for severe lymphoblastic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, neuroblastoma, sarcoma, and other cancerous diseases. Synonyms of this drug are velban, eczal, and others.

Vincristine: Vincristine, [3aR-[3aα,4β,5β,5aβ,9(3R*,5S*,7R*,9S*),10bR*,13aα]]methyl-4-(acetyloxy)-9-[5-ethyl-1,4,5,6,7,8,9,10-octahydro-5-hydroxy-9-(methoxycarbonyl)-2*H*-3,

7-methanoazacycloundecino-[5,4-b]indol-9-yl]-3a-ethyl-3a,4,5,5a,6,11,12,13a-octahydro-5-hydroxy-8-methoxy-6-formyl-1*H*-indolizino[8,1-cd]-carbazol-5-carboxylate (30.4.2), is also isolated from *V. rosea* [121–123]. There also are semisynthetic ways of making this drug [124–126].



30.4.2

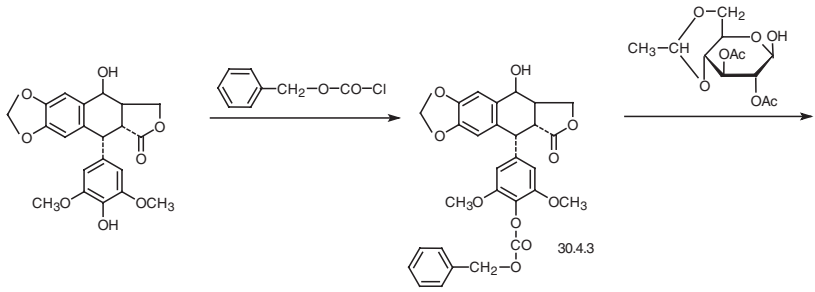
R = —$COOCH_3$

The mechanism of action of vincristine and indications for use are the exact same as with vinblastine. Synonyms of this drug are leurocristine, oncovin, and others.

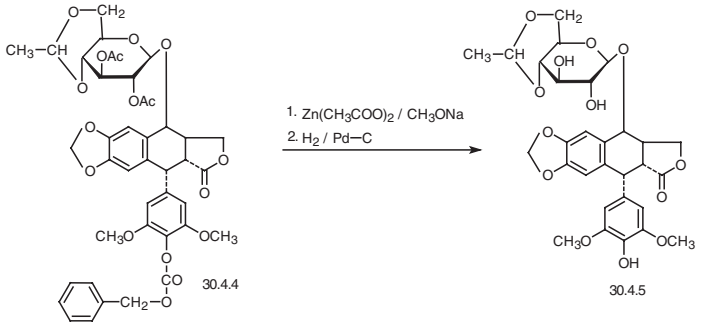
30.4.1 Epipodophyllotoxins

Etoposide and teniposide are synthetic derivatives of the extract of the American mandragora plant (May Apple). The mechanism of their action has not been completely explained; however, they act on the enzyme topoisomerase II, which disturbs the twisting of DNA. In addition, they inhibit DNA and RNA synthesis, as well as transport of nucleotides to cells. Cytotoxic action on normal cells is observed only in very high doses. These drugs exhibit significant activity in lymphomas, leukemia, Kaposi's sarcomas, and in testicular cancer.

Etoposide: Etoposide, [[5R-(5α,5aβ,8aα,9β)]-9-[4,6-*O*-ethylidene-β-D-glucopyranosyl) oxy]-] 5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)furo[3′,4′: 6,7]-naphtho[2,3-d]-1,3-dioxol-6(5a*H*)-one (30.4.5), is made from 4′-desmethylepipodophyllotoxin (30.4.3), the phenolic group of which being previously protected by benzyl chloroformate, which makes 4′-carbobenzyloxy-4′-desmethylepipodophyllotoxin (30.4.3). Next, the hydroxyl group at position C_9 is esterified with 4,6-*O*-ethylyden-2,3-di-*O*-acetyl-β-D-glucopyranose in the presence of boron trifluoride to make the corresponding glucopyranoside 30.4.4. Removing the acetyl group in the glucopyranosyl part of the molecule using zinc acetate in sodium methoxide, and also removing the benzyloxycarbonyl protection by hydrogenation using a palladium on carbon catalyst gives the desired etoposide (30.4.5) [127,128].

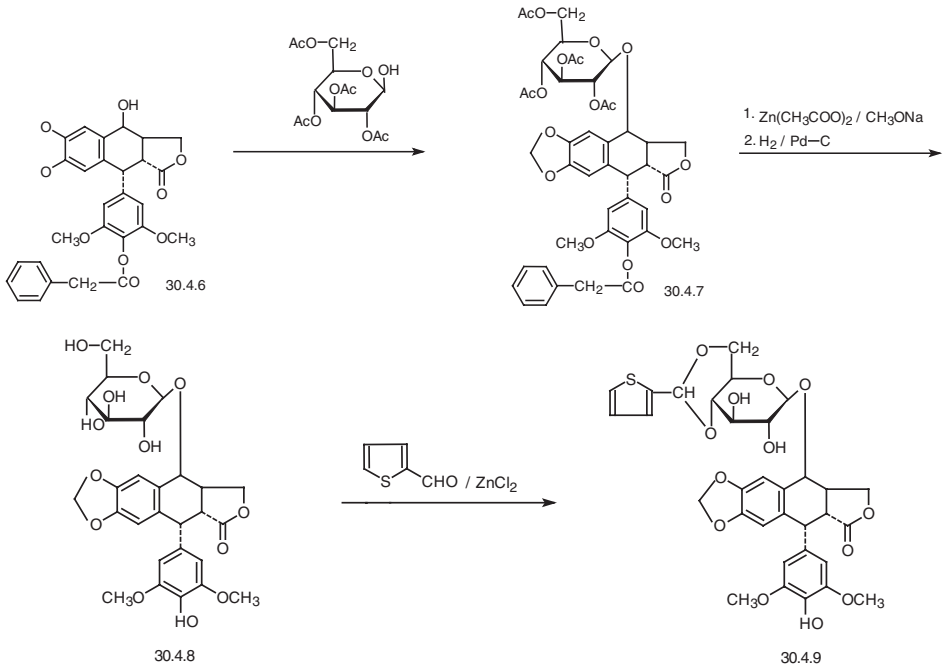


30.4.3



Etoposide is used for germinogenic tumors, ovarian, stomach, and lung cancer, Hodgkin's disease, and non-Hodgkin's lymphoma for both monotherapy and in combination therapy. Synonyms of this drug are vepesid and others.

Teniposide: Teniposide, [5R-(5α,5aβ,8aα,9β)]-9-[4,6-*O*-(2-thienylmethylene)-β-D-glucopyranosyl)oxy]- 5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)furo[3′,4′: 6,7]-naphtho[2,3-d]-1,3-dioxol-6(5a*H*)-one (30.4.9), is basically synthesized by an analogous scheme from 4′-benzyloxy-4′-desmethylepipodophyllotoxin (30.4.6), which is esterified by 2,3,4,6-tetra-*O*-acetyl-β-D-glucose in the presence of boron trifluoride etherate, giving a glycoside 30.4.7. The acetyl and benzyloxycarbonyl protecting groups in this molecule are removed by succesive use of zinc acetate and sodium methoxide, and then by subsequent hydrogen reduction, which forms the diol 30.4.8. The resulting diol is then transformed into the corresponding acetal 2-formylthiophene, which is the desired teniposide (30.4.9) [128–132].



Teniposide is used for the same indications as etoposide; however, it is 5–10 times more potent than etoposide. Synonyms of this drug are epipodophyllotoxin, vumon, and others.

30.5 HORMONAL DRUGS

Hormonal drugs are successfully used for complex treatment of malignant tumors. Tumors can be both hormone-dependent, as well as hormone-sensitive.

Hormone-dependent tumors regress in the absence of hormonal activity. Consequently, it is possible to both hinder and even prevent the development of hormone-dependent tumors using drugs. In particular, the antiestrogen drug tamoxifen prevents stimulation of cancerous breast tumor cells by estrogens. This also applies to aminoglutethimide, an inhibitor of corticosteroid synthesis by the adrenal glands.

Hormone-sensitive tumors may regress, and frequently stop growth upon introduction of certain hormones. The main hormone-sensitive forms of cancer are breast and prostate carcinoma, lymphoma, and a few other forms of carcinomas.

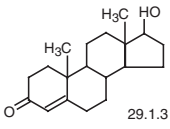
Hormonal drugs that inhibit growth of certain human tumors are steroids, including androgens, estrogens, progestins, and corticosteroids, although only glucocorticoids are used. Moreover, neither cortisol nor cortisone are used to treat malignant tumors, but instead prednisone, prednisolone, methylprednisolone, and dexametasone are used.

Hormonal drugs do not cure cancer, although they do exhibit pronounced palliative action, with the exception of the cytotoxic action of glucocorticoids on lymphoid cells. In particular, this concerns predinsone, which is used to treat lymphomas and certain leukemias in combination therapy.

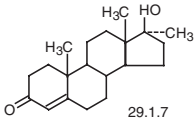
The exact mechanism of action of steroids is not fully known.

30.5.1 Androgens

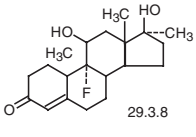
Androgens are derivatives of testosterone (29.1.5), methyltestosterone (29.1.7), fluoxymesterone (29.3.5), and testolactone (30.5.1), and are frequently used for palliative treatment of breast cancer in post-menopausal women, for which hormone therapy is used. The exact mechanism of the anticancer effect of androgens is not known. However, it is presumed that androgens block cell growth by inhibiting transport of natural hormone into the cell. Moreover, androgens can inhibit estrogen synthesis, thus depleting estrogen reserves.



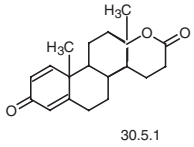
29.1.3



29.1.7



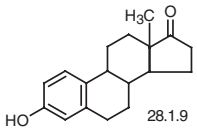
29.3.8



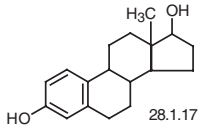
30.5.1

30.5.2 Estrogens

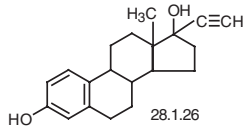
Estrogens, estrone (28.1.9), estradiol (28.1.17), ethynylestradiol (28.1.26), diethylstilbestrol (28.1.33), and chlorotrianisene (30.5.2), are used for palliative treatment of postmenopausal breast cancer, prostate cancer, and breast cancer in men. It is highly probable that the mechanism of action is similar to the mechanism of action of androgens.



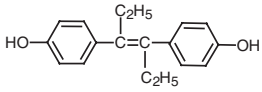
28.1.9



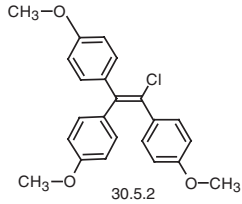
28.1.17



28.1.26



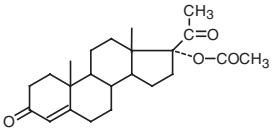
28.1.33



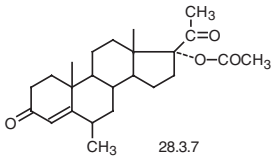
30.5.2

30.5.3 Progestins

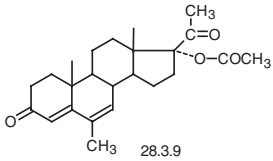
Progestins, steroid compounds similar to progesterone, such as hydroxyprogesterone caproate (28.3.6), medroxyprogesterone acetate (28.3.7), and megestrol acetate (28.3.7), are used for palliative treatment of breast carcinomas and renal tumors. Progestins can have a direct local effect on cells, and can simultaneously lower the quantity of leutenizing hormone.



28.3.6



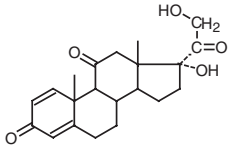
28.3.7



28.3.9

30.5.4 Corticosteroids

Corticosteroids, synthetic steroid drugs made from the natural hormone hydrocortisone, and particularly prednisone, are frequently used for combination therapy for treating severe and chronic lymphocyte leukemia, Hodgkin's and non-Hodgkin's lymphomas, multiple myeloma, and breast cancer. Corticosteroids exhibit an antitumor effect by binding with corticosteroid receptors that exist in many cancerous lymphoma cells, which leads to inhibition of both glucose transport and phosphorylation, which reduces the amount of energy necessary for mitosis and protein synthesis, which, accordingly, leads to cell lysis.

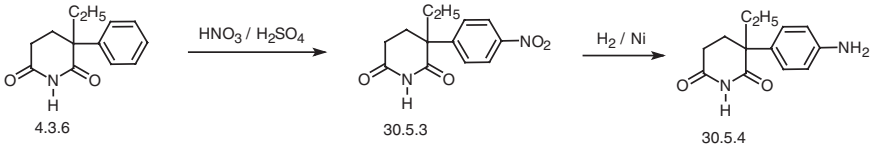


27.1.31

30.5.5 Nonhormonal drugs

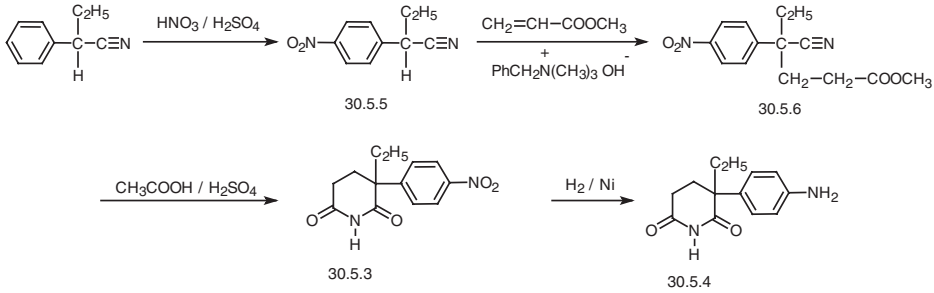
In addition to hormonal drugs, five other nonsteroids that have a direct relationship to this section are also used in cancer chemotherapy. They are aminoglutethimide, flutamide, mitotan, tamoxifen, and leuprolide.

Aminoglutethimide: Aminoglutethimide, (±)-2-(4-aminophenyl)-2-ethylglutarimide (30.5.4), is made by two methods, the first of which begins with glutethimide (4.3.6), which is nitrated to form 2-(4-nitrophenyl)-2-ethylglutarimide (30.5.3). Reducing the nitro group with hydrogen over a nickel catalyst gives the desired aminoglutethimide (30.5.4).



4.3.6 30.5.3 30.5.4

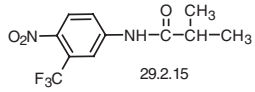
The second method starts with 2-phenylbutyronitrile, which is nitrated under analogous conditions, forming 2-(4-nitrophenyl)butyronitrile (30.5.5). The last, in Michael addition reaction conditions, in the presence of benzyltrimethylammonia hydroxide is added to methylacrylate, and the obtained product undergoes acidic hydrolysis by a mixture of acetic and sulfuric acids, during which a cyclyzation to 2-(4-nitrophenyl)-2-ethylglutarimide (30.5.3) occurs, and this product is reduced by hydrogen by the analogy to that described above, to give the desired product aminoglutethimide (30.5.4) [133,134].



30.5.5 30.5.6 30.5.3 30.5.4

This drug blocks the transformation of cholesterol into pregnenolone, and androgens into estrogens in the adrenal glands, thus completely suppressing the production of all steroid hormones. Aminoglutethimide is used for palliative treatment of prostate carcinomas and post-menopausal breast carcinomas. Synonyms of aminoglutethimide are orimeten, citadren and others.

Flutamide: Synthesis of flutamide (29.2.15) is described in Chapter 29.

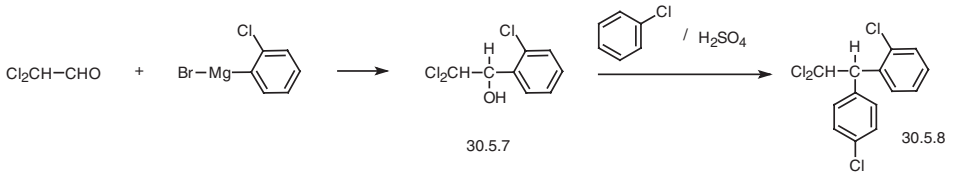


29.2.15

This drug blocks binding of androgens to tissue–muscle cells and prevents biological action of androgens, including in pancreatic tumor cells.

It is used in combination with leuprolide for prostate carcinomas. Synonyms of flutamide are chimax, drogenil and others.

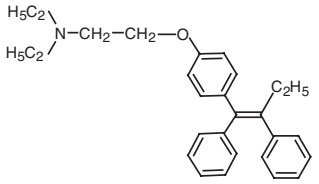
Mitotane: Mitotane, 1,1-dichloro-2-(*o*-chlorophenyl)ethane (30.5.8), is made by alkylating chlorobenzene with 1-(2-chlorophenyl)-2,2-dichloroethane (30.5.7) in the presence of sulfuric acid. The necessary 1-(2-chlorophenyl)-2,2-dichloroethanol (30.5.7) is in turn made from reacting 2-chlorophenylmagnesiumbromide with dichloroacetic aldehyde [135].



30.5.7 30.5.8

Mitotane, a derivative of the insecticide DDT, quickly lowers the level of corticosteroids, and is metabolized in the blood and urine and used on non-operable metastatic prostate carcinomas. Synonyms of this drug are lysodren and others.

Tamoxifen: Synthesis of tamoxifen (28.2.8) is described in Chapter 28.



28.2.8

This drug blocks estrogen receptors, stops the progression of cancerous diseases, and stimulates estrogens.

Tamoxifen is used for palliative treatment of breast cancer in pre- and post-menopausal women.

Leuprolide: Leuprolide, 5-oxo-L-prolyl-L-histadyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucil-L-leucil-L-arginyl-*N*-ethyl-L-prolinamide (30.5.9), is made synthetically [136–139].

*pyro*Glu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHEt

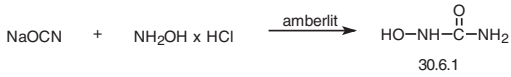
The nonapeptide leuprolide is a synthetic analog of the decapeptide, gonadotropin releasing hormone, and it exceeds the activity of the natural hormone and significantly elevates the level of testosterone and dihydrotestosterone in men, and estrogen in women. It also inhibits follicle-stimulating hormone and leutenizing hormone.

Leuprolide is used for prostate cancer, when orchiectomy or estrogen therapy is counterproductive to the patient. A synonym of this drug is lupron.

30.6 OTHER ANTINEOPLASTIC DRUGS

The drugs examined below are classified as others because either their mechanism of action or their belonging to a certain chemical class makes them hard to include in the subchapters, which follow the typically acceptable classifications of antineoplastic drugs.

Hydroxyurea: Hydroxyurea (30.6.1) is made by reacting sodium cyanate with hydroxylamine. In this reaction, hydroxylamine hydrochloride and a basic ion-exchange resin are used [140,141].

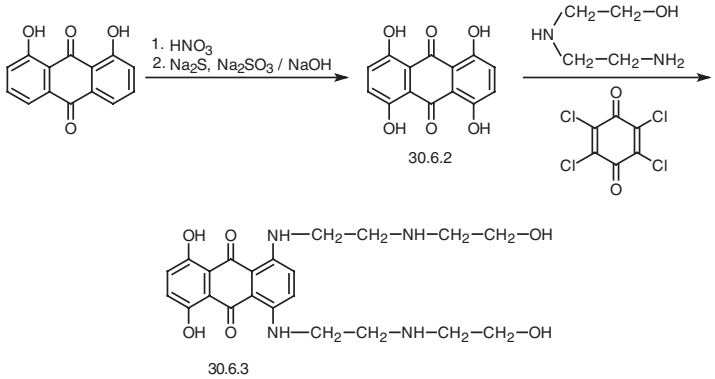


30.6.1

Hydroxyrurea acts by suppressing dihydrophosphate reductase, an enzyme that reduces ribonucleotides into deoxyribonucleotides necessary for DNA synthesis.

This drug causes a sharp increase in the amount of white blood cells in severe leukemias. It is used for leukemias, meanomas, and carcinomas. Synonyms of this drug are litalir, hydrea, onco-carbide, and others.

Mitoxantrone: Mitoxantrone, 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl) amino) ethyl]amino]]-9,10-anthracendione (30.6.3), is structurally related to the antibiotic doxorubicine. It is synthesized from danthron (1,8-dihydroxyanthraquinone), which when reacted with nitric acid, and then a mixture of sodium sulfide and thiosulfate in a base, is transformed to 1,4,5,8-tetrahydroxyanthraquinone (30.6.2). Reacting this with 2-aminoethylaminoethanol in the presence of chloranyl (2,3,5,6-tetrachlorobenzoquinone-1,4) gives the desired mitoxantrone (30.6.3), [142–145].

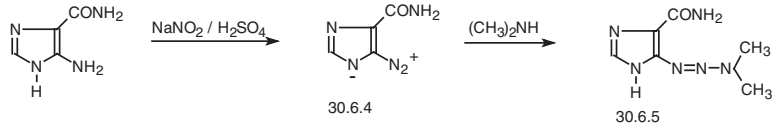


30.6.2

30.6.3

The mechanism of its action is not completely understood, although it is presumed, that mitoxantrone acts by binding with DNA, thus disturbing the twisting process of the chains. It is used intravenously for treating severe nonlymphatic leukemia, breast cancer, and so on. A synonym of this drug is novantrone.

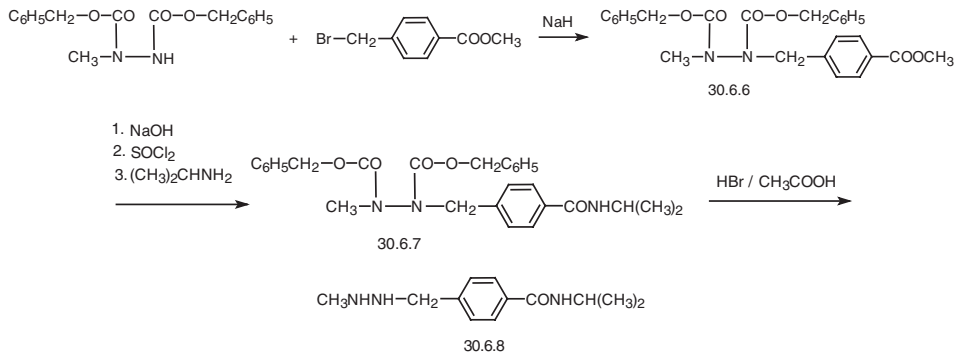
Dacarbazine: Dacarbazine, 5-(3,3-dimethyl-1-triazeno)imidazol-4-carboxamide (30.6.5), is made by diazotation of 5-aminoimidazol-4-carboxamide with nitrous acid, which results in the formation of 5-diazoimidazol-4-carboxamide (30.6.4). Reacting this with dimethylamine gives the desired dacarbazine (30.6.5) [146].



30.6.4 30.6.5

Dacarbazine is nevertheless considered the first representative of the series of triazene derivatives. It has been shown that it is an alkylating agent, and thus this drug inhibits RNA and protein synthesis to a greater degree than DNA. Dacarbazine is used intravenously for Hodgkin's disease, soft-tissue sarcoma, and metastatic melanoma. A synonym of this drug is diticene.

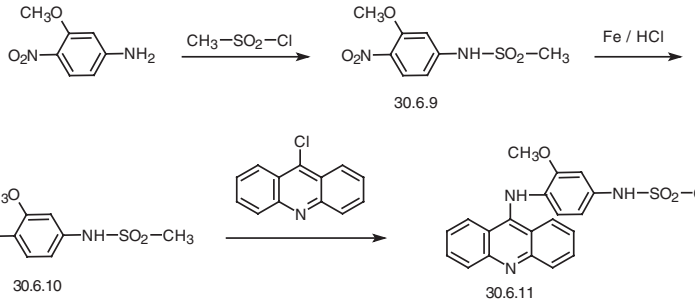
Procarbazine: Procarbazine, 1-methyl-2-(*n*-isopropylcarbamoylbenzyl)-hydrazine (30.6.8), is synthesized from 1,2-bis-(benzyloxycarbonyl)-1-methylhydrazine, which is alkylated by the methyl ester of 4-bromomethylbenzoic acid in the presence of sodium hydride, which forms 1,2-bis(benzyloxycarbonyl)-1-methyl-2-(*p*-carbomethoxy)benzylhydrazine (30.6.6). The carbomethoxy group of this molecule is hydrolyzed by sodium hydroxide, and the resulting carboxyl group is transformed into a acid chloride group, followed by a reaction of this product with isopropylamine gives 1,2-bis-(binzyloxycarbonyl)-1-methyl-2-(*p*-isopropylcarbamoyl)benzylhydrazine (30.6.7). Hydrolyzis of the benzyloxycarbonyl group in the resulting compound with hydrogen bromide in acetic acid gives the desired procarbazine (30.6.8) [147–150].



30.6.6 30.6.7 30.6.8

Procarbazine was initially synthesized as an MAO inhibitor. However, it was discovered later on that it has ability to act as an alkylating agent and inhibit DNA, RNA, and protein synthesis. Along with this, there is an opinion that procarbazine accumulates in cancerous tissue and generates peroxide and hydroperoxide radicals in cells, which imitates the effect of ionizing radiation. It is used for malignant tumors of lymphatic tissue, brain tumors, lung tumors, and Hodgkin's disease. A synonym of this drug is natulan.

Amsacrine: Amsacrine, 4-(9-acridinylamino)-3-methoxyphenyl-*N*-methansulfonamide (30.6.11), is made by sulfonating 4-nitro-*m*-anisidine with methanesulfonyl chloride, which forms a sulfonyl amide 30.6.9, and the nitro group is reduced to an amino group by hydrogen, forming 4-amino-3-methoxyphenyl-*N*-methansulfonamide (30.6.10). Reacting this with 9-chloroacridine gives amsacrine (30.6.11) [151–153].



Amsacrine is a drug undergoing intensive trials for severe leukemia and lymphoma. It is a cytotoxic drug that binds with DNA with expressed specificity to the adenosine–tyrosine pair, thus inhibiting DNA synthesis. It has been suggested to be used for severe leukemia. A synonym of this drug is amsidyl.

Asparaginase: Asparaginase is an enzyme that hydrolyzes L-asparagine to L-aspartic acid, which causes a depletion of reserves of L-asparagine, thus inhibiting protein and nucleic acid synthesis. It is effective for severe lymphocyte leukemia [154]. A synonym of this drug is elspar.

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Immunopharmacological Drugs

The ability of the body to independently protect itself from certain diseases is called immunity. In a medical sense, immunity is a state of having sufficient biological defenses to avoid infection, disease, or other unwanted biological invasion. Immunity to certain diseases can be both inherent and acquired. Most types of immunity are either acquired during the course of life in response to infection by various microorganisms (actively acquired immunity), or it can be attained by specific, directed production of antibodies in the body in response to previous artificial infection by dead or weakened microorganisms (passively acquired, artificial immunity), which is usually obtained through vaccinations. Immunization, or selective strengthening of the immune response of the body, is one of the ways of fighting infectious diseases through vaccinations, i.e. producing antigens against concrete, specific pathogens.

Undoubtedly, inflammation is also an immune response. Drugs described in other chapters, such as antihistamine agents, nonsteroid anti-inflammatory agents, antiserotonin drugs, and many others can also be formally grouped with immunopharmacological agents. However, only the drugs having a direct effect on cells that have immune functions, such as lymphocytes, plasma cells, and subtypes of these cells will be examined in this chapter. It should be noted that the vital functional products of these cells themselves, such as lymphokines, interferons, and interleukins, are very important immunopharmacological drugs. The immune system has an enormous number of antigens that differentiate between 'own' and 'alien' molecules. It plays a huge role in autoimmune diseases, hypersensitivity reactions in the body to certain irritants, and in transplant rejections.

The immune system is vitally important not only for protecting the body from foreign bodies of organic or inorganic origins, but also from our own cells that transform into foreign cells. It also serves to remove sick, dead, or foreign cells, and, in all likelihood, serves as the body's primary protection against cancer, suppressing many tumor centers and frequently preventing the formation of metastases.

Various drugs are capable of affecting specific immune reactions. They can both increase the general resistivity of the body or its nonspecific immunity, as well as suppress the body's immune reactions. Hence controlling diseases with immunological agents means either generation of the necessary immunity in the body, or suppression of undesirable immune reactions.

It is evident that immunopharmacological drugs are of great significance in diseases of the immune system, organ transplants, viral infections, and in particular, in the treatment of AIDS.

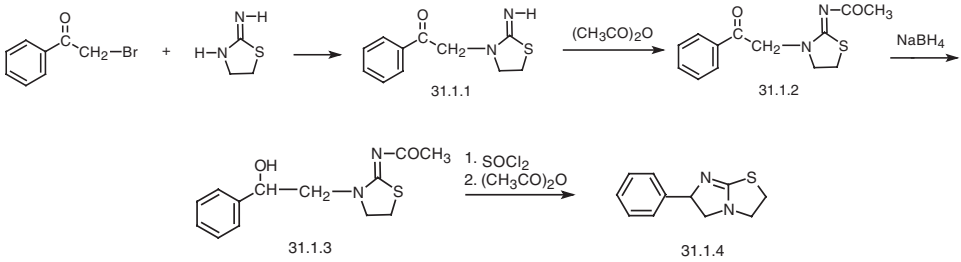
31.1 IMMUNOSTIMULANTS

Enhancing the overall resistivity of the body is observed upon treatment with a number of known drugs: immunostimulants (caffeine, phenamine, methyluracil), vitamins (retinol, ascorbic acid, vitamins of group B), nucleic acid derivatives, and also drugs of natural or genetically engineered origin made specifically for this purpose.

They include proteins such as lyphokines, in particular, interleukin-2, which is a glycoprotein containing 133 amino acids, and also the so-called colony stimulating factors (CSF) that of macrophages or granulocytes produced by a few cells, including CSF-multi or interleukin-3, granulocytosis stimulating factor (GSF) a nonglycoside protein, macrophage stimulating factor (MSF) a highly glycosylated homodimer protein, and GMSF (a factor that stimulates both granulocytes and macrophages), a monomeric glycoprotein, which stimulates proliferation, differentiation, and functionalization of target cells in various stages of development. For this purpose, drugs called FNT-α and FNT-β have been made, which are factors that cause tumor necrosis.

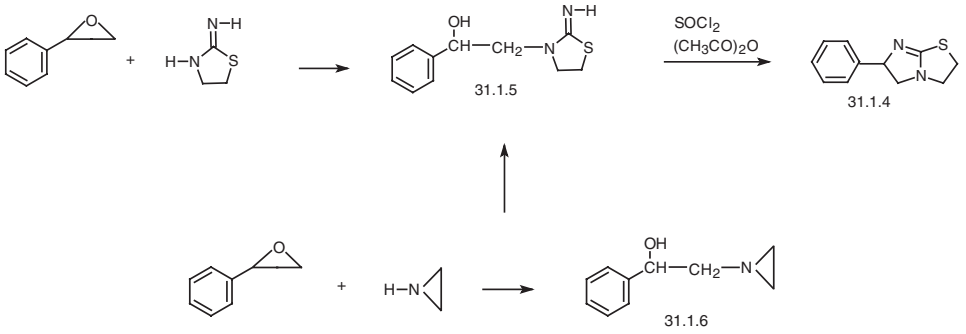
Interferons—a family of glycoproteins processed by macrophages—also are widely used as immunostimulants; (α -interferons), made in macrophages and fibroblasts; (β-interferons), made in lymphocytes; (γ-interferons), which are named for their ability to react with viral RNA and affect protein synthesis. Commercially accessible α-, β-, and γ-interferons are currently used in medicine. Practically the only purely synthetic immunostimulant drug that is used is levamisole, which was initially proposed as an anthelminthic agent, and it is currently widely used as such.

Levamisole: Levamisole, 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]thiazole (31.1.4), is synthesized in various ways. One of them begins with α-bromoacetophenone, the reaction of which with 2-imino-1,3-thiazolidine gives 3-phenacyl-2-imino-1,3-thiazolidine (31.1.1). Reacting this product with acetic anhydride gives 3-phenacyl-2-acetylimino-1,3-thiazolidine (31.1.2). The ketone group in the resulting compound is reduced to an alcohol using sodium borohydride, and the resulting hydroxyl group in (31.1.3) is replaced with chlorine using thionyl chloride. Heating the product in acetic anhydride, the imidazole cycle closes, forming the product (31.1.4).



A somewhat different approach was realized when using styrene oxide as the initial starting material. Reacting it with 2-imino-1,3-thiazolidine gives 3-(2-phenyl-2-hydroxyethyl)-2-imino-1,3-thiazolidine (31.1.5), which is subsequently treated with thionyl chloride and then acetic anhydride to give the desired levamisole (31.1.4).

Finally, the following scheme of making the product has been proposed using the same styrene oxide. Styrene oxide is reacted with aziridine, forming 2-aziridion-1-phenylethanol-1 (31.1.6). Treating this with potassium isothiocyanate or thiourea gives 3-(2-phenyl-2-hydroxyethyl)-2-amino-1,3-thiazolidine (31.1.5), and subsequent treatment with thionyl chloride (such as described above) and then with acetic anhydride gives the desired levamisole (31.1.4) [1–12].



Levamisole has immunomodulating activity. It is believed that it regulates cellular mechanisms of the immune system, and the mechanism of its action may be associated with activation and proliferative growth of T-lymphocytes, increased numbers of monocytes and activation of macrophages, and also with increased activity and hemotaxis of neutrophylic granulocytes. Levamisole also exhibits anthelmint action. It also increases the body's overall resistivity and restores altered T-lymphocyte and phagocyte function. It can also fulfill an immunomodulatory function by strengthening the weak reaction of cellular immunity, weakening strong reaction, and having no effect on normal reaction.

Levamisole is used for initial and secondary immunodeficient conditions, autoimmune diseases, chronic and reoccurring infections, large intestine adenocarcinoma, helmintosis, and rheumatoid arthritis. Synonyms of this drug are decaris, tetramizole, and others.

31.2 IMMUNODEPRESSANTS

Along with immunostimulants, drugs are needed in medical practice that suppress immunogenesis, antibody production (which is especially important in transplantation of various tissues and organs, during which the body produces antibodies that cause death of transplanted tissue), and also for treating a few autoimmune diseases. Substances of various pharmacological groups exhibit immunodepressive activity: glucocorticoids, cytostatics, and antibiotics (cyclosporine).

31.2.1 Glucocorticoids

Many synthetic glucocorticoid derivatives are widely used as immunodepressants. Glucocorticoids (cortisone, prednisone, methylprednisolone, betamethasone, dexamethasone,

triamcinolone, and others) are usually used in combination with other immunodepressants, especially in cases accompanied by inflammation.

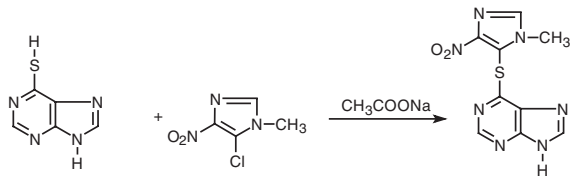
Immunodepressive action of glucocorticoids is connected with a decreased level of lymphocytes, eosinophiles, and basophiles in the blood, suppression of antigen recognition, and with suppression of the phase of lymphocyte proliferation.

31.2.2 Cytotoxic drugs

Presumably, any cytotoxic substance that destroys bone marrow and lymphoid tissue may be used as an immunosuppressant. Among these drugs, the most widely used primarily for autoimmune diseases are vincristine, methotrexate, and cytarabine. However, their use should be considered experimental. Only methotrexate is seriously and sufficiently recognized as an initial drug for treating rheumatoid arthritis.

In addition, one of the sulfur analogs of mercaptopurine, azathioprine, has been proposed as a cytotoxic drug, and it turned out to be more effective as an immunosuppressant.

Azathioprine: Azathioprine, 6-[(1-methyl-4-nitroimidazol-5-yl)thio]purine (31.2.1), is synthesized by heteroarylation of the sulfhydrile group of 6-mercaptopurine (30.1.2.9) with 5-chloro-1-methyl-4-nitroimidazol in the presence of sodium acetate as a weak base [13].

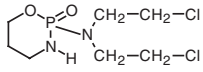


31.2.1

As a matter of fact, azathioprine is a prodrug since it turns into mercaptopurine in the body. This is a possibly reason why it is advantageous over mercaptopurine as an immunosuppressant.

The mechanism of action of azathioprine as a cytotoxic drug is not different from the mechanism of action of other antimetabolites. Azathioprine is the primary drug used for transplants, especially for kidney transplants. Today, cyclosporine is used instead of azathioprine in many places. However, azathioprine is useful in combination with cyclosporine, and it is even preferred in certain cases. Synonyms of this drug are azumec, imuran, and others.

Cyclophosphamide: Synthesis and properties of this drug are described in Chapter 30.

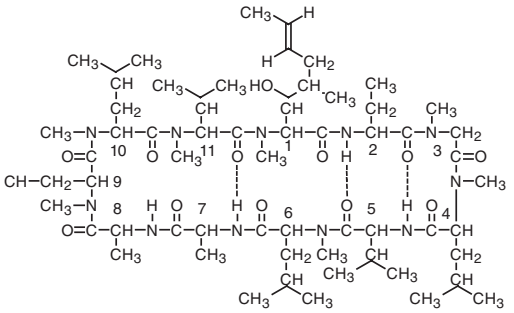


30.2.1.15

Besides being used as an alkylating agent in cancer chemotherapy, cyclophosphamide is a unique drug when used as an immunosuppressant. First, it is the most powerful of all such drugs. Second, it kills proliferating cells, and evidently alkylates a certain region of

remaining cells. Finally, its action on T-cells is such that despite its overall suppressive effect, it can, in certain environments, suppress the response of these cells to antigens. Cyclophosphamide is successfully used for bone transplants. In small doses, it is effective for autoimmune disorders.

Cyclosporine A: Cyclosporine A, [R-[R*,R*-(E)]]-cyclo-(L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-3-hydroxy-*N*,4-dimethyl-L-2-amino-6-octenoyl-L-α-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucine) (31.2.2), is extracted from a cultural liquid of products of the vital activity of the mushroom *Tolypocladium inflatum* [14–17], and which is also proposed to obtain synthetically [18–20].



31.2.2

Cyclosporine A is a powerful immunosuppressive drug intended for preventing rejection of kidney, heart, and lung transplants.

A new era in the development of immunopharmacology began with the discovery of cyclosporines.

Cyclosporines are produced by mycelial mushrooms *Tolypocladium inflatum*, *Tricoderma polysporum*, and *Cylindrocarpon lucidum*, which are found in the ground.

Cyclosporine A is the first drug to affect a specific line of protecting cells of the body. Unlike usual cytotoxics, it suppresses T-cells and acts on all cell lines simultaneously. Cyclosporine A significantly eases the 'reception' of transplants, and increases the possibility of treating autoimmune system diseases.

All cyclosporines (A,B,C, … U,V,W), are oligopeptides containing 11 amino acids closed in a cyclic form. All of these are known amino acids except the first, which sometimes has not been isolated from natural sources. All of them are L-amino acids except for the amino acids in positions 3 and 8. Because of all of the hydrogen bonds, the structure of cyclosporine is quite rigid. Cyclosporines (A,B,C, … U,V,W) only differ in the second amino acid.

Cyclosporine A itself and a number of other cyclosporines have been completely synthesized. Many structural analogs have also been synthesized, and a few patterns have been discovered in terms of their structure and activity. It is known that the activity of the drug is determined by the entire cyclic structure, and not by its separate fragments. Likewise, it is also clear, that the structure of amino acids at position 1 is an important factor of

determining activity. Despite the fact that the molecule is relatively large, cyclosporine easily diffuses through the cellular membrane. It is possible that there are no corresponding 'recognizing' receptors for cyclosporine. However, there is a cytosol cyclosporine-binding protein known as cyclophilin, which has a molecular weight of about 15,000. Cyclophilins are observed mainly in T-cells; however, they are found in other tissues, in particular, in the brain and kidneys. Their exact function and purpose are not known. It is suspected that they control RNA during the synthesis of lymphokines. Since the mechanism of action of cyclosporine is still being intensively studied, it must be noted that it is not cytotoxic in the general sense of the word, because it suppresses bone marrow function.

Despite the fact that cyclosporine has not been used for a long time, it is the number one drug used for transplants. Cyclosporine is also being studied as a substance for treating a number of autoimmune diseases, including diabetes, multiple sclerosis, myasthenia, rheumatoid arthritis, and psoriasis. It also has had a great effect in treating schistosomiasis, malaria, and filariasis. Synonyms of this drug are sandimmun and neural.

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Antibiotics

Drugs used for treating infectious diseases are called antibiotics, anti-infectious agents, and anti-microbial or chemotherapeutic drugs. Despite the fact that all of these terms are basically interchangeable, the first three—antibiotics, anti-infectious agents, and anti-microbial drugs—are generally used to describe drugs used for treating infectious diseases, while the term chemotherapeutic drugs is more associated with drugs used for treating cancer.

Antibiotics are essentially natural compounds produced by microorganisms that are capable of inhibiting growth of pathogenic microbes, bacteria, and a few of the more simple microorganisms.

Semisynthetic antibiotics generally are products that are a partially chemically altered versions of antibiotics that are isolated from natural sources.

Thus, antibiotics are compounds produced by microorganisms and that are able to kill or inhibit growth of bacteria and other microorganisms. This definition makes a specific distinction between antimicrobial drugs produced by microorganisms and completely synthetic compounds. The difference is of a completely academic nature, and today the word antibiotic is used quite often for specifying antimicrobial drugs in general. It should be noted that there are compounds produced by microorganisms with antifungal and antitumor action, which also are classified as antibiotics.

The general concept of antimicrobial action is called *selective toxicity*, which entails that the growth of the infected organism is inhibited or destroyed by certain drugs without harming host cells. All of the antimicrobial drugs used in clinical practice are selectively toxic with respect to microorgansisms. High selective toxicity of antibiotics to microorganisms is explained by the unique qualities of the organization of microbial cells, which are principally different from mammalian cells. The nature and degree of this selectivity determines whether the given antimicrobial drug is generally non-toxic in its relationship with mammalian cells or if it just exhibits certain toxicity on certain mammalian tissues. Antimicrobial drugs exhibit antibacterial effect using one or all of the following mechanisms:

1. Inhibition of cell membranes synthesis in microorganisms (beta-lactam antibiotics, vancomycin, cycloserine).
2. Inhibition of protein synthesis in microorganisms (aminoglycosides, erythromycin, clindamycin, chloramphenicol, and tetracyclines).

3. Inhibition of nucleic acid synthesis or their function in microorganisms (sulfonamides, trimethoprim, metronidazole, quinolones, and rifampicin).
4. Inhibition or alteration of function of external or cytoplasmic membranes of microorganisms (polymixin).

An effective approach of antimicrobial therapy of an infection is based on the isolation and identification of the infected organism and determining its sensitivity to antimicrobial drugs. *In vitro* tests, such as diffusion in agar and determining the minimally inhibitory concentration in a liquid medium are the most widely used tests.

In the method of diffusion in agar, a paper disc containing a certain amount of antimicrobial drug is placed on the top of the plate covered by agar containing a standard amount of bacteria. After incubating it for a certain amount of time, the diameter of clean zones around the disc are measured, which indicates the absence of bacterial growth. The diameters are interpreted as *sensitive*, *intermediate*, *and resistant* to the specific drug after comparing it with the standard. A drawback of this method is that it only shows the possible qualitative inhibitory activity.

Qualitative sensitivity is also determined by a method of determining the minimal inhibitory concentration in a liquid medium. A series of two-fold dilutions of a drug in a solution containing a standardized amount of microorganisms are observed. The results are expressed by an index of *minimal inhibitory concentration* (MIC), which is the minimal concentration of drug that inhibits visible growth after overnight incubation. *Minimal bactericidal concentration* (MBC) is determined by the absence of bacterial growth on agar plates that have been reincubated for one more night. This is the lowest concentration of drug that destroys a minimum of 99.9% of the bacterial contents of the test. The MIC and MBC must be correlated with the concentration of drug attainable in the plasma and in other tissues and fluids in the body.

Antimicrobial drugs can be classified as bacteriostatic (for example, tetracyclines, sulfonamides) and as bactericidal (for example, penicillin). Bacteriostatic drugs inhibit bacterial growth, but do not destroy these organisms in clinically attainable concentrations. It should be expected that the MBC of such drugs will be significantly higher than the MIC.

Bactericidal drugs cause death of microbial cells and their lysis at clinically attainable concentrations. For such drugs, the MBC is close or equal to the MIC. Treatment with bacteriostatics stops bacterial growth, thus allowing neutrophils and other protective powers of the body to remove the pathogen.

Resistance can be observed during the process of antibiotic use. Resistance of bacteria to antimicrobial drugs can be characterized and classified by two signs: internal resistance and acquired resistance. Internal resistance of a microorganism is the genetic ability of a microorganism that is coded in the chromosomes and spread to all lines of the given type of microorganisms. Acquired resistance means that the given line of a type of bacteria acquired the ability to oppose the given antimicrobial drug.

Acquired resistance implies a change in the DNA of the bacteria that results in the appearance of new characteristic features. Such resistance is achieved in two ways: mutation of chromosomes in bacteria or acquisition of new pieces of DNA (plasmid) that code for a function of resistance.

The biochemical mechanisms of internal and acquired resistances are identical and can be explained as the result of one of the following four reasons:

1. Inactivation or modification of drugs by bacterial enzymes.
2. Formation of a impermeable barrier, so that the drug cannot reach the desired region of action.
3. Changing the target itself so that the drug cannot bind or have an effect on it.
4. Development of altered metabolic pathways, which permits the effect of the drug to be bypassed.

If the organism undergoes simultaneous action of two antimicrobial drugs, it can result in an additive effect, synergism, or antagonism.

Drugs are considered to act additively when the activity of drugs in combination are equal to the sum of their independent activity. The overall effect of two antimicrobial drugs can be less (antagonism) or more (synergism) than the sum effect.

Synergism can occur as a result of various mechanisms of action, such as subsequent blockage of the general metabolic pathway or increasing the permeability of bacterial cells.

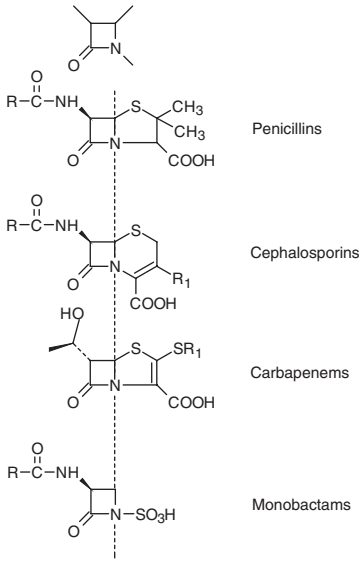
There are several ways to classify antibiotics and they are determined primarily by the professional interests of researchers.

In particular, antibiotics are classified according to their principal biological origin (for example, antibiotics developed by certain microorganisms), mechanism of their biological action (for example, antibiotics that inhibit synthesis of nucleic acids), their spectrum of biological use (for example, antibacterial antibiotics with a narrow spectrum of use, active mainly with respect to Gram-positive organisms, antibacterial antibiotics with a broad spectrum of use, antituberculosis antibiotics, antifungal antibiotics, antitumor antibiotics, and antiamebic antibiotics), and finally, according to their chemical structure, for example, beta-lactam antibiotics, tetracyclines, aminoglycosides, macrolids, and so on.

32.1 BETA-LACTAM ANTIBIOTICS

Beta-lactam antibiotics will be examined in four groups, including penicllins, cephalosporins, monobactams, and carbapenems. All of these contain a four-membered beta-lactam ring, which is necessary for exhibiting antibacterial activity. The beta-lactam ring is joined to a five-membered thiazolidine ring in penicillin, and a six-membered dihydrothiazine ring in cephalosporins. In carbapenems, the beta-lactam ring is also joined to a five-membered ring, although it is carbocyclic. Monobactams have a monocyclic beta-lactam structure, and the side sulfo-group is joined to a nitrogen atom.

The primary mechanism of the action of beta-lactam antibiotics is the inhibition of synthesis of cell membranes of bacteria, which causes them to quickly die. Their initial action is to initiate the work of autolytic enzymes, which destroy cell membranes and cause lysis of the bacteria.



The structure of the cell membrane of bacteria is unique and does not have any mammalian analogs. The cell membrane protects bacteria cells from lysis, which can occur as a result of different osmotic pressures between the cytoplasm and the surrounding medium.

The main component of bacterial cell membranes is a mixed polymer known as murein or peptidoglycan. Peptidoglycan is a long polysaccharide chain that is cross-linked with short peptides.

Polysaccharide chains are made up of two varying aminosugars—*N*-acetylglucosamine and *N*-acetylmuraminic acid. For example, *Staphylococcus aureus* (golden staphylococci), a tetrapeptide made of L-alanine, D-glutamic acid, L-lysine, and D-alanine, is joined to every one of the *N*-acetylmuraminic acid units, forming side chains of glycan chains. Many of these tetrapeptides are cross-linked with one another either directly or with short peptide chains. In *S. aureus*, L-lysine of one of the tetrapeptides is bound by a pentaglycine chain to D-alanine of the other. This kind of structure gives it a certain rigidity to bacterial membranes. The peptidoglycan layer of Gram-negative bacteria is thinner than that of Gram-positives, and it has fewer cross-(transversal) links.

The synthesis of peptidoglycan of bacterial cell membranes can be divided into three stages based on where the reaction takes place.

The first stage occurs in the cytoplasm, which results in the synthesis of precursor units—uridindiphospho-*N*-acetylmuramyl pentapeptide. Such an antibiotic, for example, cycloserine, the drug most frequently used to treat tuberculosis, blocks synthesis of cell membranes at this stage by competitive inhibition of the stage of introducing alanine into a pentapeptide.

Reactions in the second stage occur when precursor units move along the cytoplasmic membrane. In the first reaction, the *N*-acetylmuramylpentapeptide region binds (through a pyrophosphate bridge) to a carrier phospholipid that is bound to the cytoplasmic membrane. *N*-acetylglucosamine is then bound, forming a disaccharide–pentapeptide–P-P-phospholipid.

Further modification of the pentapeptide chain then occurs; for example, the binding of pentaglycine in the case of *S. aureus*. The modified disaccharide is subsequently removed from the membrane-bound phospholipid and then bound to the existing region already containing the peptidoglycan. This reaction is mediated by the enzyme peptidoglycan synthetase. The primary repeating units of the peptidoglycan are thus collected, forming a glycopeptide polymer. This process can be disrupted by antibiotics such as vancomycine, which inhibits peptidoglycan synthetase.

The third and final stage of synthesis of cell walls occurs outside the cytoplasmic membrane. Thus, the transpeptidation reaction results in transformation of the linear glycopeptide polymer into the cross-linked form. The enzyme transpeptidase, a membrane-bound enzyme, binds pentapeptide side chains by replacing terminal D-alanines.

As already noted, beta-lactam antibiotics interfere with biosynthesis of the primary component of cell membranes—peptidoglycan. Because of the fact that this process does not take place in human and other mammalian cells, beta-lactam antibiotics are relatively non-toxic to humans.

Beta-lactam antibiotics specifically bind with a number of proteins of cytoplasmic membranes known as penicillin-binding proteins (PBP). These proteins are enzymes involved in the reaction of transpeptidation during the break up of cell membranes during growth and division.

For example, *Escherichia coli* have six PBP. PBP-1a and -1b, which are transpeptidases, are involved in the synthesis of peptidoglycan. PBP-2 is necessary for supporting the "rod-shaped" form of bacteria. Selective inhibition of this enzyme causes production of other "non-rod-shaped" forms of bacteria, which eventually undergo lysis. PBP-3 is necessary to form the partition during division. Selective inhibition of this enzyme leads to the formation of a fibrous form of bacteria containing many units of rod-shaped bacteria unable to separate one from another, which results in their death. Various beta-lactam antibiotics have a selective affinity to one or a few PBP. Inactivation of certain PBP (PBP-1a, -1b, -2, or -3) causes cell death. Unlike these, inactivaition of low-molecular PBP (PBP-4, -5, and -6) is not lethal to bacteria.

Resistance of pathogenic microorganisms to beta-lactam antibiotics can result from one or a few of the mechanisms listed below: inability of the drug to directly find an active site; a change in PBP function, which is expressed in the reduction of affinity to the drug; or inactivation of the drug by bacterial enzymes.

Beta-lactam antibiotics must pass through the outer layer of the cell in order to get the desired PBP to the surface of the membrane. In Gram-positive bacteria, the cell membrane is the only layer covering the cytoplasmic membrane. In a few types of this bacteria, there is a polysaccharide capsule on the outer side of the cell membrane. However, not one of the described structures can serve as a barrier for the diffusion of small molecules such as beta-lactams. Therefore, the idea that the cause of possible resistance is the inability of beta-lactam antibiotics to get the desired PBP is not likely to be a possible mechanism of resistance for Gram-positive bacteria.

Gram-negative bacteria have a more complex cell surface. The peptidoglycan layer is also the outer layer with respect to the cytoplasmic membrane. However, besides this, they have another outer polysaccharide membrane. This outer membrane is built out of lipopolysaccharides and lipoproteins, and can be a serious barrier for permeating hydrophilic molecules.

Diffusion of beta-lactam antibiotics across this membrane is only possible through transmembrane channels made of proteins called porines. It has been shown that beta-lactam antibiotics diffuse through porine channels, and the ease of this process varies depending on their size, charge, and hydrophilic properties. Accordingly, the idea of the possible mechanism of resistance for Gram-negative bacteria being the inability of beta-lactam antibiotics to get desired PBP is also unlikely.

The second mechanism of resistance to beta-lactam antibiotics can appear as a change in target PBP, which is expressed in a reduction in the affinity to beta-lactam molecules.

Finally, the most important mechanism of resistance to beta-lactam antibiotics is the production of beta-lactamase by the bacteria. Beta-lactamases break the C–N bond in the beta-lactam ring of antibiotics. Since its existence is absolutely necessary for reacting with PBP, a break in the beta-lactam ring leads to a loss of antibacterial activity.

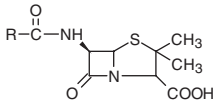
There are many beta-lactamases and they can be classified differently: by type of substrate, replacement of genes (chromosomes or plasmids), and place of production. A few of these enzymes directly hydrolyze penicillins (penicillinases), others hydrolyze cephalosporins (cephalosporinases), and others extend to a broad spectrum of substrates. A few bacteria have the ability to induce synthesis of beta-lactamase. Synthesis of beta-lactamase, which in a normal condition is suppressed, is induced in the presence of some beta-lactam antibiotics.

Thus, beta-lactam antibiotics can inihibit the process of synthesis of bacterial cell membranes in different ways, thus causing them to die quickly.

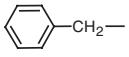
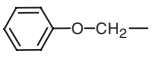
32.1.1 Penicillins

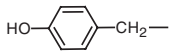
Penicillin was discovered in 1928 by Alexander Fleming, who noticed that one of his experimental cultures of staphylococcus was contaminated with mold, which caused the bacteria to lyse. Since mold belonged to the family *Penicillium*, he named the antibacterial substance penicillin.

About a decade later, a group of researchers at Oxford University isolated a crude substance made up of a few low-molecular substances, which were penicillins (F, G, K, O, V, X). Penicillin G (benzylpenicillin), the most active of these, was suggested for clinical trials in 1941.

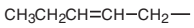


penicillins

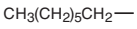
Structure of R radical	Name of Penicillin
	Penicillin G Benzylpenicillin
	Penicillin V Phenoxymethylpenicillin



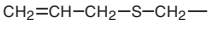
Penicillin X
p-Oxybenzylpenicillin



Penicillin F
2-Pentenylpenicillin



Penicillin K
p-Heptylpenicillin



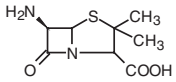
PenicillinO
Allylmercaptomethylpenicillin

Drugs of the penicillin group are effective for infections caused by Gram-positive bacteria (streptococcus, pneumococcus, and others), spirochaetae, and other pathogenic microorganisms. Drugs of this group are ineffective with respect to viruses, mycobacteria tuberculosis, fungi, and the majority of Gram-negative microorganisms.

The production of penicillin was an extremely important milestone in the development of microbiology, chemistry, and medicine, signifying the creation of the powerful antibiotic industry and formation of modern biotechnology.

There have been attempts to chemically synthesize penicillins; however, no practical methods have been found.

An extremely important progress in the development of penicillins took place in 1959, when the penicillin nucleus, 6-aminopenicillanic acid (6-APA), was removed from the side chain and isolated from a culture of *Penicillium chrysogenum.*



6-aminopenicillanic acid

Subequent acylation of 6-APA by various acid derivatives led to the formation of a large number of semisynthetic penicillins.

Currently, penicillin (benzylpenicillin, penicillin G) is made in huge amounts (tens of thousands of tons) by the microbiological industry.

Penicillin can be made by many types of *Penicillium* fungi, and also by a few types of *Asperigillus* fungi. In industrial conditions, culture fluids are made that contain more than 30 mg/mL of penicillin. About two-thirds of the produced penicillin is used for making 6-APA. Despite the possibility of pure chemical deacylation, the most prospective way of making 6-APA is an enzymatic method of hydrolyzing benzylpenicillin molecules using immobilized penicyllinamidase, an enzyme isolated from practically all penicillin-producing fungi. It should be noted that 6-APA itself is practically devoid of antibiotic proterties. However, by acylating it with various acid derivatives, more than 50,000 semisynthetic penicillins have been made, of which less than 30 are currently used in medicine.

Variations of the acyl regions of the side chain in penicillin molecules produces significant changes in the properties of resulting compounds. It was discovered that the side

chain of the acyl region of the molecule determines the antimicrobial spectrum, sensitivity to beta-lactams, and the unique pharmacokinetic features of a specific penicillin. The unique feature of a few semisynthetic penicillins (meticillin, oxacillin, cloxacillin) is their efficacy with respect to a culture of microorganisms (staphylococcus) resistant to benzylpenicillins. Moreover, some semisynthetic penicillins (ampicillin) are active with respect to the majority of Gram-negative microorganisms.

From the chemical point of view, the first type of semisynthetic penicillins, undoubtedly, are considered relatively simple derivatives of 6-APA and aromatic or aryloxycarboxylic acids (benzylpenicillin, phenoxymethylpenicillin, meticillin, naphicillin).

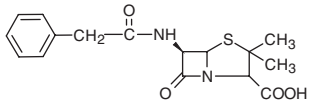
Another type of semisynthetic penicillins that are considered heteroylcarboxylic acid derivatives, in which the acyl group is represented as an aromatic heterocyclic acid derivative (oxacillin, cloxacillin, dicoxacillin).

The next type of semisynthetic penicillins are those in which the acyl group is represented by an amino acid, mainly α-aminophenylacetic acid (phenylglycine) or *p*-oxy-α-aminophenylacetic acid, and correspondingly, ampicillin and amoxicillin.

Finally, the fourth type of replacement in the side acyl region of penicillins is the replacement by dicarboxylic acid derivatives (carbenicillin, ticarcillin).

All penicillins are used as sodium or potassium salts.

Benzylpenicillin: Benzylpenicillin, [2*S*-(2α,5α,6β)]-3,3-dimethyl-7-oxo-6-(phenylacetamido)-4-tio-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (32.1.1.1), is the gold standard penicillin, which is obtained biotechnogically using the fungus *P. chrysogenum* as the producer, and phenylacetic acid as the precursor. The sodium or potassium salts of this drug are used in medicine, and it is for this reason that the extract of the cultural liquid is treated with an aqueous solution of the respective base, and the commercial product is the corresponding lyophilized salt [1–5]. There are also purely synthetic ways of making benzylpenicillin [6,7].

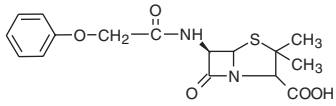


32.1.1.1

Benzylpenicillin or penicillin G has a narrow antimicrobial spectrum. It is active with respect to Gram-positive bacteria (staphylococcus, streptococcus, and pneumococci), causative agent of diphtheria, and anthrax bacillus. Gram-negative bacteria are resistant to it. Benzylpenicillin is broken down by stomach acid and destroyed by staphylococcus penicillinase.

Benzylpenicillin is the drug of choice for infections caused by sensitive organisms. This includes streptococci infections (except enterococci), gonococci, and meningococci that do not produce beta-lactam anaerobes. Benzylpenicillin is used for croupous and focal pneumonia, skin infections, soft tissue and mucous membranes, periotonitis, cystisis, syphilis, diphtheria, and other infectious diseases. Synonyms of this drug are megacillin, tradocillin, bicillin, sugracillin, vicillin, and others.

Phenoxymethylpenicillin: Phenoxymethylpenicillin, [2*S*-(2α,5α,6β)]-3,3-dimethyl-7-oxo-6-(phenoxyacetamido)-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (32.1.1.2), is also obtained biotechnologically using the fungus *P. chrysogenum* as the producer and phenoxyacetic acid as the precursor [8–11]. As with benzylpenicillin, there is a purely synthetic way of making phenoxymethylpenicillin [6,12–15].

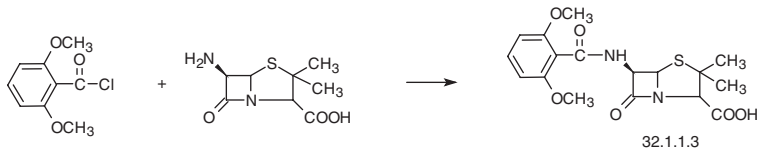


32.1.1.2

Phenoxymethylpenicillin or penicillin V is acid-resistant and used instead of penicillin G for oral use. It is active with respect to Gram-positive (staphylococcus, streptococcus, pneumococcus), and Gram-negative (meningococcus, gonococcus) cocci, spirochaeta, clostridia, and corynebacteria.

Phenoxymethylpenicillin is used for bronchitis, pneumonia, angina, scarlet fever, gonorrhea, syphilis, purulent skin and soft-tissue wounds, and other infectious diseases. Synonyms of this drug are bermycin, isocillin, cristapen, fenospen, uticillin, and others.

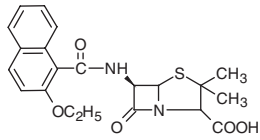
Methicillin: Methicillin, [2*S*-(2α,5α,6β)]-3,3-dimethyl-7-oxo-6-(2,6-dimethoxybenzamido)-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (32.1.1.3), is synthesized by acylating 6-APA with 2,6-dimethoxybenzoic acid chloride in the presence of triethylamine [15–17].



32.1.1.3

Like other semisynthetic penicillins, methicillin exhibits an antibacterial effect similar to that of benzylpenicillin. The main difference between methicillin and benzylpenicillin is that it is not inactivated by the enzyme penicillinase, and therefore it is effective with respect to agents producing this enzyme (staphylococci). It is used for infections caused by benzylpenicillin-resistant staphylococci (septicemia, pneumonia, empyemia, osteomyelitis, abscesses, infected wounds, and others). Synonyms of this drug are cinopenil, celbenin, staphcillin, and others.

Nafcillin: Nafcillin, [2*S*-(2α,5α,6β)]-3,3-dimethyl-7-oxo-6-(2-ethoxy-1-naphthamido)-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (32.1.1.4), is synthesized by acylating 6-APA with 2-ethoxy-1-naphthoic acid chloride in the presence of triethylamine [18–20].



32.1.1.4

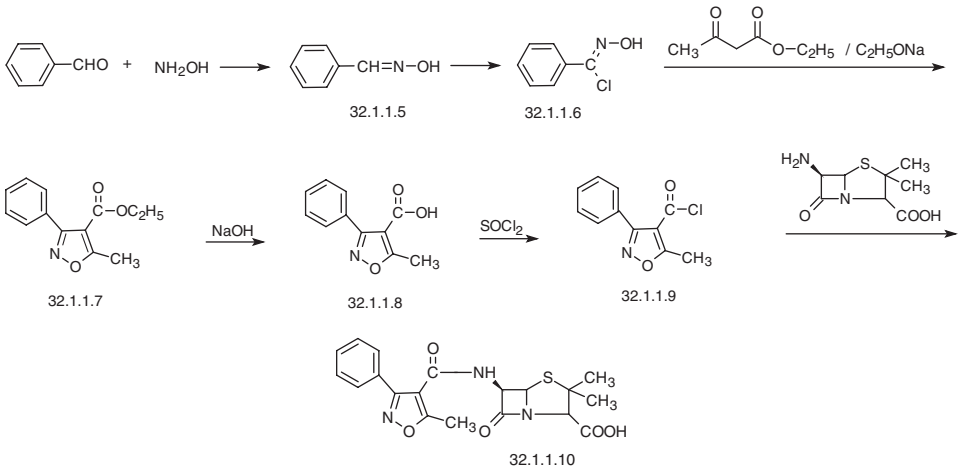
It is effective against Gram-positive cocci and staphylococci that produce penicillinase. It is used for the same indications as methicillin. Synonyms of this drug are nafcil, nalpen, unipen, and others.

Another type of semisynthetic penicillin that should undoubtedly be considered is penicillin derivatives of heteroylcarboxylic acids (as a rule an isoxazol) in the third position of which is present a substituted or nonsubstituted phenyl radical (oxacillin, cloxacillin, dicloxacillin), which plays the role of the radical in the acyl side group. These penicillins (oxacillin, cloxacillin, dicloxacillin), which are resistant to penicillinase, are active with respect to penicillin-G-resistant staphylococci. Their antimicrobial spectrum is restricted to Gram-positive microorganisms.

Penicillins that are resistant to penicillinase are the drug of choice for infections resistant to penicillin G, *Staph. aureus*, or coagulase-negative staphylococci. They are also effective for infections caused by nonenterococcus types of streptococci, such as streptococci groups A, B, C, and G, as well as pneumococci.

Oxacillin: Oxacillin, [2*S*-(2α,5α,6β)]-3,3-dimethyl-7-oxo-6-(5-methyl-3-phenyl-4-isoxazolcarboxamido)-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (32.1.1.10), is synthesized by reacting 5-methyl-3-phenyl-4-isoxazolcarboxylic acid chloride (32.1.1.9) with 6-APA in the presence of sodium bicarbonate. The 5-methyl-3-phenyl-4-isoxazolcarboxylic acid chloride (32.1.1.9) is synthesized by the following scheme.

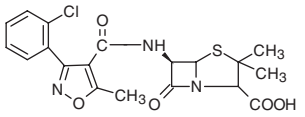
Reacting benzaldehyde with hydroxylamine gives benzaldoxime (32.1.1.5), which when oxidized by chlorine gives benzhydroxamic acid chloride (32.1.1.6). This is reacted with acetoacetic ester in the presence of sodium ethoxide, giving the ethyl ester of 5-methyl-3-phenyl-4-isoxazolcarboxylic acid (32.1.1.7). Alkaline hydrolysis of the resulting ester gives the corresponding acid (32.1.1.8), which is reacted with thionyl chloride to give the acid chloride necessary for acylation [21–24].



In terms of the spectrum of antimicrobial action, oxacillin is analogous to benzylpenicillin. However, it combines the resistance to penicillinase with durability in an acidic medium, which allows it to be used not only intramuscularly, but also orally. It is used for infections caused by

penicillinase-producing staphylococci that are resistant to benzyl- and phenoxymethylpenicillins (septicemia, pneumonia, abscesses, empyemia, osteomyelitis, infected burns, infected wounds, and others). Synonyms of this drug are cryptocillin, liucipen, optocillin, totocillin, and others.

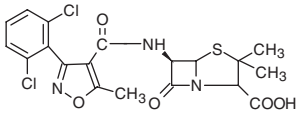
Cloxacillin: Cloxacillin, [2*S*-(2α,5α,6β)]-3,3-dimethyl-7-oxo-6-[(5-methyl-3-(*o*-chlorphenyl)-4-isoxazolcarboxamido)]-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (32.1.1.11), is synthesized from *o*-chlorobenzaldehyde by the scheme described above [21–23,25].



32.1.1.11

In terms of mechanism of action and indications for use, it is analogous to oxacillin. Synonyms of this drug are ampiclox, orbenin, totaclox, tegopen, and others.

Dicloxacillin: Dicloxacillin, [2*S*-(2α,5α,6β)]-3,3-dimethyl-7-oxo-6-[(5-methyl-3-(2,6-dichlorophenyl)-4-isoxazolcarboxamido)]-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (32.1.1.12), is also synthesized by the scheme described above using 2,6-dichlorobenzaldehyde as the starting substance [26–28].



32.1.1.12

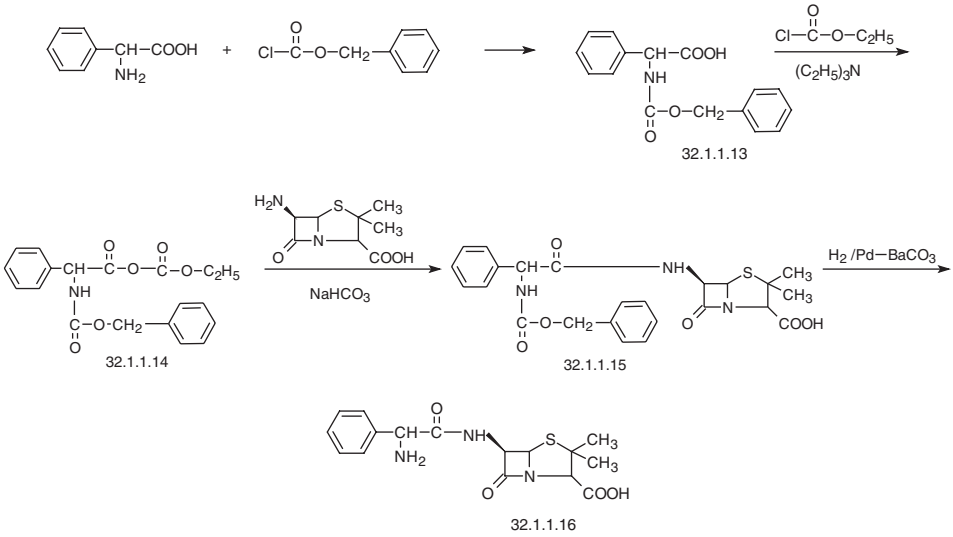
In terms of mechanism of action, antibacterial spectrum, and indications for use, it is essentially no different than oxacillin and cloxacillin. Synonyms of this drug are diclocil, novapen, diclex, and others.

The following type of semisynthetic penicillins that should be considered are those in which amino acids, mainly α-aminophenylacetic or *p*-oxy-α-amino-phenylacetic acids, act as the acyl radical (ampicillin, amoxacillin).

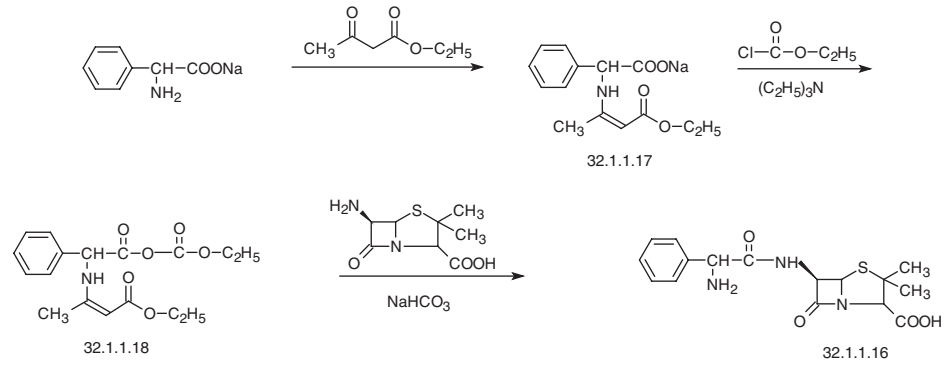
The antimicrobial spectrum of aminopenicillins is similar to penicillin G, with the exception that they also act on a number of Gram-negative microorganisms. Both aminopenicillins are destroyed by staphylococcus penicillinase.

Ampicillin: Ampicillin, [2*S*-[2α,5α,6β(*S*)]]-3,3-dimethyl-7-oxo-6-(2-amino-2-phenylacetamido)-4-thia-azabicylco[3.2.0]-heptan-2-carboxylic acid (32.1.1.16), is synthesized in various ways using different methods of protection of amino group in the starting phenylglycine. One of the most widely used methods uses the benzyl chloroformate. Reacting this with phenylglycine initially forms benzyloxycarbonylphenylglycine (32.1.1.13). Treating this with ethyl chloroformate in the presence of triethylamine gives a mixed anhydride (32.1.1.14) with a protected amino group that easily reacts with 6-APA

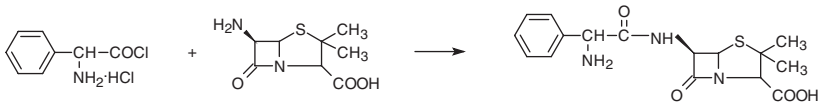
in the presence of sodium bicarbonate, to form the sodium salt of the *N*-benzyloxycarbonyl-protected ampicillin (32.1.1.15). Removing the protecting group by hyrogenolysis using a palladium on barium carbonate catalyst gives the desired ampicillin (32.1.1.16) [29–35].



Another method of making ampicillin is analogous to the method described above, and it differs in the method of protecting the α-amino group in the initial phenylglycine. In order to do this, acetoacetic ester is reacted with the sodium salt of phenylglycine, which forms an intermediate—aminocrontonic ester (32.1.1.17). Subsequent transformation of this product to the mixed anhydride (32.1.1.18) followed by a reaction with 6-APA in the presence of sodium bicarbonate gives ampicillin (32.1.1.16) in the form of a sodium salt [36].



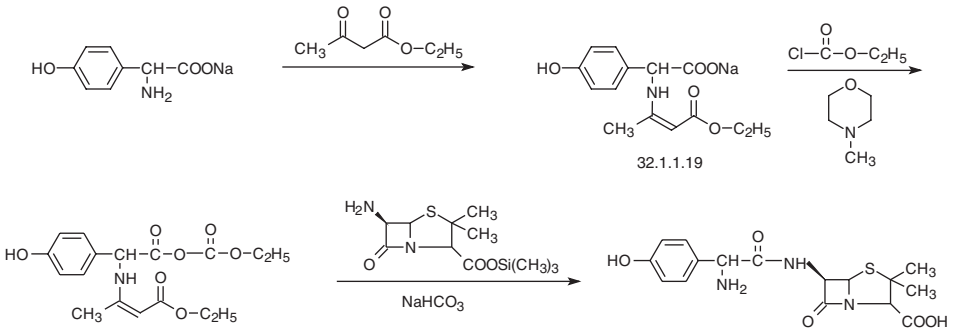
A method of directly acylating 6-APA with phenylglycine chloride hydrochloride also has been proposed [37].



32.1.1.16

Ampicillin has a broad spectrum of action and is effective for infections caused by various sensitive organisms; it is active with respect to Gram-positive and Gram-negative cocci, intestinal bacilli, salmonella, shigella, enterococci, listeria, and a few strains of hemophilic bacilli. Ampicillin is the drug of choice for infections caused by beta-lactamase negative types of *Haemophilus influenzae, Listeria monocytogenes*, and enterococci. It is used for bronchitis, pneumonia, dysentery, salmonella, whooping cough, pyelonephritis, endocarditis, sepsis, and so on. Synonyms of this drug are amblocin, binotal, liucipen, totapen, amfipen, ampicil, penberin, and many others.

Amoxycillin: Amoxycillin, [2*S*-[2α,5α,6β(*S*)]]-3,3-dimethyl-7-6-[[amino-(4-hydroxyphenyl)-acetyl]amino]-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (32.1.1.21), is synthesized in two ways. The first uses an enamine protection of the amino group of 4-hydroxyphenylglycine, which begins with the sodium salt of 4-hydroxyphenylglycine, which is reacted with the acetoacetic ester to form an enamine—the sodium salt of a p-hydroxyphenyl acetic acid, α-[(3-ethoxy-1-methyl-3-oxo-1-propenyl)amino]-4-hydroxy- (32.1.1.19). Reacting the resulting aminocrotonate with the ethyl chloroformate in *N*-methylmorpholine gives the corresponding mixed anhydride (32.1.1.20), which is reacted with trimethylsilyl ester of 6-APA [38,39].

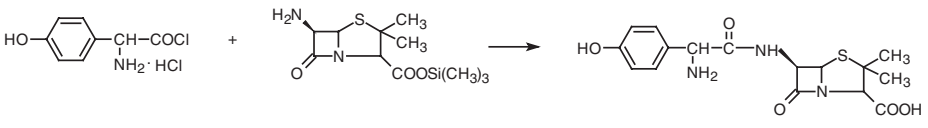


32.1.1.19

32.1.1.20

32.1.1.21

The second method uses a direct reaction of D-(−)-2-(4-hydroxyphenyl)glycine chloride hydrochloride with trimethylsylil ester of 6-APA [40].



32.1.1.21

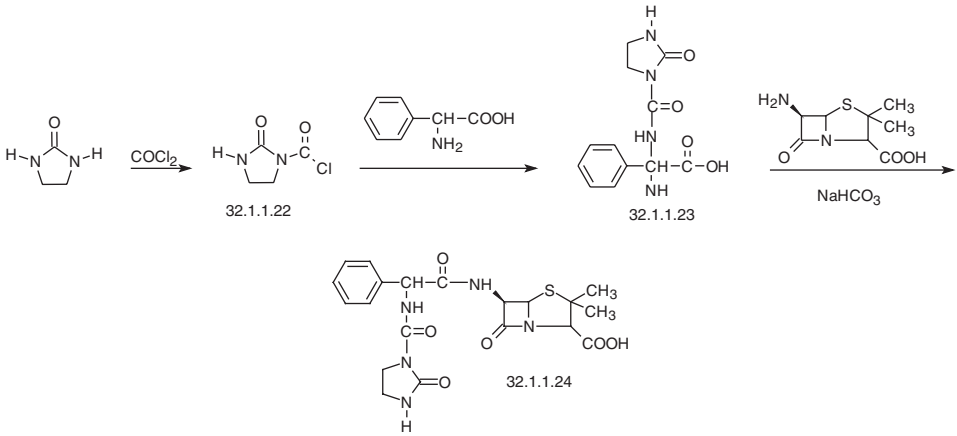
The trimethylsilyl ester of 6-APA needed for the reaction is in turn synthesized by reacting trimethylchlorosilylane with 6-APA in the presence of trimethylamine.

Amoxycillin, like ampicillin, has a broad spectrum of use.

Indications for use are the same as with ampicillin. Synonyms of this drug are amoxican, amoxil, larotid, robamox, trimox, vimox, utimox, and others.

Undoubtedly, analogs of ampicillin that are substituted at the amine fragment of phenylglycine (azolcillin, mezlocillin, piperacillin) should be included in this same group of compounds.

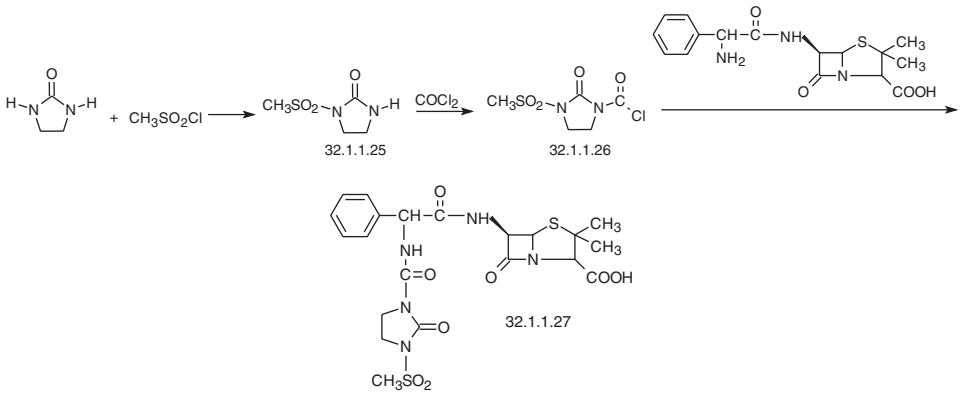
Azlocillin: Azlocillin, (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[(*R*)-2-(2-oxoimidazolidin-1-carboxamido)-2-phenylacetamido]-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (32.1.1.24), is synthesized by the following scheme. 2-Imidazolidinone is acylated with phosgene, forming 1-chlorocarbonyl-2-imidazolidinone (32.1.1.22). The resulting 1-chlorocarbonyl-2-imidazolidinone (32.1.1.22) is reacted with D(–)-α-phenylglycine, forming *N*-(2-oxoimidazolidin-1-carboxamido)-phenylglycine (32.1.1.23). Reacting this with 6-APA in the presence of triethylamine gives the desired azlocillin (32.1.1.24) [41–43].



Azlocillin is active with respect to Gram-positive and Gram-negative aerobic and anaerobic microorganisms. It is highly effective with respect to bacillus pyocyaneus, including strains that are resistant to carbenicillin and aminoglycosides. It is destroyed by beta-lactamases. It is used for bacterial infections such as pyelonephritis, uretritis, cystitis, endometritis, cholecystitis, sepsis, peritonitis, endocarditis, meningitis, pneumonia, infections of the skin and soft tissues, infected burns, and so on. Synonyms of this drug are securopen and azlin.

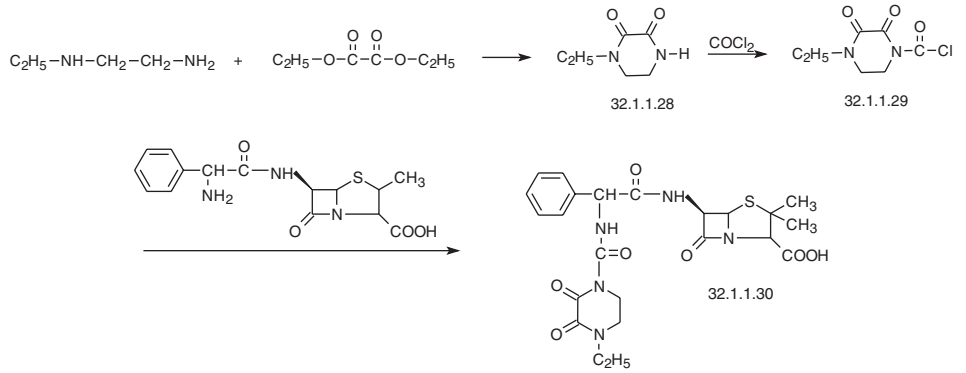
Mezlocillin: Mezlocillin, (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[(*R*)-2-[(3-methylsulfonyl)-2-oxoimidazolidin-1-carboxamido]-2-phenylacetamido]-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (32.1.1.27), is synthesized by acylating ampicillin (32.1.1.16) with 3-chlorocarbonyl-1-methansulfonyl-2-imidazolidinone (32.1.1.26) in the presence of triethylamine. The necessary 3-chlorocarbonyl-1-methansulfonyl-2-imidazolidinone (32.1.1.26) is synthesized by sulfonating 2-imidazolidinone with methanesulfonyl chloride, which forms

1-methanesulfonyl-2-imidazolidinone (32.1.1.25) and its subsequent reaction with phosgene [44–46].



Like azlocillin, mezlocillin is used for infections of the urinary tract, gynecological infections, intraabdominal infections, skin infections, and respiratory tract infections. Synonyms of this drug are baypen, mezlin, and optocillin.

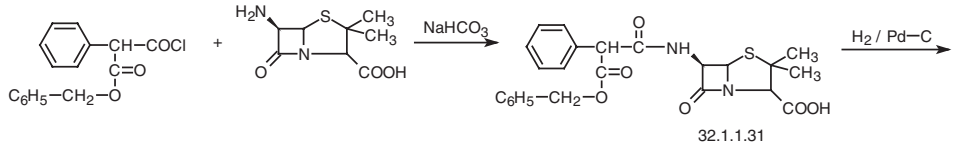
Piperacillin: Piperacillin, (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[(2R)-2-[(4-ethyl-2,3-dioxo-1-piperazinyl)formamido]-2-phenylacetamido]-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (32.1.1.30), is also synthesized by acylating ampicillin (32.1.1.16), but with 1-chlorocarbonyl-4-ethylpiperazin-2,3-dione (32.1.1.29). The necessary 1-chlorocarbonyl-4-ethylpiperazin-2,3-dione (32.1.1.29) is synthesized by reacting *N*-ethylethylenediamine with diethyloxalate, forming 4-ethylpiperazin-2,3-dione (32.1.1.28), and then acylating this with phosgene after initial silylation of the product at the nitrogen atom with trimethylchlorosilane [47–50].



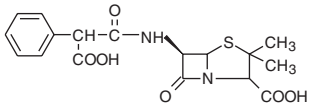
The spectrum of use is the same as that of azlocillin and mezlocillin. Synonyms of this drug are pipril, pipracil, avocin, and others.

Finally, the fourth type of substitution of the side acyl region of penicillins that should be considered is the substitution of dicarboxylic acid derivatives (carbenicillin, ticarcillin).

Carbenicillin: Carbenicillin, [2*S*-(2α,5α,6β)]-3,3-dimethyl-7-oxo-6-(2-carboxy-2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (32.1.1.32), is synthesized by direct acylation of 6-APA in the presence of sodium bicarbonate by phenylmalonic acid monobenzyl ester chloride, which forms the benzyl ester of carbenicillin (32.1.1.31), the hydrogenolysis of which using palladium on carbon or calcium carbonate as catalyst gives the desired product (32.1.1.32) [51–58].



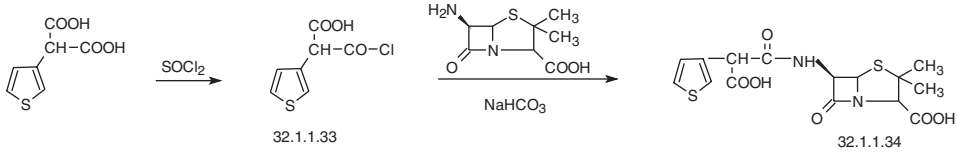
32.1.1.31



32.1.1.32

Carbenicillin has a broad spectrum of antibacterial use with respect to Gram-negative and Gram-positive microorganisms. However, using this drug for infections caused by Gram-positive microorganisms is pointless. It is used for diseases such as urinary tract infections, septicemia, endocarditis, meningitis, osteomelitis, peritonitis, purulent otitis, infected wounds, infected burns, and so on that are caused by Gram-negative microorganisms which are sensitive to such antibiotics. Synonyms of this drug are carindapen, pyopen, geopen, gripenin, and others.

Ticarcillin: Ticarcillin, [2*S*-(2α,5α,6β)]-3,3-dimethyl-7-oxo-6-[2-carboxy-2-(3-thienyl) acetamido]-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (32.1.1.34), is also synthesized by direct acylation of 6-APA in the presence of sodium hydroxide, but with 3-thienylmalonic acid chloride (32.1.1.33), which gives ticarcillin [52–57,59].



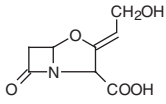
32.1.1.33

32.1.1.34

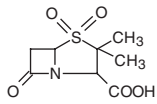
In terms of antimicrobial spectrum of action and area of use, ticarcillin is similar to carbenicillin. Synonyms of this drug are betabactyl, ticar, timentin, and others.

Beta-lactamase inhibitors

Clavulanic acid and sulbactam: An addition of beta-lactamase inhibitors, such as clavulanic acid (32.1.1.35) and sulbactam (32.1.1.36) to penicillins or to aminopenicillins of a broad spectrum of action significantly expands their antimicrobial spectrum.



32.1.1.35

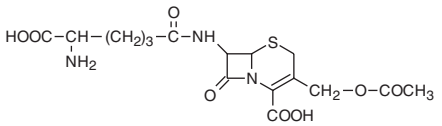


32.1.1.36

Clavulanic acid is isolated from *Streptomyces clavuligerus* [60–66], and sulbactam, a sulfone of penicillanic acid, is synthesized from 6-APA [67–69]. Both compounds have extremely weak antibacterial properties and act by forming irreversible complexes with beta-lactamase, which inactivates the enzyme, and as a result the beta-lactam antibiotic has time to destroy the microorganism. Currently, a number of combined drugs containing various combinations of beta-lactamase antibiotics and inhibitors are used.

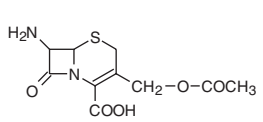
32.1.2 Cephalosporins

A number of antibiotics (cephalosporins P, N, C) were isolated from the products of fermentation of the fungus *Cephalosporium acremonicum.* The major component of the mixture is cephalosporin C, an amide, the acid part of which is α-aminoadipic acid, and amine part—7-aminocephalosporanic acid.

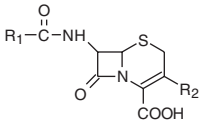


Cephalosporin C

Chemical or enzymatic hydrolysis of this compound allows to obtain large quantities of 7-aminocephalosporanic acid. A number of semisynthetic beta-lactam cephalosporin antibiotics were created by acylating the amino group of the last with various acid derivatives (analogous to the semisynthetic penicillin series) and currently there are about 25,000 of them, of which about 100 are used in medicine. Unlike penicillins, semisynthetic cephalosporins are synthesized not only by expanding the spectrum of various acids by which 7-aminocephalosporanic acid is acylated, but also by internal modifications of aminocephalosporanic nucleus (R_1 and R_2).



7-aminocyepalosporanic acid

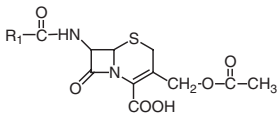


Semisynthetic cephalosporins

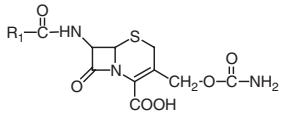
The cephalosporin nucleus is synthesized with a beta-lactam ring attached to a six-membered dihydrothiazine ring. Unlike the penicillin nucleus, the cephalosporin nucleus is much more resistant to beta-lactamase. Moreover, it has large areas for possible modifications. Modifications R_1 in the acyl side chain alter the antibacterial activity, while modifications of R_2 are associated with changes in the pharmacokinetics and metabolic parameters of the drug.

Radicals R_1 in the acyl side chain are basically the same or differ slightly from those used in penicillin synthesis.

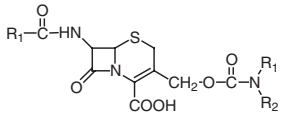
At the same time, modifications of R_2 are quite essential and can be determined as the following:



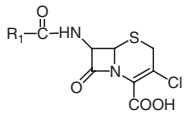
cephalothin, cefotaxim, cephapirin



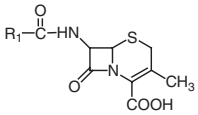
cefuroxime, cephoxytin



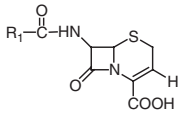
cefepime, cefpirome, cephtazidim



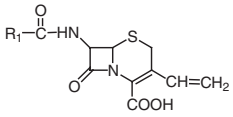
cefaclor



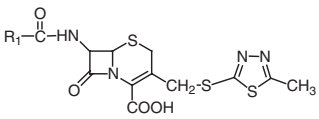
cephalexin, cephradin, cefadroxil



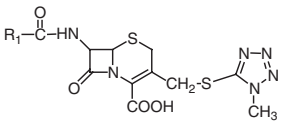
ceftizoxime



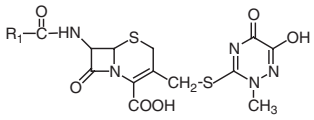
cephixim



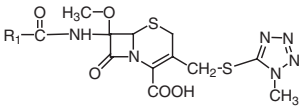
cephazolin



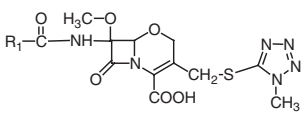
cefamandole, cefotetan, cephoperazon



cephtriaxone



cefotetan, cefaclon



moxalactam

In addition, the last of the shown drugs, moxalactam, contains a hydrooxazine ring instead of the dihydrothiazine ring common to all other cephalosporins. A few cephalosporins contain an additional methoxy group at position C_7 of aminocephalosporanic acid (cefotetan, cefaclor).

Cephalosporins are classified by four groups or subdivided into four generations based on the spectrum of their activity. Compounds of one generation differ from one another mainly by their pharmacokinetic unique features, although there may be differences with respect to separate microorganisms.

First-generation cephalosporins (cefalotin, cefaloridin, cephalexin, cephapirin, cefazolin, cefadroxil, cephradine, and others) possess high biological activity with respect to staphylococci, streptococci, pneumococci, and many types of enterobacteria.

Second-generation cephalosporins (cefuroxime, cefamandole, cefoxitin, cefotetan, cefaclor, and others) are characterized by high activity with respect to Gram-positive microorganisms that are resistant to beta-lactamase action. They do not have a noticible effect on enterococci.

Third-generation cephalosporins (cefotaxim, ceftizoxime, ceftriaxone, ceftazidime, cefoperazone, and many others) differ in the highly antimicrobial activity against enterobacteria,

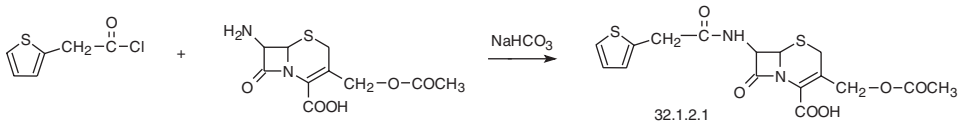
including those resistant to antibiotics. This group is resistant to the effects beta-lactamase formed by Gram-negative bacteria. However, they are moderately active with respect to staphylococci.

Fourth-generation cephalosporins (cefepime and cefpirome) are active with respect to a broad spectrum of Gram-positive and Gram-negative aerobes. They have an unusually low affinity with beta-lactamase and the ability to quickly pass through the periplasmatic space.

First-generation cephalosporins

First-generation cephalosporins (cephalothin, cephazolin, cephapirin, cephradin, cephalexin, and cefadroxil) possess high biological activity with respect to staphylococci, streptococci, pneumococci, and many types of enterobacteria, including *E. coli* and *Proteus mirabilis.* They are hydrolyzed by many beta-lactamases produced by Gram-negative bacteria, and therefore have a relatively narrow spectrum of activity with respect to Gram-negative bacteria. First-generation cephalosporins are an alternative to penicillins for treating staphylococci and nonenterococci infections in patients that cannot tolerate penicillin. They are widely used for the prevention of cardiovascular, orthopedic, and other surgical interventions.

Cefalotin: Cefalotin, (6*R-trans*)-3-[(acetyloxy)methyl]-8-oxo-7-[(2-thienylacetyl) amino]-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.1), is synthesized by direct interaction of 2-thienylacetic acid chloride with 7-aminocephalosporanic acid in the presence of sodium bicarbonate [70–74].

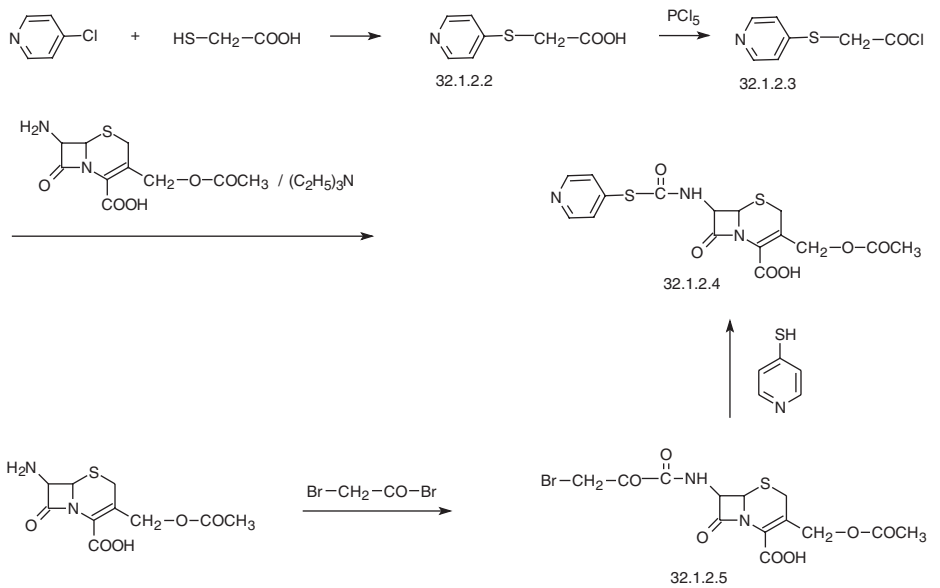


Cefalotin is an antibiotic with a broad spectrum of antimicrobial action; it is active with respect to Gram-positive (staphylococci, streptococci, pneumococci, diphtheria bacilli, anthrax) and Gram-negative microorganisms (meningococci, gonococci, shigella, salmonella, intestinal and hemophilia bacilli, klebsiella), and ineffective with respect to blue-pus bacillus, mycobacteria tuberculosis, and anaerobic microorganisms.

Cefalotin is used for bacterial infections of the lower respiratory tract, urinary tract, skin, soft tissues, bones and joints, sepsis, peritonitis, osteomyelitis, mastitis, infected wounds, and post-operational infections. Synonyms of this drug are ceflin, seffein, coaxin, and others.

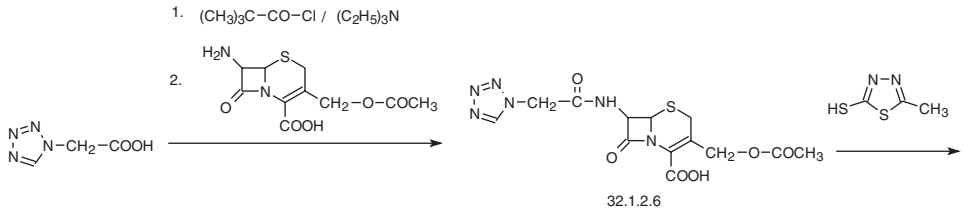
Cephapirin: Cephapirin, (6*R-trans*)-3-[(acetyloxy)methyl]-8-oxo-7-[[(4-pyridinylthio) acetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.4), is synthesized by acylating 7-aminocephalosporanic acid with 4-pyridylthioacetic acid chloride (32.1.2.3), which is synthesized by reacting 4-chloropyridine with mercaptoacetic acid in the presence of a base, forming 4-pyridylthioacetic acid (32.1.22), and further transforming the resulting acid to the acid chloride by reacting it with phosphorous pentachloride.

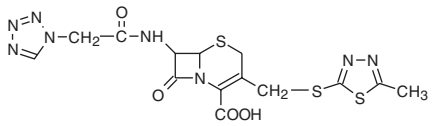
An alternative way of making cephapirin is the acylation of 7-aminocephalosporanic acid by bromoacetyl bromide, which gives a bromoacetyl derivative (32.1.2.5), and which is then reacted with 4-mercaptopyridine in the presence of triethylamine, forming the desired cephapirin (32.1.2.4) [75–78].



The spectrum of action and indications for use of cephapirin are the same as those of cephalothin. Synonyms of this drug are bristocef, cefarin, cefatrexyl, cefadil, and others.

Cefazolin: Cefazolin, (6*R-trans*)-3[[(5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl]-8-oxo-7-[(1*H*-tetrazol-1-ylacetyl)amino]-5-thia-1-azabycyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.7), is synthesized by reacting 7-aminocephalosporanic acid with a mixed anhydride (32.1.2.6), which is the result of a reaction of tetrazolylacetic acid with pivalic (trimethylacetic) acid chloride. Further reaction with 2-mercapto-5-methyl-1,3,4-thiadiazole results in a substitution of the 3-acetoxy group with a mercaptothiadiazol group, giving cefazolin (32.1.2.7). The major structural difference of this drug from the other examined first-generation cephalosporins is the replacement of the 3-acetoxymethyl group to a 1,3,4-thiadiazol-2-ylthiomethyl group [79–81].

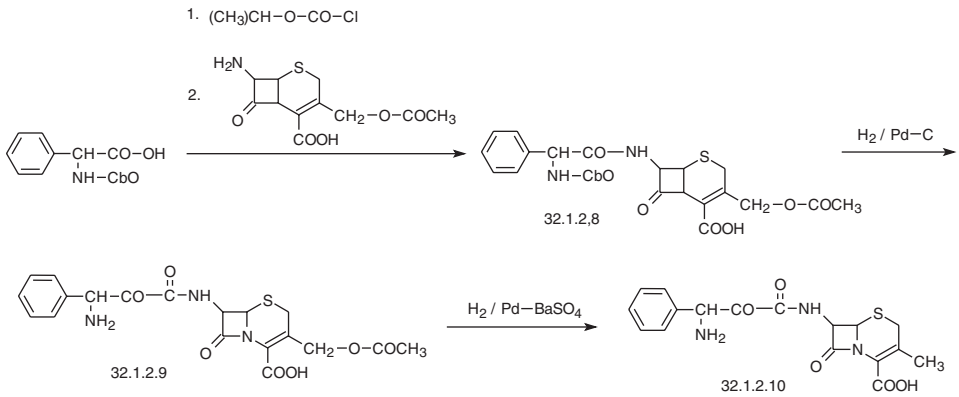




32.1.2.7

The spectrum of action of cephazolin and indications for use are the same as with cephalothin. Synonyms of this drug are cefacidal, cefazol, cefamezin, cefazil, zolin, ancef, and many others.

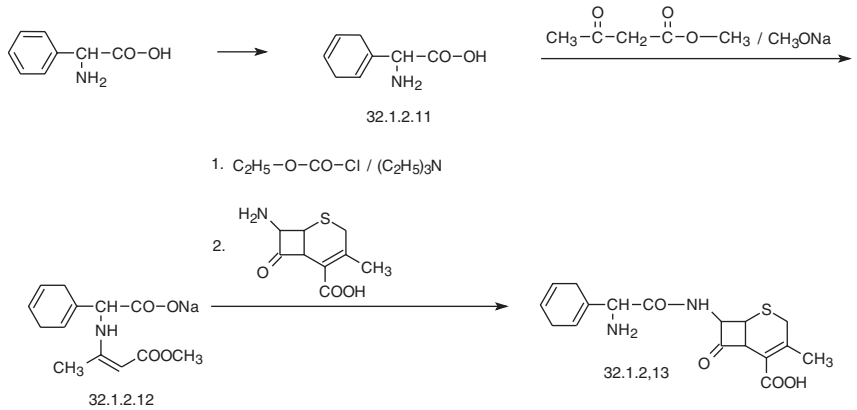
Cephalexin: Cephalexin, [6*R*-[6α,7β(*R*)]]-3-methyl-8-oxo-7-[(aminophenylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.10), to some degree can be considered as an analog of ampicillin, because the acyl fragment introduced into the structure of 7-aminocephalosporanic acid, is just the same phenylglycine fragment as it is in the case of ampicillin. Besides, the structure of the given drug, as well as a number of other cephalosporins examined below, are somewhat simplified by the replacement of the 3-acetoxymethyl group with a methyl group. Cephalexin is synthesized from cephalophenylglycine (32.1.2.9), which is synthesized by reacting 7-aminocephalosporanic acid with a mixed anhydride synthesized by reacting *N*-carbobenzoxyphenylglycine and isobutyl chloroformate in the presence of triethylamine. Removing the *N*-carbobenzoxy protective group from the resulting product (32.1.2.8) using hydrogen and a palladium on carbon catalyst gives cephalophenylglycine (32.1.2.9) in the form of an internal salt. Reducing this product with hydrogen using a palladium on barium sulfate catalyst results in the deacetoxylation at the third position of 7-aminocephalosporanic acid, making the desired cephalexin (32.1.2.10) [82–86].



Cephalexin has a broad spectrum of antimicrobial action; it is active with respect to Gram-positive and Gram-negative microorganisms. It is ineffective with respect to blue-pus bacillus, mycobacteria tuberculosis, and anaerobic microorganisms. It is used for bacterial infections of the upper and lower respiratory tract, urinary tract, skin, and soft tissues. Synonyms of this drug are ceporexin, oracef, ceflex, cefazal, and others.

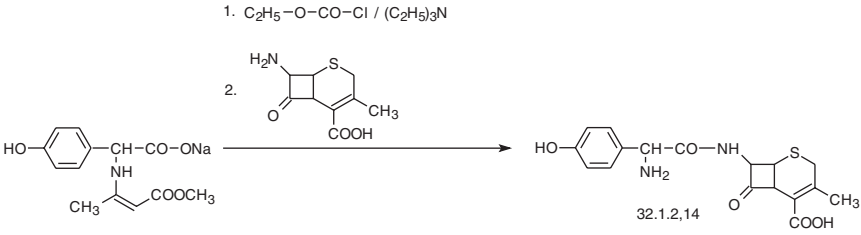
Cefradin: Cefradin, [6*R*-[6α,7β(*R*)]]-3-methyl-8-oxo-7-[(amino-1,4-cyclohexadien-1-ylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.13), is a close

analog of cephalexin and differs in that the phenyl group in phenylglycine is partially hydrated to a 1,4-cyclohexadienyl moiety. It is synthesized from phenylglycine, which is partially reduced by lithium in liquid ammonia, which forms 1,4-cyclohexadienylglycine (32.1.2.11), and the amino group in this compound is protected by reacting it with methyl acetoacetate in the presence of sodium methoxide. The resulting salt (32.1.2.12) is transformed into a mixed anhydride by a reaction with ethyl chloroformate in triethylamine, and reacted with deacetoxylated 7-aminocephalosporanic acid, which gives cefradin (32.1.2.13) [87–89].



The spectrum of action and indications of use of cephradin are the same as with cephalexin. Synonyms of this drug are velosef, sefril, cefro, and others.

Cefadroxil: Cefadroxil, [6*R*-[6α,7β(*R*)]]-3-methyl-8-oxo-7-[[amino(4-hydroxyphenyl) acetyl]amino]-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.14), is an analog of cephalexin and differs only in the presence of a hydroxyl group in the fourth position of the phenyl ring of phenylglycine, and is synthesized by a scheme analogous to the scheme of cephradin synthesis [90–96].



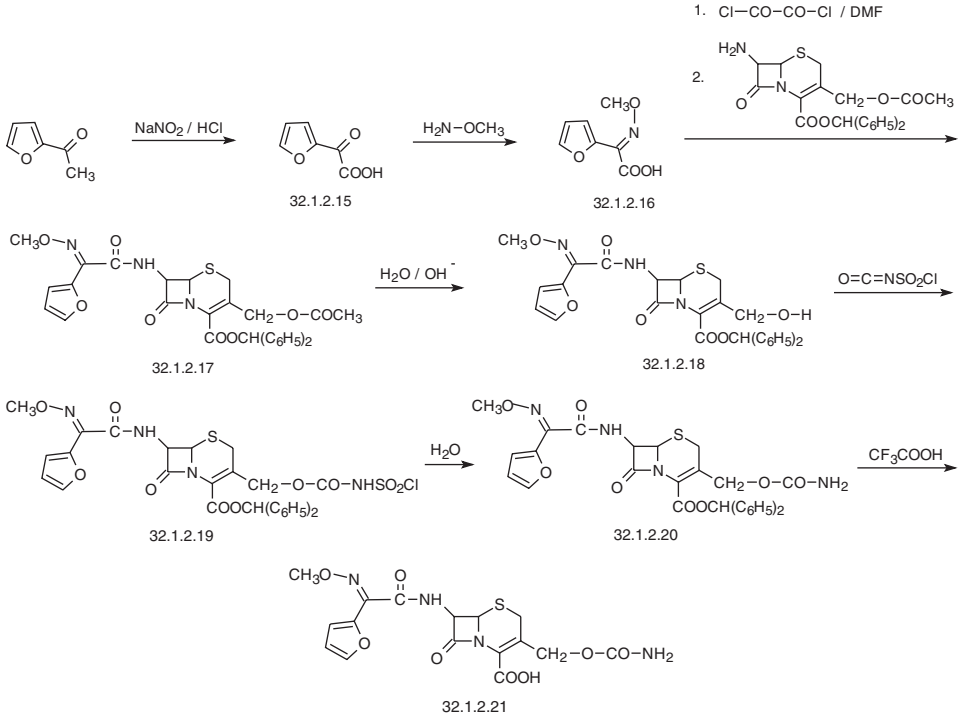
Cefadroxil has a broad spectrum of antimicrobial action; it is active with respect to Gram-positive and Gram-negative microorganisms. Like all of the other drugs described above, it acts as a bactericide by disrupting the process of restoring the membranes of bacteria. Synonyms of this drug are bidocef, cefadril, duracef, ultracef, and others.

Second-generation cephalosporins

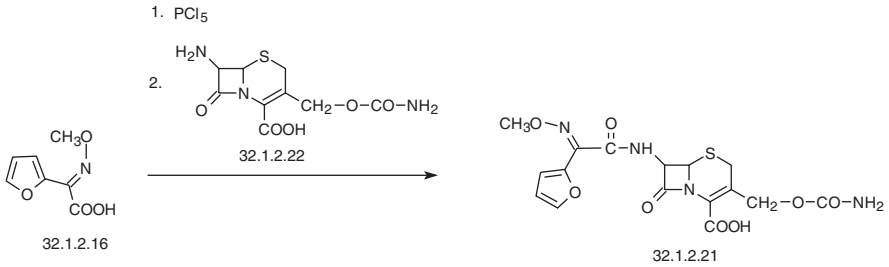
Second-generation cephalosporins (cefuroxime, cefamandole, cefonicid, ceforanide) are characterized by more expressed activity with respect to Gram-negative bacteria in comparison

with first-generation cephalosporins. They have high beta-lactam resistance, although they do not have a noticeable effect on enterococci, *Pseudomonas aeruginosa.* In addition, drugs belonging to the second-generation cephalosporins are cefoxithin, synthesized from cefamicin C, cefotetan, a semisynthetic derivative of organomycin G, and also cefaclor. Cefoxithin and cefotetan are used for mixed aerobic–anaerobic infections. Their unique chemical feature is the presence of an additional methoxy group in position C_7 of the aminocephalosporanic acid fragment, and the unique chemical feature of cefaclor, the absence of a substituted group at position C_3 of the aminocephalosporanic acid fragment is also characteristic of all cephalosporins.

Cefuroxime: Cefuroxime, (*Z*)-mono(*O*-methyloxim) (6*R*,7*R*)-7-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid carbamate (32.1.2.18), is synthesized from 2-acetylfuran. Oxidizing this compound with nitrous acid gives 2-furylglyoxalic acid (32.1.2.15), which is reacted with methoxylamine to give the corresponding oxime, *syn*-2-methoxyamino-2-(2-furyl)acetic acid (32.1.2.16), which is then transformed into a mixed anhydride when reacted with oxaloyl chloride in diemethylformamide, and then reacted with benzhydryl ester of 7-aminocephalosporanic acid. The resulting product (32.1.2.17) undergoes enzymatic hydrolysis in an alkaline medium, in which the benzhydryl protection is not affected, and only the acetoxy group of the molecule at position C_3 of the aminocephalosporanic acid is hydrolyzed. The resulting product with a free hydroxymethyl group (32.1.2.18) is reacted with chlorosulfonyl isocyanate, with intermediate formation of the corresponding *N*-chlorosulfonyl urethane (32.1.2.19), which is hydrolyzed by water to the urethane (32.1.2.20). Finally, removal of the benzhydryl protection using trifluoroacetic acid gives the desired cefuroxime (32.1.2.21) [97–109].



Another simpler way of the synthesis of cefuroxime is by direct acylation of 7-amino-3-aminocarbonyloxymethyl-3-cefem-4-carboxylic acid (32.1.2.22), which is isolated from the cultural fluid of *Streptomyces lactamdurans*, using *syn*-2-methoxyamino-2-(2-furyl)acetic acid chloride, which is synthesized by reacting the corresponding acid with phosphorous pentachloride [110,111].

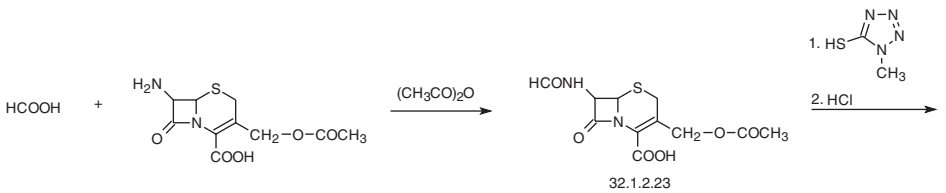


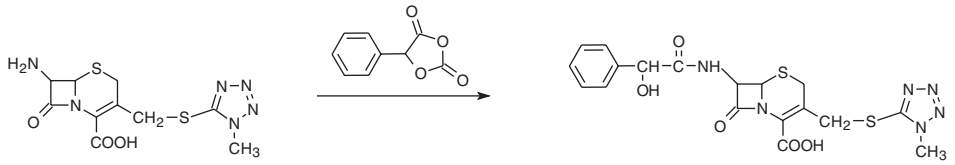
Cefuroxime acts bactericidally. It has a narrow spectrum of antimicrobial action. It is resistant to beta-lactamase action. It is highly active with respect to Gram-negative microorganisms (intestinal and hemophilial bacilli, salmonella, shigella, enterobacteria, and gonococci). It is also active with respect to Gram-positive microorganisms (staphylococci, streptococci). It is inactive with respect to various types of *Pseudomonas*, most strains of enterococci, many strains of *Enterobacter cloacae,* methylcillin-resistant staphylococci, and *L. monocytogenes*.

It is used for bacterial infections caused by microorganisms that are sensitive to the drug. These may be abdominal and gynecological infections, sepsis, meningitis, endocarditis, infections of the urinary and respiratory tracts, bones, joints, skin, and soft tissues. It is widely used for pneumonia as well as bacterial meningitis in children, and for post-operational infectious complications. Synonyms of this drug are ceftin, zinacef, curoxim, kefox, and many others.

Cefamandole: Cefamandole, 7-D-mandelamido-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio] methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.25), is synthesized from 7-aminocephalosporanic acid.

Protecting free amino group in 7-aminocephalosporanic acid by formylation with formic acid in the presence of acetic anhydride produces 7-formamidocephalosporanic acid (32.1.2.23). The acetoxy group of this compound is replaced by a reaction with 1-methyl-1,2,3,4-tetrazol-5-thiol, after which the *N*-formyl protection is removed by hydrochloric acid, giving 7-amino-3-(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl-3-cefem-4-carboxylic acid (32.1.2.24). Reacting this with a mixed anhydride synthesized from mandelic acid and phosgene gives the desired cefamandole (32.1.2.25) [112–119].

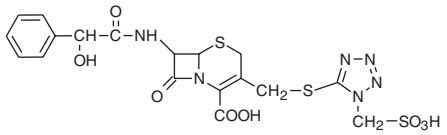




32.1.2.24 32.1.2.25

The pharmacological action and indications for use of cefamandole is analogous to that of cefuroxime and cefamandole. Synonyms of this drug are mandoxef, kefandol, kefadol, and many others.

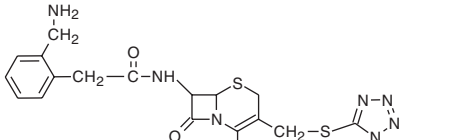
Cefonicid: Cefonicid, 7-D-mandelamido-3-[[(1-sulfomethyl]-1*H*-tetrazol-5-yl]thio] methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.26), is structurally similar to cefamandole and differs in the presence of a sulfonic acid group in the methyl substituent of the tetrazol ring. It is synthesized by a method analogous to that of the synthesis of cefamandole [120–123].



32.1.2.26

The pharmacological action, antimicrobial spectrum, and indications for use are analogous to those of cefamandole. A synonym of this drug is monocid.

Ceforanide: Ceforanide, (6R, 7R)-7[2-(α-amino-*o*-tolyl)acetamido]-3-[[[1-carboxymethyl-1*H*-tetrazol-5-yl]-thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (32.1.2.27), is also structurally related to cefamandole, differing in that the acylating acid was *o*-aminomethylphenylacetic acid, and also in the presence of a carboxyl group in the methyl substituent of the tetrazol ring. It is also synthesized by methods analogous to the synthesis of cefamandole [124–128].

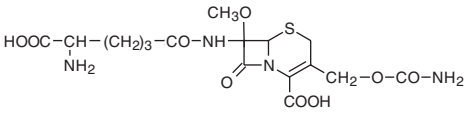


32.1.2.27

The pharmacological action, antimicrobial spectrum, and indications for use are analogous to those of cefamandole. A synonym of this drug is precef.

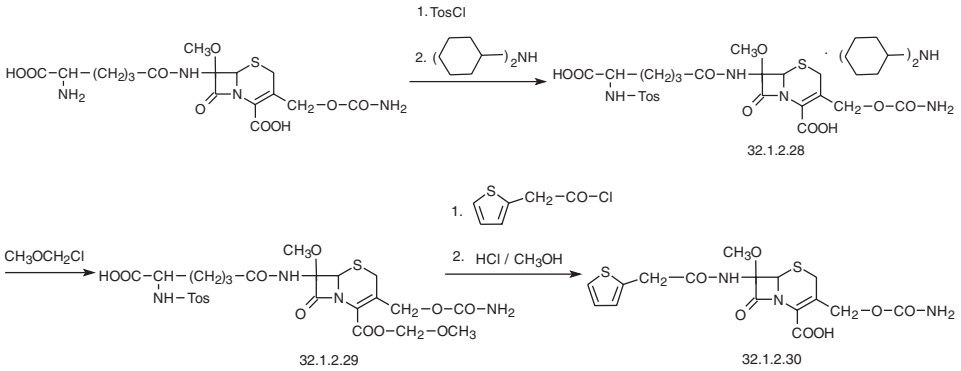
Cefoxitin and cefotetan, which are cephamicins and differ from other cephalosporins principally in the presence of a methoxy group at position 7 of the cephalosporanic system, which significantly increases their resistibility with respect to beta-lactamases, belong to the second-generation cephalosporins.

Cefoxitin: Cefoxitin, 3-(hydroxymethyl)-8-oxo-7-methoxy-7-[(2-thienylacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid carbamate (32.1.2.30), is synthesized in various ways starting from cefamicin C-7β-(D-5-amino-5-carboxyvaleramido)-3-aminocarbonylhydroxymethyl-7-methoxy-3-cefem-4-carboxylic acid, in which a methoxy group is initially present at C_7, and the task of making the desired drug essentially consists of a transamidation reaction.



cefamicin C

The other way is to start synthesis from 7-aminocephalosporanic acid, to which it is necessary to insert a methoxy group at C_7. In one of the examples of the synthesis of cefoxitin starting from cefamicin C, the free amino group is initially protected via tosylation, and the product in the form of a well-crystallizing dicyclohexylamine salt is isolated (32.1.2.28). Next, the carbonyl group at position 2 of the cephalosporanic system is esterified using methylchloromethyl ether. The resulting compound (32.1.2.29) is reacted with 2-(2-thienyl)acetylchloride, then the ester protection is removed from the carboxylic group with hydrogen chloride in methanol, producing the desired cefoxitin (32.1.2.30) [129].



32.1.2.28

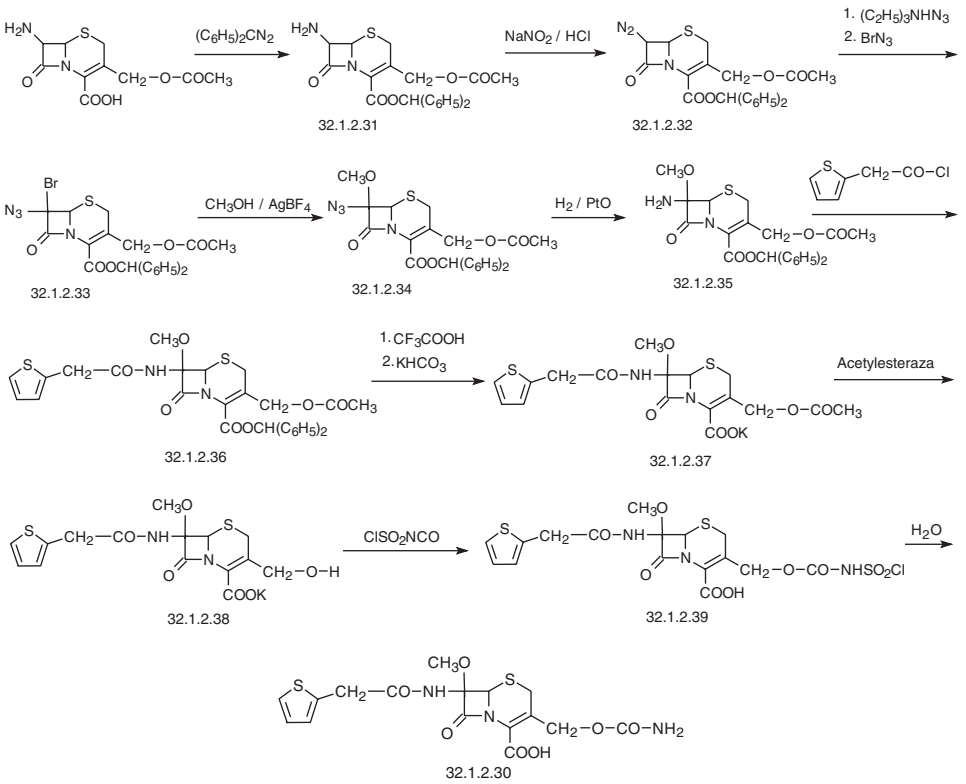
32.1.2.29

32.1.2.30

Another way for the synthesis of cefoxitin is started from 7-aminocephalosporanic acid, more correct, from its benzhydryl ester (32.1.2.31), which is synthesized by previous tosylation of the amino group of the initial 7-aminocephalosporanic acid, esterification of the carboxyl group by diphenyldiazomethane, and subsequent removal of the tosyl protection.

When reacted with nitrous acid, the product is diazotized, giving the diphenyl methyl ester of 7-diazocephalosporanic acid (32.1.2.32). A subsequent reaction of the resulting compound with triethylammonium azide in dichloromethane and then with bromine azide gives the diphenyl methyl ester of 7-bromo-7-azidocephalosporanic acid (32.1.2.33). Treating this with methanol in the presence of silver borofluoride results in the replacement of the bromine atom, giving the diphenylmethyl ester of 7-methoxy-7-azidocephalosporanic acid (32.1.2.34). The resulting azide is reduced by hydrogen in the presence of a platinum

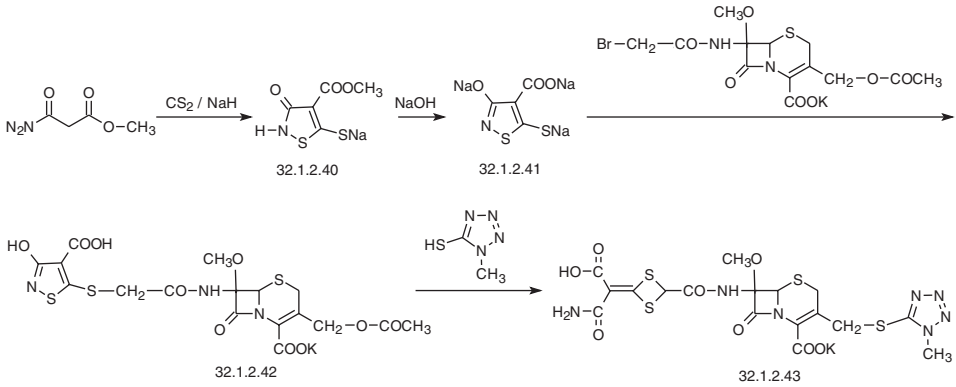
oxide catalyst, forming the diphenyl methyl ester of 7-methoxy-7-aminocephalosporanic acid (32.1.2.35). Acylation of this compound with 2-(2-thienyl)acetylchloride gives the benzhydryl ester of 7-methoxy-7-[2-(2-thienyl)-acetamido]cephalosporanic acid (32.1.2.36), the ester protecting group of which is hydrolyzed using trifluoroacetic acid and then upon reacting the resulting acid with sodium bicarbonate, it is transformed to the potassium salt (32.1.2.37). The resulting product is then hydrolyzed by the enzyme *Citrusi* acetylesterase to the potassium salt of 3-hydroxymethyl-7-methoxy-7-[2-(2-thienyl)acetamido]-3-cefem-4-carboxylic acid (32.1.2.38). Using the method described above, i.e. the initial reaction with chlorosulfonyl isocyanate followed by hydrolysis with water, the resulting compound, (32.1.2.38), is transformed to the desired cefoxitin (32.1.2.20) [130–138].



The pharmacological action, antimicrobial spectrum, and indications for use are analogous to those of cefamandole. Synonyms of this drug are mefoxitin, betacef, cefoxinol, and tifox.

Cefotetan: Cefotetan, 7β-[(-carbamoylcarboxylatomethylen)-1,3-dithietan-2-yl]-carboxamido-7-methoxy-3-(1-methyltetrazol-5-yl)-thiomethyl-3-cefem-4-carboxylic acid (32.1.2.43), is synthesized by the following scheme. First, trisodium salt of 4-carboxy-3-hydroxy-5-mercaptoisothiazole (32.1.2.41) undergoes S-alkylation by 7β-bromoacetamido-7α-methoxycephalosporanic acid, which is synthesized by a scheme described previously (32.1.2.31) $\rightarrow$ (32.1.2.37), the only difference being that the acylation in the stage (32.1.2.35) $\rightarrow$ (32.1.2.36)

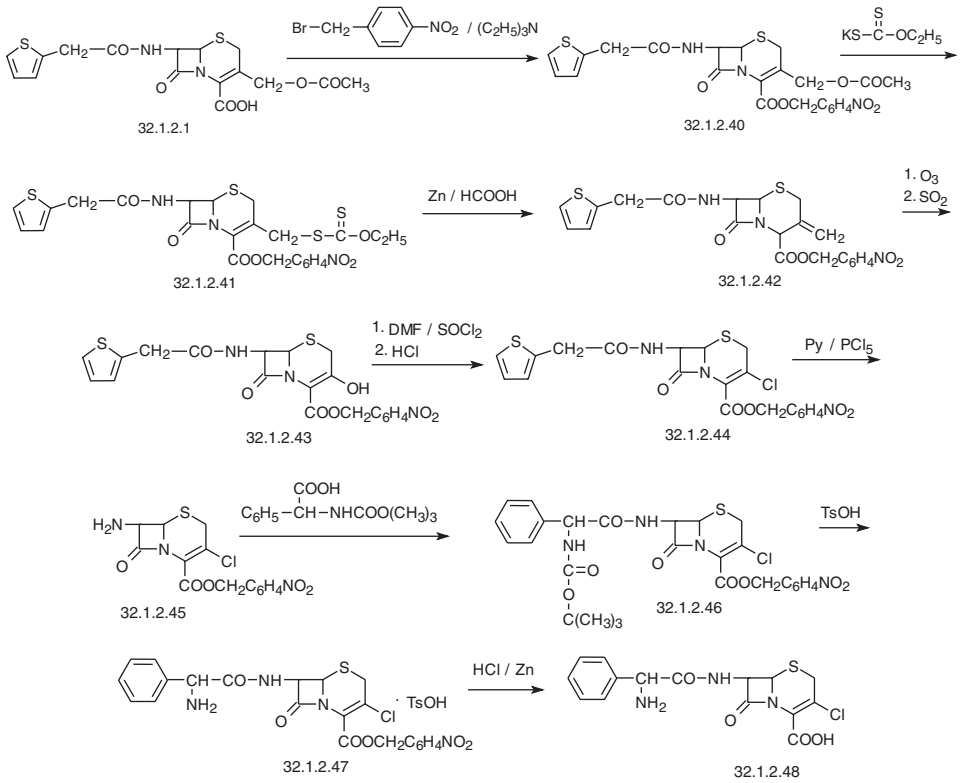
is accomplished not with 2-(2-thienyl)acetylchloride, but with bromoacetyl bromide. Next, upon reacting the resulting product (32.1.2.42) with 1-methyl-1,2,3,4-tetrazol-5-thiol in the presence of sodium bicarbonate with the expected replacement reaction, in the reaction conditions a ring rearrangement takes place in which the isothiazole ring is opened, and transformed into a derivative of carbamoylcarboxylatomethylen-1,3-dithiethane, namely cefotetan (32.1.2.43) [139,140].



The pharmacological action, antimicrobial spectrum, and indications for use of cefotetan are analogous to those of cefamandole. Synonyms of this drug are cefoten, apatef, cepan, darvilen, and others.

Cefaclor: Cefaclor, (6*R*,7*R*)-7-[(*R*)-2-amino-2-phenylacetamido]-3-chloro-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.48), differs from those antibiotics of all generations of cephalosporin series both examined as well as used in medical practice by the presence of a chlorine atom in the place of the substituted methyl group at position 3 of cephalosporanic acid. This drug is synthesized from the most accessible antibiotic of this series, cefalotin (32.1.2.1), in which the carboxyl group is protected by esterification by a reaction with 4-nitrobenzylbromide in triethylamine, giving the 4-nitrobenzyl ester of 7-(2-thienylacetamido)-cephalosporanic acid (32.1.2.40). Reacting this with potassium ethyl xantogenate replaces the acetoxy group in the third position of the cephalosporin system, giving the corresponding *S*-derivative (32.1.2.41). Upon reducing this compound using zinc in formic acid, the product is desulfurized, giving the 4-nitrobenzyl ester of 3-*exo*-methylen-7-(2-thienylacetamido)-cefem-4-carboxylic acid (32.1.2.42). The *exo*-methylene group is oxidized by ozone and the resulting dicarbonyl derivative tautomerizes to the enol form (32.1.2.43) upon reaction with sulfur anhydride. Then, the hydroxyl group is replaced with a chlorine atom upon reaction with thionyl chloride, giving the 4-nitrobenzyl ester of 3-chloro-7-(2-thienylacetamido)-3-cefem-4-carboxylic acid (32.1.2.44). The resulting product undergoes deacylation upon reaction with a mixture of pyridine with phosphorous pentachloride in isobutanol, forming the hydrochloride of 4-nitrobenzyl ester of 7-amino-3-chloro-3-cefem-4-carboxylic acid (32.1.2.45). This is acylated with an N-protected derivative of phenylglycine, (*N*-*tert*-butoxycarbonyl)-D-α-phenylglycine in the presence of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline in tetrahydrofuran, giving

the product (32.1.2.46). The *tert*-butoxycarbonyl protection in this molecule is removed by heating in acetonitrile in the presence of *p*-toluenesulfonic acid. Finally, upon hydrogen reduction using zinc and hydrochloric acid in dimethylformamide, the 4-nitrobenzyl protecting group is removed from the resulting tosylate (32.1.2.47) giving cefaclor (32.1.2.48) [141–143].



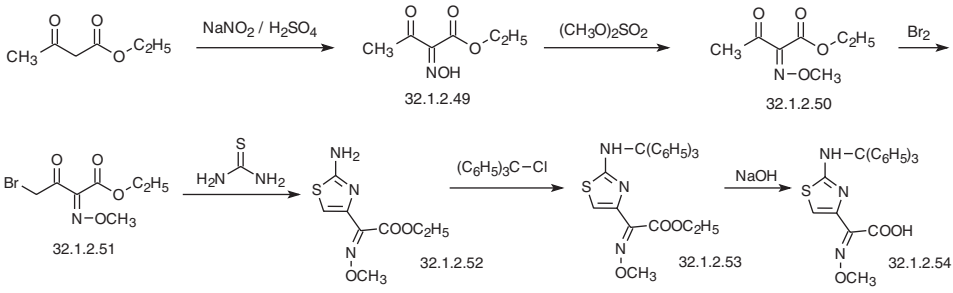
The pharmacological action, antimicrobial spectrum, and indications for use of cefaclor are analogous to those of cefamandole. Synonyms of this drug are panoral, alfatil, distaclor, panecef, ceklor, and others.

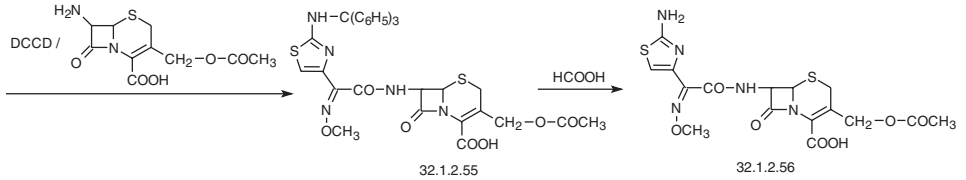
Third-generation cephalosporins

The third generation of cephalosporins (cefotaxim, ceftizoxime, ceftriaxone, ceftazidime, cefoperazone, and moxalactam) differs in their high antimicrobial activity against enterobacter, including those resistant to other antibiotics. They are relatively more resistant to hydrolysis by beta-lactamases, and they have the broadest spectrum of Gram-negative activity. Characteristic of these drugs is increased antibiotic activity with respect to *E. coli*, as well as a number of strains of *Proteus Enterobacter*. At the same time, they exhibit moderate activity with respect to staphylococci, and are used in polyresistant Gram-negative infections for treating bacterial meningitis and gonorrhea. It should be noted that moxalactam contains

a dihydrooxazine ring in place of the dihydrothiazine ring common in all other cephalosporins. Thus, it is not a cephalosporin, a cefamicin, or penicillin; however, in terms of the pharmacological action, it is a compound related to the three antibiotics listed above and is classified as a third-generation cephalosporin. From a chemical point of view, the thing that unifies them is that practically are all derivatives of 7-aminocephalosporanic acid that are acylated at the amino group of 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetic acid. In terms of the pharmacological action of third-generation cephalosporins, they generally differ one from another in their pharmacokinetic unique features, as well as in a few differences with respect to their relationship with *P. aeruginosa* and *S. aureus.*

Cefotaxime: Cefotaxime, α-*O*-methyloxime acetate (6*R*, 7*R*)-7-[2-(2-amino-4-thiazolyl)-glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.56), is synthesized by acylating of 7-aminocephalosporanic acid with 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetic acid, which is protected at the amino group by a trityl protection (32.1.2.54). After removing the trityl protection from the resulting product (32.1.2.55) with dilute formic acid, the desired cefotaxime (32.1.2.56) is formed. The ethyl ester of 2-(2-amino-4-thiazolyl)-2-methoxyminoacetic acid necessary for this synthesis, as well as for the synthesis of a number of other antibiotics of the cephalosporin series, is synthesized from acetoacetic ester. Nitrosation of acetoacetic ester with nitrous acid gives isonitrosoacetoacetic ester (32.1.2.49). *O*-Methylation of the hydroxyl group of obtained product with dimethylsulfate in the presence of potassium carbonate gives ethyl 2-(methoxyimino)acetoacetate (32.1.2.50). Brominating the resulting product with bromine in methylene chloride in the presence of *p*-toluenesulfonic acid gives 4-bromo-2-methoxyiminoacetoacetic ester (32.1.2.51). Reacting this with thiourea according to the classic scheme of preparing of thiazoles from α-bromocarbonyl compounds and thioamides gives the ethyl ester of 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetic acid (32.1.2.52). Reacting this with triphenylchloromethane in the presence of triethylamine results in a trityl protection of the amino group, forming the ethyl ester of 2-(2-tritylamino-4-thiazolyl)-2-methoxyminoacetic acid (32.1.2.52), which is hydrolyzed to the acid (32.1.2.54) using sodium hydroxide. The resulting acid (32.1.2.54), as was already stated, is used for acylating of 7-aminocephalosporanide acid in the presence of dicyclohexylcarbodiimide, giving tritylated cefotaxime, α-*O*-methyloxime acetate 7-[2-(2-tritylamino)-4-thiazolyl-glycoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-en-2-carboxylic acid (32.1.2.55). Finally, removing the trityl protection from the synthesized product (32.1.2.55) using dilute formic acid gives cefotaxime (32.1.2.56) [144–148].



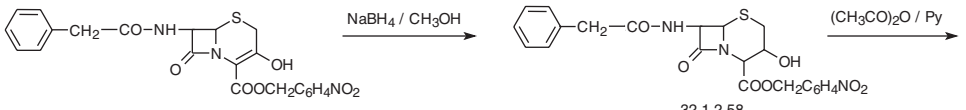


32.1.2.55 32.1.2.56

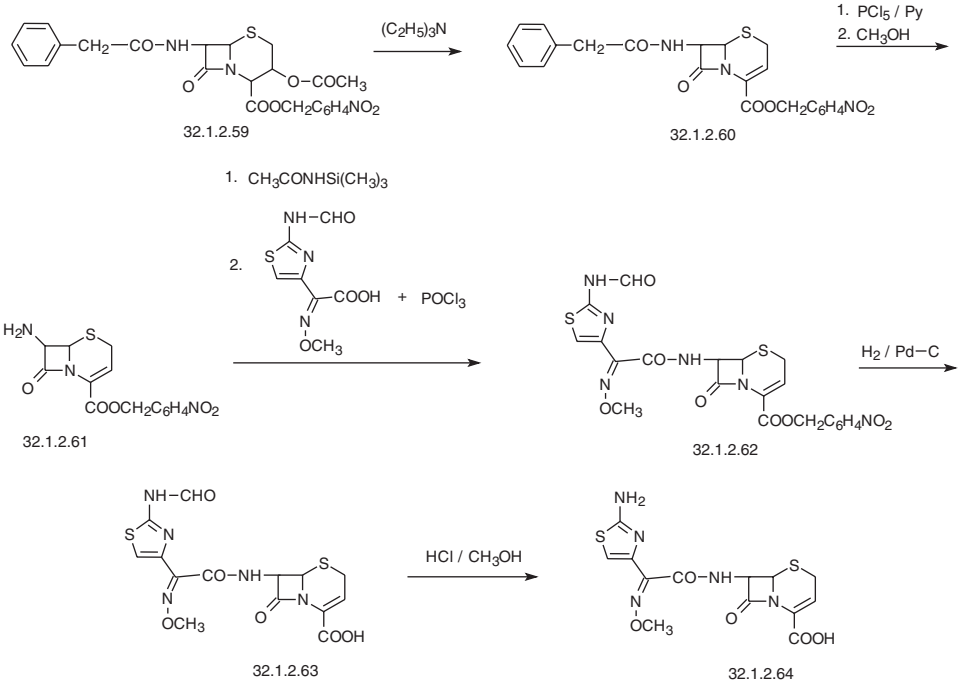
Cefotaxime has a broad spectrum of antibicrobial use. It acts bactericidally. It is highly active with respect to Gram-negative microorganisms (*E. coli*, *Citrobacter*, *Proteus mirabilis*, *P. indole*, *Providencia*, *Klebsiella*, *Serratia*), and a few strains of *Pseudomonas*, *H. influenzae* that are resistant to other antibiotics. Cefotaxime is less active with respect to streptococci, pneumococci, meningococci, gonococci, and bacteroides. It is resistant to the majority of beta-lacatamases of Gram-positive and Gram-negative microorganisms.

This drug is used for severe bacterial infections caused by microorganisms that are sensitive to the drug such as peritonitis, sepsis, abdominal infections, infections of the pelvis minor, infections of the lower respiratory tract, urinary tract, bones, joints, skin, soft tissues, and infected wounds and burns. Synonyms of this drug are claforan, zarivis, and others.

Ceftizoxime: Ceftizoxime, *α-O*-methyloxime of (6*R*,7*R*)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.64), is synthesized by the scheme described below, which begins with 4-nitrobenzyl ester of 3-hydroxy-7-(2-phenylacetamido)-3-cefem-4-carboxylic acid (32.1.2.57), which is synthesized using a number of methods used to synthesize cefaclor (32.1.2.48). Reducing the C_3–C_4 double bond in the initial 4-nitrobenzyl ester of 3-hydroxy-7-(2-phenylacetamido)-3-cefem-4-carboxylic acid (32.1.2.57) with sodium borohydride in methanol, 4-nitrobenzyl ester of 3-hydroxy-7-(2-phenylacetamido)-3-cefam-4-carboxylic acid (32.1.2.58) is obtained, the hydroxyl group in which it is acylated by acetic anhydride in pyridine, forming acetate (32.1.2.59). Reacting this with triethylamine removes a molecule of acetic acid, giving the 4-nitrobenzyl ester of 7-(2-phenylacetamido)-3-cefem-4-carboxylic acid (32.1.2.60). Reacting this with phosphorous pentachloride in pyridine, followed by subsequent methanolysis deacylates the amide fragment of the molecule, giving the 4-nitrobenzyl ester of 7-amino-3-cefem-4-carboxylic acid (32.1.2.61). Preliminary silylation of the amino group of this compound with trimethylsilylacetamide and subsequent acylation with 2-(2-formamido-4-thiazolyl)-2-methoxyminoacetic acid chloride synthesized directly in reaction conditions by reacting with phosphorous chloroxide in dimethylformamide gives the 4-nitro-benzyl ester of *α-O*-methyloxime of 7-[2-(2-formamido-4-thiazolyl)glyoxylamido]-8-oxo-t-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.62). Reducing this with hydrogen using a palladium on carbon catalyst removes the 4-nitrobenzyl protection from the carboxyl group, forming the acid (32.1.2.63). Finally, hydrolysis of the formamide region of the molecule using hydrogen chloride in methanol gives the desired ceftizoxime (32.1.2.64) [149–151].



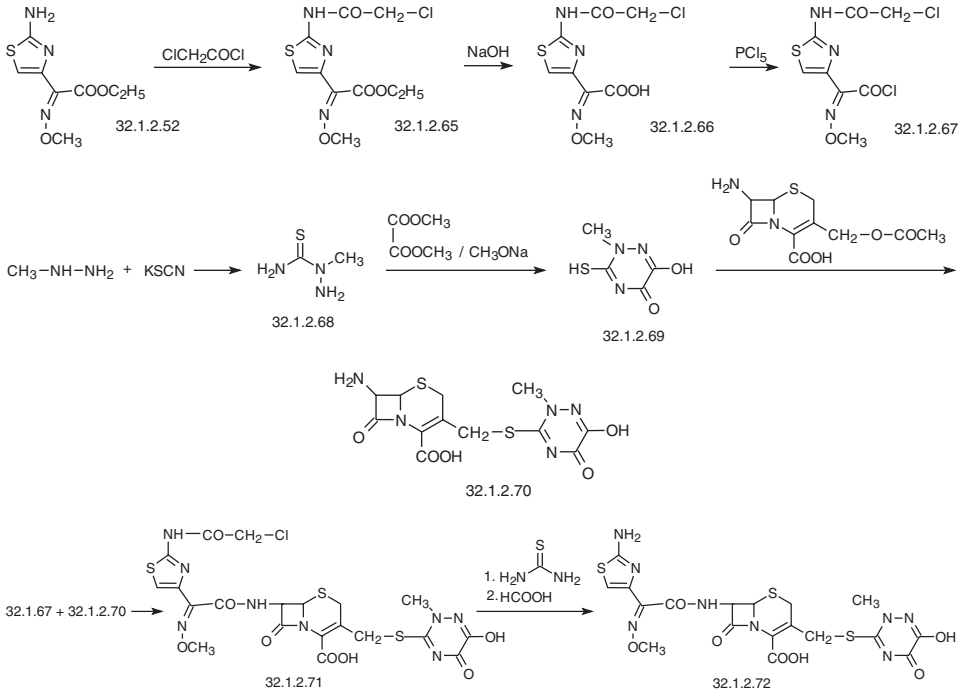
32.1.2.57 32.1.2.58



Ceftizoxime is used for bacterial infections of the lower respiratory tract, infections of the urinary tract, infections of the bones, joints, skin, soft tissues, and abdominal infections. Synonyms of this drug are ceftix and eposerin.

Ceftriaxone: Ceftriaxone, 7-[[(2-amino-4-thiazolyl)-2-(*Z*)-(methyoximino)acetyl]amino]-8-oxo-3-[[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thio]methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.72), is synthesized by acylating 7-amino-3-[[(2,5-dihydro-6-hydroxy-2-methyl-1,2,4-triazin-5-on-3-yl)thio]methyl]3-cefem-4-carboxylic acid (32.1.2.70), by the 2-(4-thiazolyl)-2-methoxyiminoacetic acid chloride, which is protected at the amino group by a chloroacetyl group, namely with 2-(2-chloroacetamido-4-thiazolyl)-2-methoxyiminoacetylchloride (32.1.2.67). The last is synthesized from ethyl ester of 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetic acid (32.1.2.52), the amino group of which is protected by the acylation with chloracetic acid chloride in dimethylacetamide, giving ethyl ester of 2-(2-chloroacetamido-4-thiazolyl)-2-methoxyiminoacetic acid (32.1.2.65). Hydrolysis of the ester group of this compound by potassium hydroxide to an acid (32.1.2.66), and its subsequent reaction with phosphorous pentachloride in the presence of trimethylamine gives 2-(2-chloroacetamido-4-thiazolyl)-2-methoxyiminoacetylchloride (32.1.2.67). The synthesis of 7-amino-3-[[(2,5-dihydro-6-hydroxy-2-methyl-1,2,4-triazin-5-on-3-yl)thio]methyl]-3-cefem-4-carboxylic acid (32.1.2.70) is done in parallel. In order to do this, methylhydrazine is reacted with potassium thiocyanate to give 1-amino-1-methylthiourea (32.1.2.68), which is reacted with dimethyloxalate in the presence of sodium methoxide to form a heterocyclization product, 2,5-dihydro-6-hydroxy-2-methyl-3-mercapto-1,2,4-triazin-5-on (32.1.2.69). Reacting this with 7-aminocephalosporanic acid replaces the acetoxy group

giving 7-amino-3-[[(2,5-dihydro-6-hydroxy-2-methyl-1,2,4-triazin-5-on-3-yl)thio]methyl]-3-cefem-4-carboxylic acid (32.1.2.70). Acylating this with the acid chloride synthesized earlier (32.1.2.67) in tetrahydrofuran in the presence of sodium hydroxide gives the desired product (32.1.2.71). Removal of the chloroacetyl protection in this molecule is accomplished in the following manner. Subsequent reaction of the product (32.1.2.71) with thiourea in the presence of sodium bicarbonate results in the formation of a new thiazole derivative. Subsequent cleaving of the resulting secondary heteroaromatic amine with formic acid gives ceftriaxone (32.1.2.72) [152–156].



This drug has a broad spectrum of antimicrobial action that includes the majority of the clinically significant microorganisms: Gram-positive, Gram-negative, aerobic, anaerobic, and blue-pus bacillus. It is resistant with respect to most beta-lactamases of Gram-positive and Gram-negative bacteria.

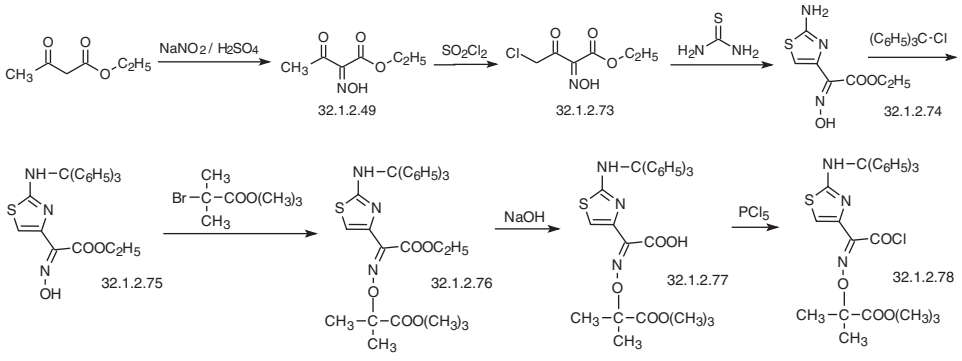
It is used for peritonitis, sepsis, meningitis, cholangitis, empyema of the gall bladder, pneumonia, lung abscesses, pyelonephritis, infections of the bones, joints, skin, soft tissues, abdominal and gynecological infections, and for infected wounds and burns. The main synonym of this drug is rocefin.

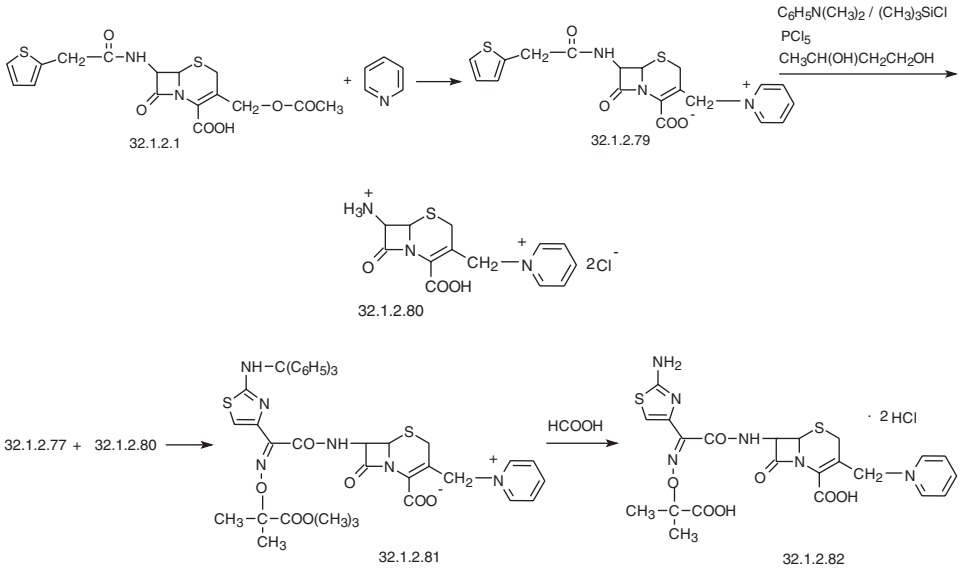
Ceftazidime: Ceftazidime is 1-[[7-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy) imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]pyridin-2-carboxylic acid (32.1.2.82). As is the case in synthesis of ceftriazone, the synthesis of ceftazidime requires the preliminary synthesis of two starting compounds. 7-Amino-3-(1-pyridinomethyl)cef-3-en-carboxylic acid dihydrochloride is used

as the cephalosporin fragment, while the acyl fragment is a modified structure of (32.1.2.77), which is not a derivative of 2-(2-amino-4-thiazolyl)-2-methoxyminoacetic acid, but a derivative of 2-(2-amino-4-thiazolyl)-2-(2-*tert*-butoxycarboxyl-2-propyloxyimino)acetic acid, which is synthesized by the following scheme. Nitration of acetoacetic ester gives isonitrosoacetoacetic ester (32.1.2.49), which undergoes chlorination by sulfuryl chloride in methylene chloride to form 4-chloro-2-hydroximinoacetoacetic ester (32.1.2.73).

Reacting this with thiourea in the classic scheme of thiazole synthesis by reacting of α-halogencarbonyl compounds with thioamides forms the ethyl ester of (*Z*)-2-(2-aminothiazole-4-yl)-2-hydroxyminoacetic acid (32.1.2.74). The amino group in this molecule is protected by a reaction with triphenylchloromethane in dimethylformamide in the presence of triethylamine, which gives the ethyl ester of (*Z*)-2-(2-tritylaminothiazole-4-yl)-2-hydroxyminoacetic acid (32.2.3.75). The hydroxyl group in the resulting compound is alkylated with the *tert*-butyl ester of α-bromoisobutyric acid in dimethylsulfoxide in the presence of potassium carbonate, giving ethyl ester of 4-thiazoleacetic acid, α-[[2-(1,1-dimethylethoxy)-1,1-dimethyl-2-oxoethoxy]imino]-2-[(triphenylmethyl)amino], (*Z*) (32.1.2.76). The ethoxycarbonyl group in this molecule is hydrolyzed by sodium hydroxide, and upon working up the reaction mixture with an acid, the corresponding acid (32.1.2.77) is isolated (32.1.2.77). Upon interaction with phosphorous pentachloride the acid chloride (32.1.2.78) is obtained, which is used further as the acylating reagent.

The second necessary fragment, 7-amino-3-(1-pyridinomethyl)cef-3-en-carbonic acid (32.1.2.80), is synthesized from cefalosporidin (32.1.2.79), a cephalosporin antibiotic that is used independently in medicine and which is synthesized in the form of an internal salt by reacting cefalotin (32.1.2.1) with pyridine to replace the acetoxyl group with a pyridine group. Initially treating cephaloridin with trimethylchlorosilane in the presence of dimethylaniline and then with phosphorous pentachloride, followed by a reaction with 1,3-butandiol results in the creation of 7-amino-3-(1-pyridinomethyl)cef-3-en-carboxylic acid (32.1.2.80). This is acylated by the acid chloride (32.1.2.78) synthesized earlier, forming the product (32.1.2.81), which is treated with a mixture of formic and hydrochloric acids to remove both protective groups (triphenylmethyl and *tert*-butyl), giving ceftazidime (32.1.2.82) in the form of a dihydrochloride [157–162].

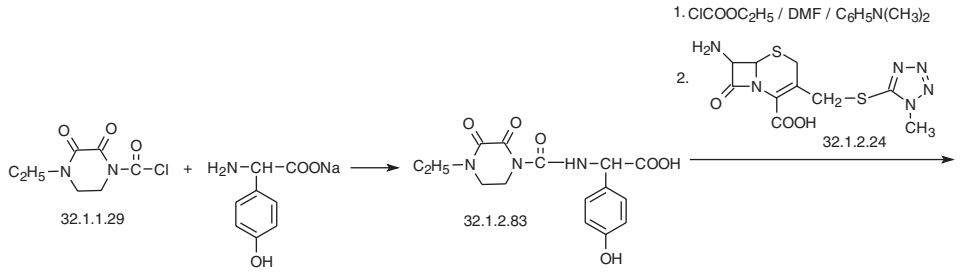


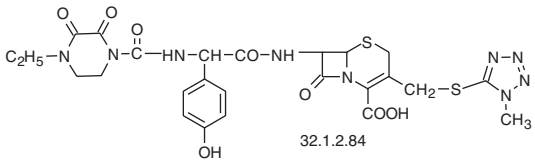


Like most of the third-generation cephalosporin antibiotics described above, ceftazidime has a broad spectrum of antimicrobial action, including the most clinically important microorganisms: Gram-positive, Gram-negative, aerobic, and anaerobic. It is resistant to most beta-lactamases of Gram-positive and Gram-negative bacteria.

It is used for treating most serious bacterial infections. Synonyms of this drug are fortum, ceftim, stacef, and tazicef.

Cefoperazone: Cefoperazone, (6*R*,7*R*)-7-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazincarboxamido)-2-(*p*-hydroxyphenyl)acetamido]-3-[[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid (32.1.2.84), is synthesized by acylating 7-amino-3-(1-methyl-1,2,3,4-tetrazol-5-yl)-thiomethyl-3-cefem-4-carboxylic acid (32.1.2.24) with a mixed anhydride synthesized from ethyl chloroformate and α-(4-ethylpiperazin-2,3-dion-1-carbonylamino)-4-hydroxyphenylacetic acid (32.1.2.83), which in turn is synthesized from 4-ethylpiperazin-2,3-dion-1-carboxylic acid (32.1.1.29) and the sodium salt of 4-hydroxyphenylglycine [163–168].





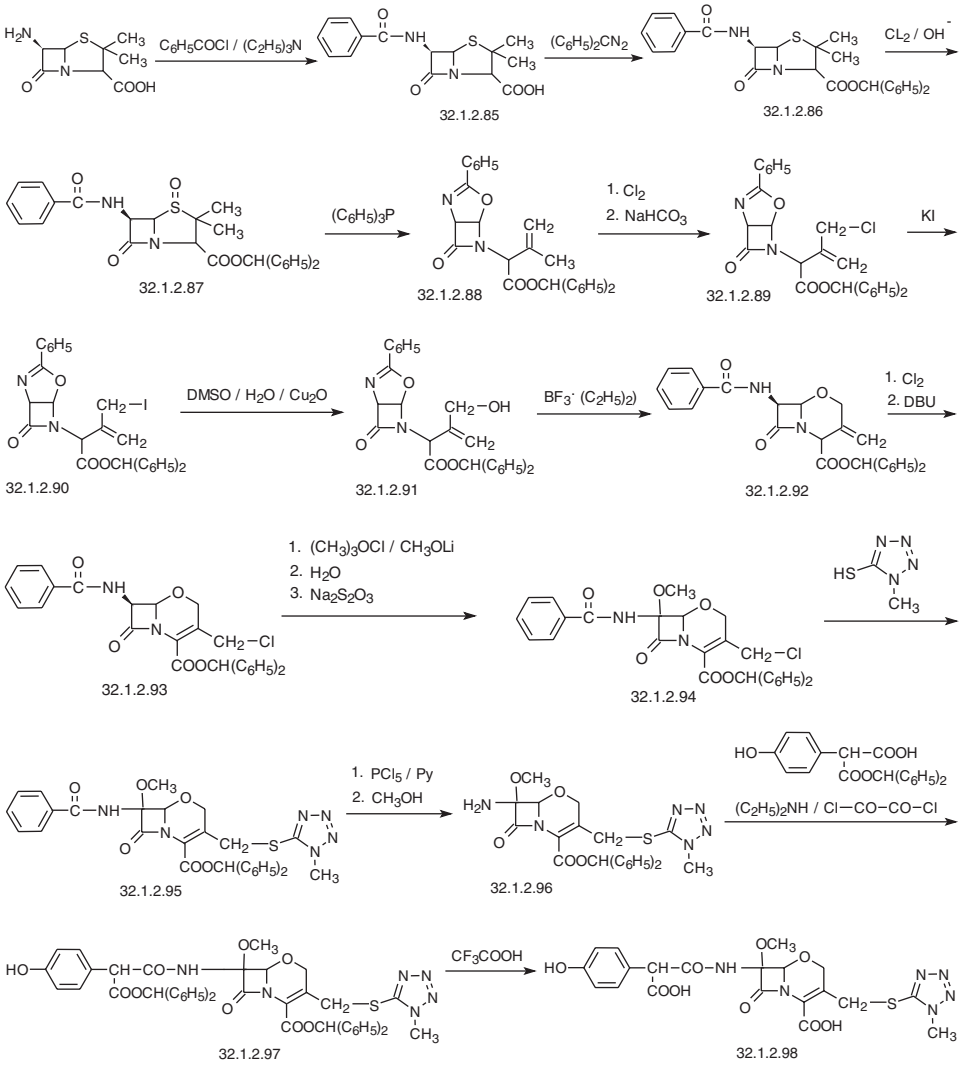
32.1.2.84

Cefoperazone also has a broad spectrum of antimicrobial action, including most clinically significant microorganisms: Gram-positive, Gram-negative, aerobic, and anaerobic. It is stable with respect to most beta-lactamases of Gram-positive and Gram-negative bacteria.

Cefoperazone is used for bacterial infections of the lower respiratory tract, urinary and sexual tracts, bones, joints, skin, soft tissues, abdominal, and gynecological infections. Synonyms of this drug are cefazon, cefobid, cefobis, and many others.

Moxalactam: Moxalactam, 7β[2-carboxy-2-(4-hydroxyphenyl)acetamido]-7α-methoxy-3-(1-methyltetrazol-5-yl)-thiomethyl-1-oxa-dethia-3-cefem-4-carboxylic acid (32.1.2.98), is synthesized in a multi-stage synthesis from 6-APA, which is acylated by benzoylchloride in the presence of triethylamine to give 6-benzoylpenicillin (32.1.2.85). The carboxyl group of this compound is protected by a reaction with diphenyldiazomethane, to form the 3-diphenylmethyl ester of 6-benzoylpenicillin (32.1.2.86). Oxidation of this product with molecular chlorine under basic conditions gives the *S*-oxide of the 3-diphenylmethyl ester of 6-benzoylpenicillin (32.1.2.87). Upon reacting this with triphenylphosphine, the expected reduction of sulfoxide to sulfide does not occur, but rather the thiazine ring is opened, causing sulfur to be released while also resulting in its simultaneous substitution with oxygen and subsequent formation of a cyclic iminoester (32.1.2.88). Chlorinating the double bond of this product with chlorine and subsequent treatment of obtained dichloro derivative with sodium bicarbonate gives a chloromethyallyl derivative (32.1.2.89), which upon reaction with potassium iodide substitutes the chlorine with iodine, forming an iodomethylallyl derivative (32.1.2.90), and finally, hydrolyzing this product in dimethylsulfoxide in the presence of copper(I) oxide forms the corresponding allylic alcohol (32.1.2.91). Upon heating this in the presence of boron trifluoride–diethyl etherate, it recyclizes back to form an oxazine ring and the reverse transformation of the cyclic iminoester into the amide form (32.1.2.92). The exocyclic double bond of the resulting product undergoes chlorination and subsequent treatment of the product with a base using 1,7-diazabicyclo-[4.5.0]undec-6-ene (DBU), gives the 3-chloromethyl derivative (32.1.2.93). Reacting this with *tert*-butyl hypochlorite, obviously to make an *N*-chloro derivative, and then with lithium methoxide, after acidification and treatment with sodium thiosulfate gives diphenylmethyl ester of 7β-benzoylamido-7α-methoxy-3-(chloromethylyl)-1-oxa-dethia-3-cefem-4-carboxylic acid (32.1.94). Reacting this with the sodium salt of 5-mercapto-1-methyl-tetrazol gives the diphenylmethyl ester of 7β-benzoylamido-7α-methoxy-3-(1-methyltetrazol-5-yl)-thiomethyl-1-oxa-dethia-3-cefem-4-carboxylic acid (32.1.95). Debenzoylation of this product and subsequent treatment with phosphorous pentachloride in pyridine and then with methanol and diethylamine gives the diphenylmethyl ester of 7β-amino-7α-methoxy-3-(1-methyltetrazol-5-yl)-thiomethyl-1-oxa-dethia-3-cefem-4-carboxylic acid (32.1.2.96). Acylating this compound with the mixed anhydride synthesized from mono-diphenylmethyl ester of (4-hydroxyphenyl)malonic acid and oxalylchloride in the presence of triethylamine gives the *bis*-diphenylmethyl ester

protection on both carboxyl groups of the desired product (32.1.2.97). Finally, removing the indicated protecting groups from both carboxyls by boiling it with trifluoroacetic acid in toluene gives the desired moxalactam (32.1.2.98) [168–173].



As was already stated, and which is visible from the scheme of synthesis, moxalactam contains a dihydrooxazine ring instead of the dihydrothiazine ring common to all cephalosporins, and thus this compound cannot be formally numbered with cephalosporins, cephamicins, or penicillins; however, in terms of pharmacological action, it is related to all three of the antibiotics listed above, and it is classified as a third-generation cephalosporin.

Moxalactam is resistant to the action of beta-lactamase, penicillinase, and cephalosporinase, which are produced by Gram-negative and Gram-positive bacteria. Many strains of

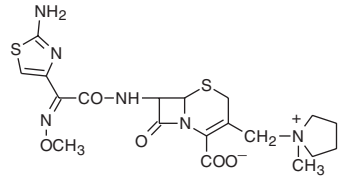
a number of microorganisms that possess multiple resistance to other antibiotics—semisynthetic penicillins, cephalosporins, and aminoglycosides—are sensitive to moxalactam.

This drug is used for infections of the respiratory organs, urinal tract, abdominal cavity, as well as for gynecological infections, infections of the bones, joints, skin, soft tissues, and for gonorrhea. Synonyms of this drug are latamoxef, festamoxin, moxacef, moxam, and many others.

Fourth-generation cephalosporins

Fourth-generation cephalosporins (cefepime, cefpirome) possess an even broader spectrum of action, as they are active against most Gram-positive and Gram-negative aerobic and anaerobic microorganisms. In terms of their spectrum of action, they are similar to the third-generation cephalosporins cefotaxime and ceftriaxon, which contains an aminothiazolylmethoxyiminoacetamido group in the 7-position, and a quaternary nitrogen atom, which is included in the heterocyclic system at the 3-position, which gives its molecules the properties of a zwitterion; however, they exceed third-generation drugs in terms of activity against *P. aeruginosa,* and *S. aureus*, including a few methicillin-resistant strains. In therapeutically significant concentrations, they act on *Streptococcus faecalis.* They are active against *E. cloacae* and *Klebsiella pneumonia.* They are transformed very quickly in the periplasmatic space, and resistance of sensitive strains of enterobacteria to these drugs is practically not observed.

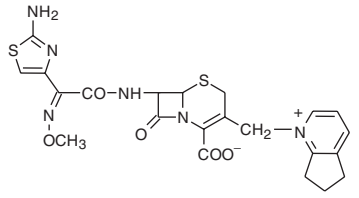
Cefepime: Cefepime, {6*R*-[6α,7β(*Z*)]}-1-[(7-{[(2-amino-4-thiazolyl)-(methoxyimino) acetyl]-amino}-2-carboxy-8-oxo-5-thia-1-(azabicyclo[4.2.0]oct-2-en-3-yl)methyl-1-methyl]pyrrolidine chloride (32.1.2.99), is synthesized by a combination of methods described for the synthesis of third-generation cephalosporins, in particular, cefaloridin (32.1.2.79) and ceftazidime (32.1.2.82) [174–196].



32.1.2.99

Cefepime is used for bacterial infections caused by microorganisms that are sensitive to drugs in septicemia, bacteriemia, complicated infections of the upper and lower sections of the urinary system, pneumonia, pulmonary abscesses, emphysema of the pleura, fever in patients with neutropenia, and infected skin and soft tissue wounds. Synonyms of this drug are maxipime, cepim, cepimex, and others.

Cefpirome: Cefpirome, {6*R*-[6α,7β(*Z*)]}-1-[(7-{[(2-amino-4-thiazolyl)-(methoximino) acetyl]amino}-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl)methyl-1-methyl]pyrrolidine chloride (32.1.2.100), is also synthesized by methods described for synthesizing third-generation cephalosporins, in particular, ceftazidime (32.1.2.82) [177,178].

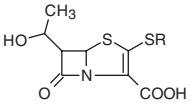


32.1.2.100

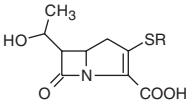
This drug is resistant with respect to a broad spectrum of beta-lactamases. Its spectrum of activity is analogous to that of the third-generation cephalosporin cefotaxime (32.1.2.56), although it is more active with respect to some staphylococci, enterococci, and also a few enterobacteria. Synonyms of this drug are cefrom, cedixen, and others.

32.1.3 Penems and carbapenems

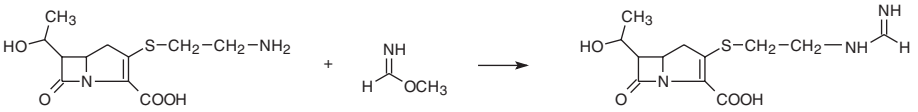
Besides penicillins and cephalosporins, which are synthesized by mycelial fungi, substances also belonging to the beta-lactam antibiotic group include those that are produced by streptomycetes, which are called penems. This class of antibiotics is chemically similar to derivatives of penicillanic acid; however, it differs from the others in the presence of an endocyclic double bond conjugated with the carboxyl group, which gives them a certain familiarity with cephalosporanic acid; in the presence of a five-membered ring of the *S*-alkyl substituent instead of two methyl groups in the second position, and in the absence of an amino group in the sixth position. Penems SCH-29482 (R = CH_2CH_3) and -34343 (R = $CH_2CH_2OCONH_2$) have not yet found use in medicine.



Carbapenems are representatives of another class of antibiotics that differ from penems in the absence of a sulfur atom in the penem ring. They include: thienamicin (R = $CH_2CH_2NH_2$), olivanic acid (R = $CH{=}CHNH_2$), and imipenem (R = $CH_2CH_2NHC{=}NH$).



Imipenem: Imipenem, [5*R*-[5α,6α(*R*)]]-6-(1-hydroxyethyl)-3-[[2-[(iminomethyl)amino] ethyl]thio]-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carboxylic acid (32.1.3.1), is the only carbapenem presently used in clinics. It is synthesized from thienamycin isolated from *Streptomyces cattleya* by reacting it with the methyl formimidate [179–182].



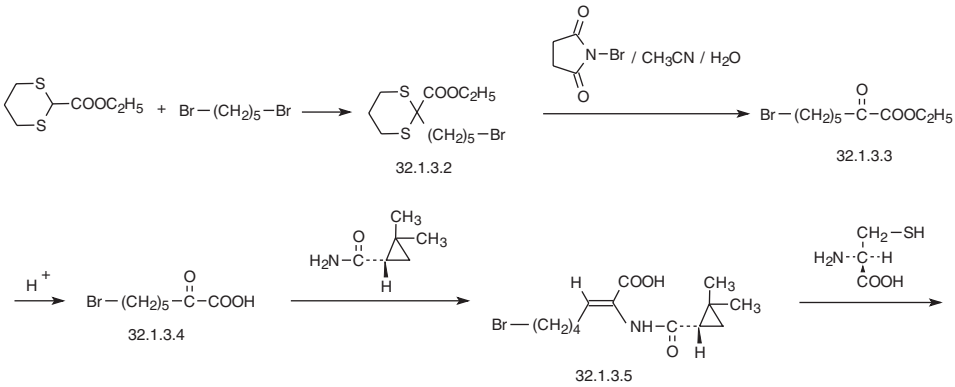
32.1.3.1

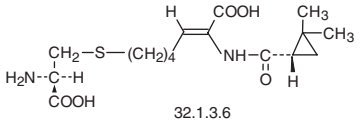
Unlike penicillins and cephalosporins, which have a side aminoacyl group joined to the beta-lactam ring, imipenem has a α-hydroxyethyl side chain. Significant resistance to hydrolysis by beta-lactamases is observed in this compound, evidently thanks to the *trans*-configuration of the side chain, while the side chain of penicillins and cephalosporins have a *cis*-configuration.

Imipenem has a broad spectrum of antimicrobial action, which includes most clinically significant microorganisms: Gram-positive, Gram-negative, aerobic, and anaerobic. It is resistant with respect to most beta-lactamases of Gram-positive and Gram-negative bacteria. It is used for bacterial infections of the lower respiratory tract, infections of the urinary and sexual tracts, infections of bones, joints, skin, soft tissues, intraabdominal and gynecological infections, bacterial septicemia, and endocarditis.

Imipenem undergoes enzymatic inactivation in the kidneys. In order to avoid this problem, it is used in a 1:1 ratio in combination with cilastatin—the sodium salt of [*R*-[*R*,*S*-(*Z*)]]-7-[(2-amino-2-carboxyethyl)thio]-2-[[(2,2-dimethylcyclopropyl)aminocarbonyl-2-heptenoic acid (32.1.3.6), which inhibits metabolisms of imipenem in the kidneys. This combination of two compounds is also used in medicine under the name primaxin.

Cilastatin: Cilastatin, (*Z*)-7-[(2-amino-2-carboethoxyethyl)thio]-2-[[2,2-dimethylcyclopropyl) carbonyl] amino]-2-heptenoic acid (32.1.3.6), is synthesized from the ethyl ester of 1,3-dithian-2-carboxylic acid (which is ethyl glyoxylate, protected at the aldehyde group with 1,3-propanedithiol), which is alkylated by 1,5-dibromopentane in the presence of sodium amide, forming the ethyl ester of 7-bromo-2-[2-(1,3-dithiano)]hepthanoic acid (32.1.3.2). Oxidative hydrolysis of this product with *N*-bromosuccinimide in a mixture of acetonitrile–water solvents leads to the formation of the ethyl ester of 7-bromo-α-ketoheptanoic acid (32.1.3.3). Acidic hydrolysis of this product using hydrogen bromide in acetic acid gives 7-bromo-α-ketoheptanoic acid (32.1.3.4). This is reacted with 2,2-dimethylcyclopropancarboxylic acid amide to form the corresponding enamide, (*Z*)-7-bromo-2-(2, 2-dimethylcycloprotancarboxamido)-2-heptenoic acid (32.1.3.5). The resulting product is used for S-alkylation of L-cysteine, which results in the production of the desired cilastatin (32.1.3.6) [183,184].



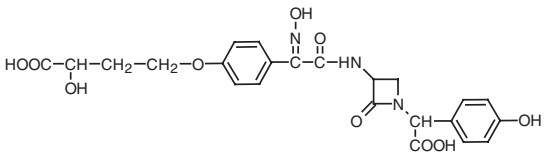


32.1.3.6

Cilastatin is used for treating diseases caused by polyresistant Gram-negative microorganisms and serious complex infections, including infection of *S. aureus.* Because of its strong activity against anaerobic bacteria, cilastatin is effective in monotherapy of intraabdominal infections. It is used for infectious diseases of the lower respiratory tract, urinary tract, gynecological infections, bacterial septicemia, and infections of the bones, skin, and so on.

32.1.4 Monobactams

Some types of microorganisms, in particular *Chromobacterium violaceum*, which in the process of performing vital functions can synthesize specific beta-lactam antibiotics that have a monocyclic structure are called monobactams. Nocardicins, in particular nocardicin A, are examples of such monobactams.

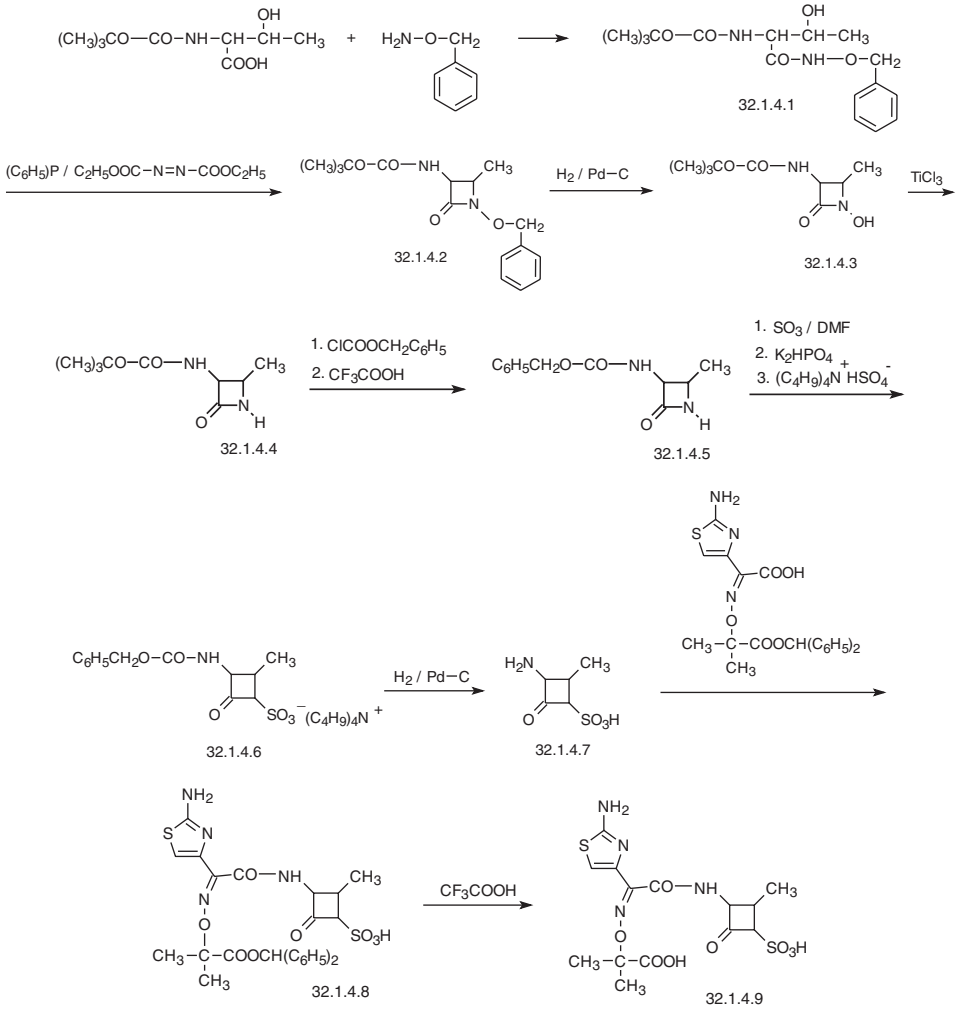


nocardicin A

The first completely synthetic monocyclic beta-lactam antibiotic was aztreonam. The antimicrobial activity of this drug is exhibited mainly with respect to a broad spectrum of aerobic Gram-negative bacteria. It is resistant to beta-lactamases and does not induce their formation. The mechanism of its action is identical to that of other beta-lactam antibiotics with respect to Gram-negative bacteria. PBP are inactivated in the presence of aztreonam.

Aztreonam: Aztreonam, (*Z*)-2[[[(2-amino-4-thiazolyl)[[(2*S*,3*S*)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]cabamoyl]methylen]amino]oxy]-2-methylpropionoic acid (32.1.4.9), is synthesized from *tert*-butyloxycarbonylthreonine, which is reacted with *O*-benzylhydroxylamine in the presence of dicyclohexylcarbodimide and 1-hydroxybenzotriazole, to form the benzyl hydroxamide derivative (32.1.4.1). This product undergoes a reaction with triphenylphosphine and ethyl azodicarboxylate, which results in the cyclodehydration of the product to (3*S*-*trans*)-*N*-benzyloxy-3-*tert*-butyloxycarbonylamino-4-methyl-azetidinone (32.1.4.2). Debenzylating this by hydrogen reduction using a palladium on carbon catalyst forms (3*S*-*trans*)-*N*-hydroxy-3-*tert*-butyloxycarbonyl-amino-4-methyl-azetidinone (32.1.4.3). The hydroxyl group in this compound is removed by reducing it with titanium trichloride, which forms azetidinone (32.1.4.4). Removing the *tert*-butyloxycarbonyl protection using trifluoroacetic acid and subsequent acylation of the resulting product with the benzyl chloroformate gives (3*S*-*trans*)-benzyloxycarbonylamino-4-methylazetidinone (32.1.4.5). Sulfonating this product with a mixture of sulfur trioxide

and dimethylformamide gives the corresponding *N*-sulfonic acid. Turning the resulting *N*-sulfonic acid into a potassium salt by reacting it with potassium hydrophosphate, followed by replacing the potassium cation with a tetrabutylammonium cation by reacting it with tetrabutylammonium sulfate gives the product (32.1.4.6). Reducing this with hydrogen using a palladium on carbon catalyst gives 3-amino-4-methyl-monobactamic acid (32.1.4.7). Acylating this with (*Z*) 2-amino-α-[[2-(diphenylmethoxy)-1,1-dimethyl-2-oxoethoxy]imino] 4-thiazoleacetic acid in the presence of dicyclohexylcarbodiimide and 1-hydroxy-benzotriazole gives the diphenylmethyl ester of the desired aztreonam (32.1.4.8), which is hydrolyzed to aztreonam (32.1.4.9) using trifluoroacetic acid [185–187].



It is believed that the methyl group at position 4 increases the stability of the beta-lactam ring with respect to most beta-lactamases, and at the same time it does not induce formation of beta-lactamase as cephalosporins and imipenems do.

The aminoacyl side chain of this drug, which is analogous to that of ceftazidime, is responsible for the high activity with respect to Gram-negative aerobic bacteria. The spectrum of use of aztreonam is very similar to the antimicrobial spectrum of aminoglycosides, and in the majority of cases it is a potential replacement.

Aztreonam is used for treating infections of the urinary tract and gastric tract, osteomyelitis, gonorrhea, intraabdominal and gynecological infections, infections of the bones, skin, etc., which are caused by aerobic Gram-negative microorganisms. In patients with known or suspected combined infections, it should be used in combination with other drugs such as clindamycin, metronidazole, nafcillin, or vancomycin.

32.2 MACROLIDE ANTIBIOTICS

Macrolide antibiotics currently used in clinics include a prototype of these compounds—erythromycin, which is isolated from *Streptomyces erythreus* and two relatively new drugs, clarithromycin and azithromycin. They belong to a group of antibiotics known by the name macrolides, because they contain a macrocyclic lactone ring (14-membered in erythromycin and clarithromycin, which as a matter of fact is 6-methoxyerythromycin; and 15-membered ring in azithromycin, due to the presence of an additional nitrogen atom in the ring) to which deoxysugar residues are joined.

There are also known macrolides with a 12-membered lactone ring, which received the name of patulolides, as well as those with a 16-membered lactone ring, which are called isenamycins. Today, there are about 100 compounds that make up this group of macrolide antibiotics, and they are generally produced by streptomycetes.

Macrolides have important clinical significance. There are direct indications for their use, and at the same time they are an alternative to penicillins for those who are allergic to penicillin. Today, macrolides are considered some of the safest antibiotics.

Macrolides, both erythromycin and others, inhibit the synthesis of bacterial proteins. The primary mechanisms of protein synthesis are identical in humans and bacteria. However, there is a significant difference that allows a specific antibiotic to exhibit selective toxicity with respect to bacteria.

As is well known, the first stage in synthesizing proteins is transcription of genetic code from DNA to messenger RNA (mRNA), a process that depends on RNA polymerase (transcriptase). A strand of nucleotides in RNA mirrors the order of nucleotides in DNA, thus containing information in a certain sequence in which amino acids must be bound to form the corresponding protein. Protein synthesis takes place on ribosomes, which can be represented as certain machines in which proteins and various amino acids are assembled.

Bacteria contain 80 S ribose, which is synthesized of two unequal components: a large 50 S subunit and small 30 S subunit. These two subunits have various functions. Messenger RNA binds with the 30 S subunit, while the 50 S subunit serves to bind amino acids, as well as to serve as the region that maintains the growing peptide chain. These regions are known as acceptor (A) and donor (R) regions, respectively, and they are located very close to one another.

Amino acids are supplied to the ribosome complex of mRNA by transport RNA (tRNA). There is a specific tRNA for each amino acid that must be included into the proteins being synthesized. Every tRNA is in turn specific with respect to one nucleotide region (nucleotide

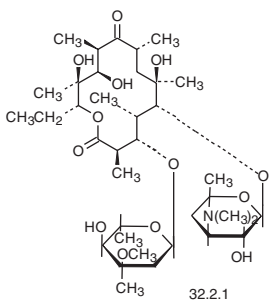
triplet or codon) in mRNA. Thus, tRNA is a double-ended molecule in which one end is specific with respect to one amino acid, and the other group is specific to the region of three nucleotides in mRNA. Aminoacyl tRNA binds with region A at the 50 S subunit. Growth of the peptide chain is accomplished by the transfer and binding of a peptide chain from region R to region A by catalysis of peptidyltransferase. After forming a peptide bond, a complex process of "translocation" of the tRNA is transferred from regions A to R and 30 S subunits move ahead one codon along the mRNA. Region A is freed and becomes ready to accept another amino acyl tRNA predetermined by the following triplet codon on the mRNA. This process of joining continues until the protein chain has been completed. Macrolides inhibit synthesis of bacterial proteins by binding with the bacterial 50 S subunit chain, thus preventing the growth of the peptide chain, most likely by interfering with translocation.

At the same time, these drugs do not bind to ribosomes in mammals, which is a reason for their selective toxicity. Macrolides can appear as bacteriostatics as well as bactericides depending on the concentration of the drug, sensitivity of the microorganisms, their growth rate, and as a matter of fact, the size of their colony.

Antibacterial activity of macrolides depends on the acidity of the medium. High activity is observed in neutral and basic media in comparison with acid. In particular, erythromycin is inactivated in the acidic medium of the stomach. Macrolides have a relatively broad spectrum of use, and they are active with respect to Gram-positive and Gram-negative microorganisms, achiomycetes, mycoplasma, spirochaeta, chlamydia, Bacteria Rickettsia, certain mycobacteria, Colon bacillus, blue-pus bacillus, shigella, salmonella, and so on.

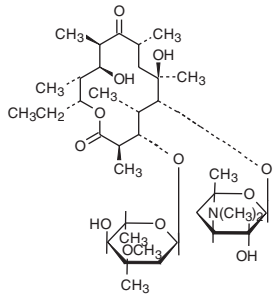
Erythromycin: Erythromycin, (3*R*,4*S*,5*S*,6*R*,7*R*,9*R*,11*R*,12*R*,13*S*,14*R*)-4-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)-oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecan-2,10-dione (32.2.1), is more specifically called erythromycin A. It was first isolated in 1952 from the culture liquid of microorganisms of the type *Streptomyces erytherus*. Minor amounts of erythromycin B and C were also found in the culture fluid. Erythromycin B differs from A in that a hydrogen atom is located at position 12 in the place of a hydroxyl group, while erythromycin C differs from A in that the residue of a different carbohydrate, micarose (2-6-di-deoxy-3-*C*-methyl-L-ribohexose), is bound to the macrocycle in position 3 in the place of cladinose (4-methoxy-2,4-dimethyl-tetrahydropyran-3,6-diol).

Erythromycin A is produced only microbiologically using active strains of microorganisms of the type *Saccharopolospora erythraea* [188–191].

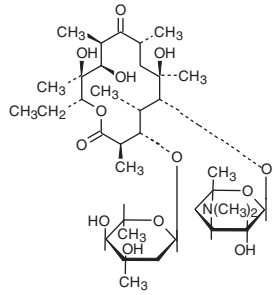


32.2.1

Erythromycin A



Erythromycin B



Erythromycin C

As was already stated, erythromycin and other antibiotics discussed in this chapter inhibit the synthesis of bacterial proteins.

Erythromycin inhibits bacterial protein synthesis by reversibly binding with their 50 S ribosomal subunit, thus blocking the formation of new peptide bonds. Erythromycin is classified as a bacteriostatic antibiotic.

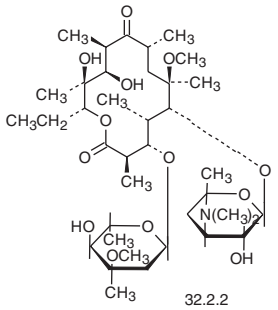
However, it can also exhibit a bactericidal effect against a few types of microbes at certain concentrations.

Bacterial resistance to erythromycin can originate by two possible mechanisms: the inability of reaching the cell membrane, which is particularly relevant in the case of the microorganisms *Enterobacteriaceae*, or in the case of the presence of a methylated alanine in the 23 S ribosomal RNA of the 50 S subunit, which lowers the affinity of erythromycin to it.

Erythromycin acts on Gram-positive (staphylococci both produced and not produced by penicillinase, streptococci, pneumococci, clostridia) and a few Gram-negative microorganisms (gonococci, brucelli, hemophile and whooping cough bacilli, legionelli), mycoplasma, chlamydia, spirochaeta, and Rickettsia. Colon and blue-pus bacilli, as well as the bacilli shigella, salmonella, and others are resistant to erythromycin.

Erythromycin is used for bacterial infections such as diphtheria, whooping cough, trachoma, tonsillitis, scarlet fever, otitis, sinusitis, cholecystitis, pneumonia, gonorrhea, and so on. Erythromycin is an alternative to penicillin for treating infections caused by sensitive organisms. It is the drug of choice for pneumonia, diphtheria, enteritis, and so on. Synonyms of this drug are ilozon, meromycin, erythroped, and many others.

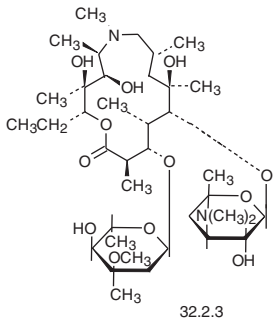
Clarithromycin: Clarithromycin, (2*R*,3*S*,4*S*, 5*R*,6*R*,8*R*,10*R*,11*R*,12*S*,13*R*)-3-(2,6-dideoxy-3-*C*-3-*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-6-methoxy-9-oxo-11,12-dihydroxy-2,4,6,8,10,12-hexamethyl-5-(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyloxy) cyclopentadecan-13-olide (32.2.2), is a semisynthetic analog of erythromycin A, in which the hydroxyl group at C_6 is replaced with a methoxyl group [192,193].



32.2.2

Clarithromycin is better absorbed and irritates the gastrointestinal tract less than erythromycin. It is presumed that its activity exceeds that of erythromycin by 2–4 times with respect to a number of streptococci and staphylococci, and to a few other microorganisms. It is used for treating bacterial bronchitis, pneumonia, skin and sexual infections. It is believed that clarithromycin is the most active macrolide for treating atypical mycobacteria. Synonyms of this drug are biaxin and others.

Azithromycin: Azithromycin, [2R-(2*R*,3*S*,4*R*, 5*R*, 8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-3-(2,6-dideoxy-3-*C*-methyl-3- *O*-methyl-α-L-*ribo*-hexopyranosyloxy)-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[(3,4,6-trideoxy-3-dimethylamino)-β-D-*xylo*-hexopyrano syl]-oxy]-1-oxa-6-azacyclopentadecan-15-one (32.2.3), is also a macrolide antibiotic that is synthesized semisynthetically [194,195].

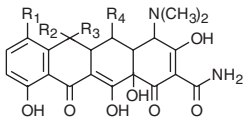


32.2.3

It is 2–4 times less active than erythromycin with respect to a number of streptococci and staphylococci, and to a number of other organisms; however, it is more active than other macrolides with respect to certain anaerobic organisms. Like other macrolides, it is active with respect to pathogens of the respiratory tract and pathogens transmitted sexually. It is used for treating bacterial bronchitis, pneumonia, skin, and sexual infections. Synonyms of this drug are zithromax and others.

32.3 TETRACYCLINES

Tetracyclines are a class of chemically similar drugs that are unified by the presence of four rings joined in a hydronaphthacene system, and the differences in activity are determined by various substituents on the base structure.



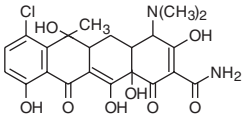
The first antibiotic of the tetracycline series, chlorotetracycline, which was isolated from a culture liquid of *Streptomyces aureofaciens*, was introduced into medical practice in 1948. Consequently, there were another six drugs of the tetracycline series that were introduced into medical practice between 1950 and 1972. Oxytetracycline is isolated from *Streptomyces rimosus*; tetracycline (semisynthetic), demeclocycline is isolated from the mutant type of *S. aureofaciens*; methacycline (semisynthetic), doxycycline (semisynthetic), and minocycline (semisynthetic). Methods of synthesis of the tetracycline series antibiotics have been suggested; however, they are purely of an academic interest and do not have any practical value.

Despite the few differences in these drugs in terms of pharmacokinetic features, their broad spectrum of antimicrobial action is similar in many regards.

Tetracyclines, like macrolides, inhibit protein synthesis in bacteria. The vital element of this process is the energy-requiring transfer of the drug through the cytoplasmic membrane, which leads to its accumulation in the cell. Inside the cell, it reversibly binds with 30 S ribosomal subunits of the bacteria. This process prevents aminoacyl tRNA from binding with mRNA (30 S ribosome), which leads to an inhibition of protein synthesis. The selective toxicity of tetracyclines lies in its diverse ability to penetrate bacterial cells and mammalian cells that lack a proper system of transport. The antimicrobial spectrum of all tetracyclines is practically the same. The difference is only observed in the degree of activity with respect to these or other microorganisms. Tetracyclines are active with respect to a huge variety of microorganisms, including Gram-positive, Gram-negative, aerobic, and anaerobic. They are active with respect to spirochaeta, mycoplasma, Bacteria Rickettsia, chlamydia, and a few protozoal infections. However, they are not active with respect to streptococci infections, blue-pus bacillus, and a few others. Resistance to tetracyclines is exhibited as a reduced ability of bacteria to accumulate the antibiotic inside the cell. This process is mediated by plasmids. As a rule, resistance with respect to any of these tetracyclines indicates resistance to all of the others.

Tetracyclines are the drug of choice with respect to a broad number of infections, including chlamydia, Bacteria Rickettsia, and others.

Chlorotetracycline: Chlorotetracyline, 7-chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-oxtahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacencarboxamide (32.3.1), is obtained biosynthetically as a result of the activity of a microorganism, the actinomycete *S. aureofaciens* [196–201].

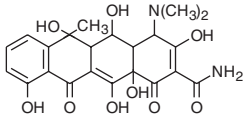


32.3.1

Chlorotetracycline, an antibiotic with a broad spectrum of action, causes a bacteriostatic effect with respect to Gram-positive (staphylococci, including those that produce penicillinase; streptococci, pneumococci; clostridia, listeria, and anthrax bacillus) and Gram-negative microorganisms (gonococci, whooping cough bacillus, colon bacillus, enterobacteria, klebisella, salmonella, shigella), as well as Rickettsia, chlamydia, mycoplasma, and spirochaeta. Blue-pus bacillus, proteus, serracia, most strains of *Bacteroides fragilis*, most fungi, and small viruses are resistant to this drug. It is used for pneumonia, bronchitis, empyema of the lungs, angina, cholecystitis, whooping cough, endocarditis, endometritis, intestinal infections, prostatitis, syphilis, gonorrhea, brucellosis, osteomyelitis, purulent infections of soft tissues, and others caused by microorganisms sensitive to this drug. Synonyms of this drug are aureomycin, biomycin, xanthomycin, and others.

Oxytetracycline: Oxytetracycline, 4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-2-naphthacencarboxamide (32.3.2), is

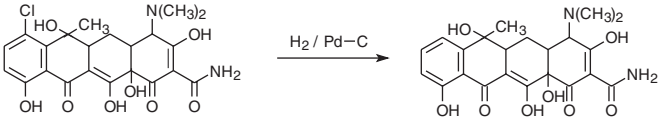
synthesized biosynthetically as a result of the activity of actinomycete *S. rimosus* [202–205].



32.3.2

In terms of antibacterial spectrum, this drug is similar to chlorotetracycline. It is used for the same indications. It belongs to the group of short-lasting tetracyclines. Synonyms of this drug are tetramycin, oxymycin, and others.

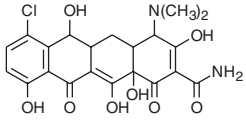
Tetracycline: Tetracycline, 4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacencarboxamide (32.3.3), is synthesized by reducing chlorotetracycline with hydrogen using a palladium on carbon catalyst. However, it can be synthesized microbiologically using the actinomycete *Streptomyces viridifaciens*, as well as a certain mutant *S. aureofaciens* [206–214].



32.3.1 32.3.3

In terms of antibacterial spectrum, oxytetracycline is similar to chlorotetracycline. It also belongs to the group of short-lasting tetracyclines, and is used for the same indications as chlorotetracycline. Synonyms of oxytetracycline are acromycin, bicyclin, cyclopar, sarcocyclin, and many others.

Demeclocycline: Demeclocycline, 7-chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahdroxy-1,11-dioxo-2-napthacencarboxamide (32.3.4), is produced by a mutant strain of *S. aureofaciens*, in which the mechanism of transferring methyl groups is disrupted, and thus demeclocycline or demethylchlorotetracycline differs from chlorotetracycline, oxytetracycline, and tetracycline in the absence of a methyl group at C_6 of the hydronaphthacene system. As a result, an antibiotic is synthesized that is more resistant to acids and bases in comparison with the methyl homologs [215–221].

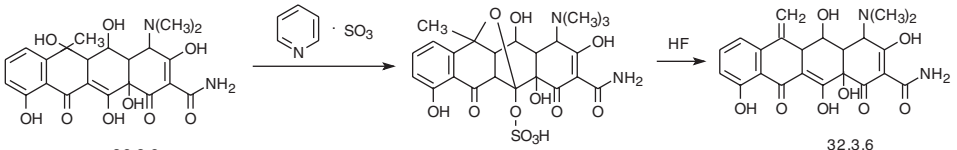


32.3.4

In terms of antibacterial spectrum, demeclocycline differs little from the whole tetracycline series; however, its half-life is somewhat longer than that of the short-lasting antibiotics described above, and therefore it belongs to the group of medium or intermediate-lasting

tetracyclines. Demeclocycline is used for the same indications as other antibiotics of the tetracycline series. Synonyms of this drug are ledermycin, biotetricin, decyclin, and declomycin.

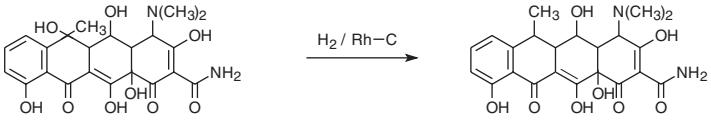
Methacycline: Methacycline, 4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methylen-1,11-dioxo-2-naphthacencarboxamide (32.3.6), is synthesized from oxytetracycline (32.3.2), which is reacted with a sulfur trioxide—pyridine complex, resulting in an oxidation reaction. Simultaneous sulfonation gives a naphthacen–sulfotetrahydrofuran derivative intermediate (32.3.5), which when reacted with hydrofluoric acid forms methacycline (32.3.6) [222–225].



32.3.2 32.3.5 32.3.6

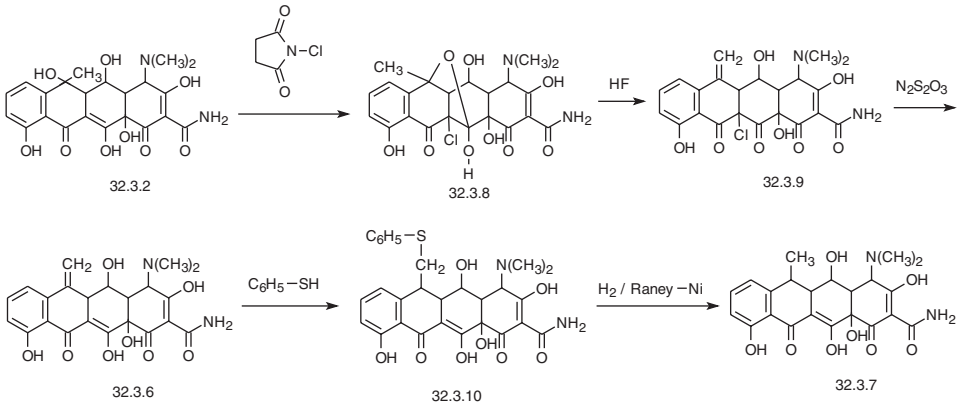
Methacycline is used for the same indications as other antibiotics of the tetracycline series. In some cases it is tolerated better than tetracyclines. Synonyms of this drug are rondomycin, methamycin, adramycin, and others.

Doxycycline: Doxycycline, 4-dimethylamino-1,4,4a,5,5a,6,11,12a-oxtahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2,naphthacencarboxamide (32.3.7), is an isomer of tetracycline that differs only in the placement of one hydroxyl group. Doxycycline can be formally viewed as the result of transferring the C_6 hydroxyl group of tetracycline to C_5. Doxycycline is synthesized in two different ways from oxytetracycline (32.3.2). One of the ways suggests dehydrating oxytetracycline at C_6 by reducing the tertiary hydroxyl group with hydrogen using a rhodium on carbon catalyst [226,227].



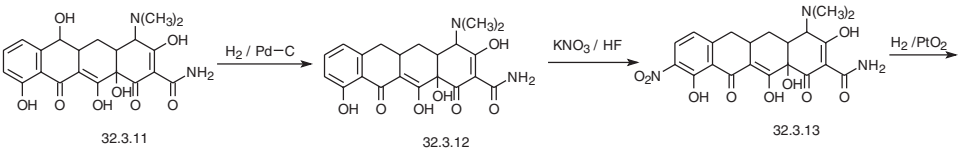
32.3.2 32.3.7

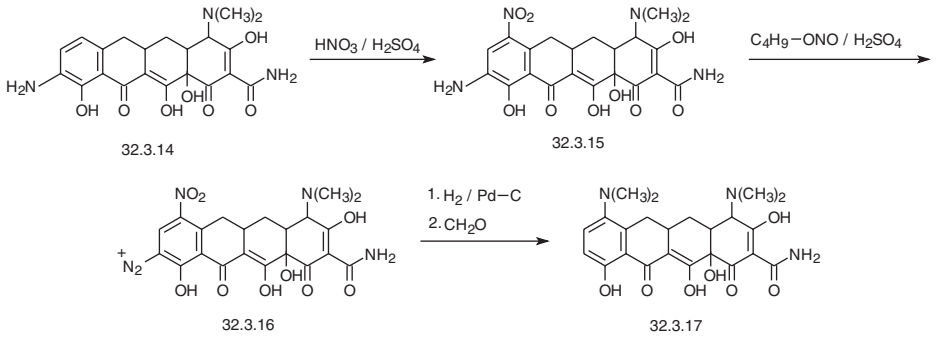
The second way is analogous to that of giving methacycline, which suggests an oxidation stage of the homoallyl system, except that *N*-chlorosuccinimide is used as the oxidant, which results in the formation of a naphthacentetrahydrofuran derivative (32.3.8), and which upon being reacted with hydrofluoric acid breaks apart to form an 11a-chloro-6-exomethylene derivative (32.3.9). Reductive dechlorination of this product using sodium thiosulfate forms the intermediate methacycline (32.3.6), and thiophenol is joined to the methyl group that carry out radical reactions, forming the derivative (32.3.10). This product is reduced by hydrogen over a Raney nickel catalyst, during which reductive desulfurization takes places, giving doxycycline [225,228–230].



Doxycycline is used for the same indications as other antibiotics of the tetracycline series; however, it belongs to the group of long-lasting tetracyclines. In some cases it is more active with respect to a number of organisms, and is better tolerated than other tetracyclines. Synonyms of this drug are azudoxat, codidoxal, eftapan, vibramycin, and others.

Minocycline: Minocycline, 4,7-*bis*(dimethylamino)-1,4,4a,5,5a,6,11,12 a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacencarboxamide (32.3.17), is synthesized from 6-dimethyl-tetracycline (32.3.11), which is synthesized as a result of the vital activity of *S. aureofaciens*, in which the mechanism of transferring methyl groups is disrupted, or from a common strain of the same microorganisms, but with the addition of compounds such as ethionin, D-norleucine or D-methionine to the medium for developing this actinomycete, which are antimetabolytes of methionine, the primary donor of methyl groups in microbiological synthesis of tetracycline molecules. Hydrogenolysis of the aforementioned 6-demethyltetracycline (32.3.11) with hydrogen using a palladium on carbon catalyst gives 4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-napthacencarboxamide (32.3.12), which is nitrated at position 9 by potassium nitrate in aqueous hydrofluoric acid, which forms the nitro compound (32.3.13). This is reduced to the corresponding amino derivative (32.3.14) by hydrogen over platinum dioxide. The resulting aminophenyl compound (32.3.14) is then nitrated with nitric acid in the presence of sulfuric acid to make 7-nitro-9-amino-4-naphthacencarboxamide (32.3.15). This undergoes diazotization when reacted with butylnitrate in sulfuric acid, and the resulting diazo derivative (32.3.16) is reduced with hydrogen using a palladium on carbon catalyst. During this, the product is deazotized, while the nitro group is simultaneously reduced to an amino group, which undergoes exhaustive methylation by formaldehyde into minocycline (32.3.17) [231–237].

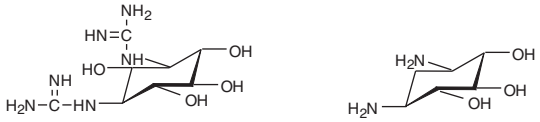




Minocycline is used for the same indications as other antibiotics of the tetracycline series. In a few cases, it is tolerated worse than other tetracyclines, and in particular, it has an effect on the vestibular apparatus. In addition, as seen already from the synthesis scheme, it is much more expensive than other tetracyclines, which are synthesized in a purely microbiological manner. Synonyms of this drug are clinocin, minocyn, vectrin, and others.

32.4 AMINOGLYCOSIDES

Aminoglycosides are compounds that contain two or more amino sugars joined by glycoside bonds with an aminocyclitol ring (aglycon). The six-membered aminocyclitol ring is either streptidine (1,3-diguanidino-2,4,5,6-tetrahydroxycyclohexane), as in streptomycin, or 2-deoxystreptamine (1,3-diamino-4,5,6-trihydroxycyclohexane), as in all other aminoglycosides.



2-Deoxystreptamine antibiotics can be further differentiated by the number and type of sugars bound to the aminocyclitol ring. Thus, neomycines, including neomycin itself and paromomycin, have three sugar residues (two aminohexoses and one non-amino sugar pentose) bound to 2-deoxystreptamine. Analogs of kanamycin (kanamycin, tobramycin, amikacin) and gentamicin (gentamicin, sysomycin, netilmicin) each have two aminohexoses bound to the central aglycon. The last two series differ in the type of 3-aminohexoses. For a number of canamycines this is kanosamine, and for a number of gentamicines this is garosamine. Variations inside the aminoglycoside series themselves are caused by differences in the amino sugars and aglycon side chains.

Of the eight aminoglycosides that are currently used, five are synthesized from different versions of *Streptomyces*: streptomycin (isolated from *Streptomyces griseus*), neomycin (isolated from *Streptomyces fradiae*), paromomycin (isolated from *S. rimosus*), kanamycin (isolated from *Streptomyces kanamyceticus*), and tobramycin (isolated from

Streptomyces tenebrarius). Gentamicin is isolated from *Micromonospora purpurea*, and it consists of a mixture of approximately equal amounts of three compounds: gentamicines C_1, C_{1a}, and C_2. Amikacin and netilmicin are semisynthetic drugs. Amikacin is a chemical modification of kanamycin. Netilmicin is a semisynthetic derivative of schizomycin, which is isolated from *Micromonospora inyoensis.*

Aminoglycoside antibiotics are bactericides. They inhibit protein synthesis and lead to incorrect reading of the genetic code. The common element in the process leading to the lethal outcome of bacteria is the active transfer of the drug from the surrounding medium into the bacterial cell, which leads to a large accumulation of medicine inside the cell exceeding that of the surroundings. Aminoglycosides easily diffuse through the outer membrane of the bacteria and enter the periplasmic space. The initial intracellular region of aminoglycoside action is the bacterial ribosome. There is evidently a minimum of two different types of ribosomal binding: one is specific to streptomycin, and the other acts by binding with other aminoglycosides. Streptomycin binds with the 30 S ribosomal subunit. Other aminoglycosides bind to different regions of 30 S and 50 S ribosomal subunits, and cannot compete with streptomycin for binding with 30 S ribosomes.

Binding between aminoglycosides and ribosomes is expressed as both direct inhibition of protein synthesis as well as incorrect reading of the genetic code from the matrix of mRNA, which leads to the insertion of incorrect amino acids into polypeptide chains. However, none of these effects fully explains the bactericidal effect of aminoglycosides. Aminoglycosides are drugs used predominantly against aerobic and a few Gram-negative microorganisms, *S. aureus*, and mycobacteria. These antibiotics are not active with respect to anaerobic microorganisms.

Bacterial resistance with respect to aminoglycosides can be explained by changes in binding regions on ribosomes, decline in intracellular transport, and deactivation of drugs by microbial enzymes.

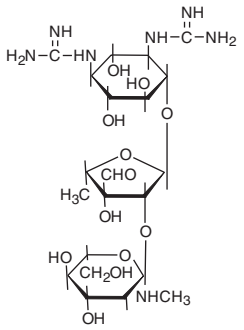
Streptomycin binds with specific proteins (S_{12}) on 30 S subunits of ribosomes. A change in this protein as a result of a mutation makes the ribosomes unable to bind with streptomycin, which makes the organism resistant. Mutational resistance to streptomycin occurs frequently. Gentamicin, tobramycin, netilmicin, and amikacin bind with many regions on both subunits of the ribosomes, and therefore mutational resistance to them is not common.

The second mechanism of resistance makes transport into the cell more difficult, which leads to resistance to all aminoglycosides. This type of resistance is not common among Gram-negative, aerobic, and a few other microorganisms. Since the transport of aminoglycosides through the cytoplasmic membrane is an oxygen-requiring process, anaerobic bacteria always exhibit resistance with respect to these bacteria.

The most important mechanism of resistance is the enzyme production by plasmids, which phosphorylate, adenylate, or acetylate specific amino or hydroxyl groups in the aminoglycoside molecules. These enzymes are not produced outside the cell. They are found in the periplasmic region. As soon as the drug passes through the outer membrane and reaches the perplasmic space, it undergoes a change by enzymes. The altered drug (along with the unchanged drug) competes for entrance into the cell, but it turns out that they are unable to bind with ribosomes. As a result, the energy-requiring phase of aminoglycoside uptake is inhibited. About 20 similar enzymes have been found. In turn, aminoglycosides differ in terms of their ability to resist enzymatic inactivation.

Gentamicin and tobramycin are sensitive to some of these same enzymes; netilmicin is somewhat more resistant to such enzyme modifications. Amikacin is the most resistant to the presently described enzymes. Gentamicin, tobramycin, netilmicin, and amikacin are effective in treating aerobic infections and other Gram-negative bacilli. In serious infections caused by *P. aeruginosa*, these drugs are used in combination with antibiotics with a broad spectrum, such as penicillin, ceftazidin, imipenem, or aztreonam. Streptomycin is the drug of choice for treating rabbit fever, plague, and brucellosis (in combination with tetracycline). It is not used for treating other Gram-negative bacterial infections because of the high likelihood of developing resistance, which can develop as a result of only one mutation. However, it should be especially noted that practically all antibiotics of the aminoglycoside series are not metabolized in the body, but build up in the kidneys and have a certain oto- and nephrotoxicity.

Streptomycin: Streptomycin, *trans*-2,4-diguanidino-3,5,6-trihydroxycyclohexyl-5-deoxy-2-*O*-(2-deoxy-2-methylamino-α-L-glucopyranosyl)-3-*C*-hydroxymethyl-β-L-lyxo-pentofuranoside (32.4.1), is isolated from a culture liquid of the vital activity of the actinomycete *S. griseus* [238–247].

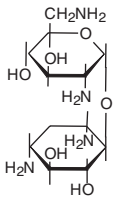


32.4.1

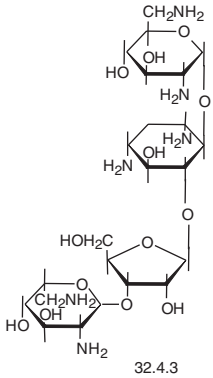
Streptomycin has a broad spectrum of antibacterial activity. It is effective with respect to most Gram-negative and a few Gram-positive bacteria; staphylococci, streptococci, pneumococci, gonococci, meningococci, stimulus of dysentery, brucellosis, tuberculosis, rabbit fever, plague, and others. It is used for various diseases caused by microorganisms that are sensitive to it in bacterial endocarditis, periotonitis, meningitis, infections of the urinary tract, gastric infections, and so on. Synonyms of this drug are streptan, streptocol, and others.

Neomycin: Neomycin is a complex mixture of antibiotics (neomycins A, B, C, D, E, and F), that is formed by the actinomycete *S. fradiae.* Neomycin A, also called neamine, is 2-deoxy-4-*O*-(2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl)-D-streptamine (32.4.2), and it does not display antibiotic properties. At the same time, neomycin B, *O*-2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl(1→4)-O-[O-2,6-diamino-2,6-dideeoxy-β-L-idopyranosyl-(1→3)-β-D-ribofuranosyl-(1→5)]-2-deoxy-D-streptamine (32.4.3), differs from neomycin A in the presence a second glycoside residue and exhibits powerful antibacterial

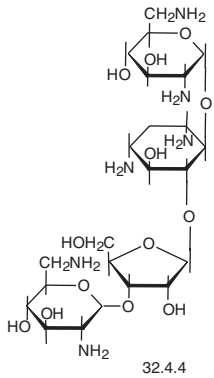
activity. Neomycin C (32.4.4) differs from neomycin B in the orientation of the aminomethyl group in the neozamine part of the molecule [248–255].



32.4.2



32.4.3

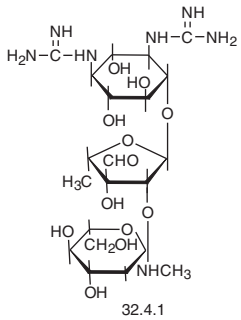


32.4.4

Neomycin, like streptomycin, has a broad spectrum of antibacterial activity. It is effective with respect to the majority of Gram-negative and a few Gram-positive bacteria; staphylococci, pneumococci, gonococci, meningococci, and stimulants of dysentery. It is not very active with respect to streptococci. The antibiotic effect of neomycin with respect to many types of bacteria is higher than that of streptomycin. At the same time, microorganisms sensitive to neomycin become resistant to a lesser degree than streptomycin.

It is used for various gastrointestinal diseases caused by microorganisms sensitive to it, including enteritis, which is caused by microbes that are resistant to antibiotics. However, because of its high oto- and nephrotoxicity, its local use is preferred for infected skin diseases, infected wounds, conjunctivitis, keratitis, and others. Synonyms of this drug are framycetin, soframycin, tautomycin, and others.

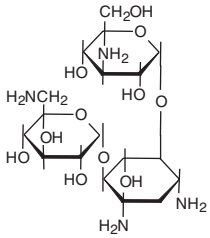
Paromomycin: From a chemical point of view, paromomycin, *O*-2-amino-2-deoxy-α-D-glucopyranosyl(1→4)-O-[O-2,6-diamino-2,6-dideoxy-β-L-idopyranoxyl-(1→3)-β-D-ribofuranosyl-(1→5)]-2-deoxy-D-streptamine (32.4.5), differs from neomycin B only in the replacement of the 6-amino group in the glucopyranosyl region of the molecule with a hydroxyl group, and it is isolated from a culture fluid of the actinomycete *S. rimosus* [256–258].



32.4.1

The antibacterial activity and indications for using paromomycin are analogous to those of neomycin. In addition, it is recommended for treating severe and chronic forms of gastric amebiasis. Synonyms of this drug are aminosidine, catenulin, crestomycin, hydroxymycin, monomycin, zygomycyn, and others.

Kanamycin: Kanamycin, *O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)-O-[6-deoxy-6-amino-α-D-glucopyranosyl-(1→4)]–2-deoxy-D-streptamine (3.4.6), is isolated from a culture liquid of the actinomycete *S. kanamyceticus*, which produces three antibiotics—kanamycines A, B, and C [259–262].

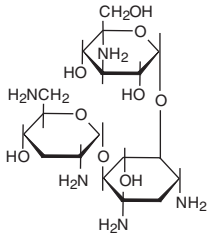


32.4.6

Kanamycin A is similar to streptomycin and neomycines and has a broad spectrum of antimicrobial action. It is active with respect to most Gram-positive as well as Gram-negative microorganisms (staphylococci, gastric bacilli, rabbit fever, Fridlender's bacillus, proteus, shigella, salmonella).

It is used for treating sepsis, meningitis, osteomyelitis, periotonitis, pneumonia, pyelonephritis, pyelocystitis, infected wounds, and post-operational purulent complications caused by microorganisms sensitive to the drug. Synonyms of this drug are karmycin, kamaxin, resistomycin, and many others.

Tobramycin: Tobramycin, *O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)-O-[2,6-amino-2,3,6-trideoxy-α-D-*ribo*-glucopyranosyl-(1→4)]-2-deoxy-D-streptamine (3.4.7), is isolated from a culture liquid of the vital activity of the actinomycete *S. tenebrarius* [263–270].

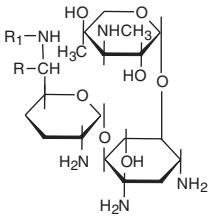


32.4.7

Tobramycin is highly active with respect to Gram-negative microorganisms (blue-pus bacillus and gastric bacilli, rabbit fever, serratia, providencia, enterobacteria, proteus, salmonella, shigella), as well as Gram-positive microorganisms (staphylococci, including those resistant to penicillin and some cephalosporins), and a few strains of streptococci.

It is used for severe bacterial infections: peritonitis, sepsis, meningitis, osteomyelitis, endocarditis, pneumonia, pleural empyema, pulmonary abscess, purulent skin infections and soft tissue infections, and infections of the urinary tract caused by microorganisms that are sensitive to the drug. Synonyms of this drug are nebicine, obracine, and others.

Gentamicin: Gentamicin is a complex of antibiotics isolated from a culture liquid of the actinomycete *M. purpurea*, which consists of a mixture of approximately equal amounts of three compounds: gentamicines C_1, C_{1a}, and C_2 [271–278].



32.4.8

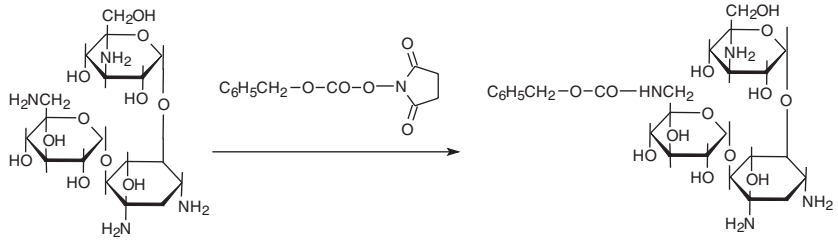
Gentamicin C_1 (R = R_1 = CH_3)
Gentamicin C_2 (R = CH_3, R_1 = H)
Gentamicin C_{1A} (R = R_1 = H)

Gentamicin has a broad spectrum of biological action, and is highly active with respect to strains of staphylococci that are resistant to penicillins and other antibiotics, many Gram-negative microorganisms: blue-pus bacillus, rabbit fever, enterobacter, salmonella, shigella, and proteus.

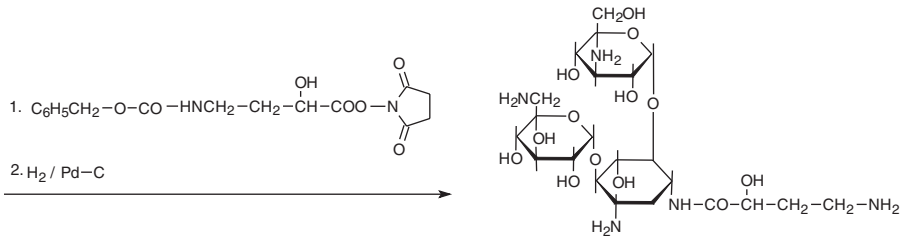
It is used for pyelonephritis, cystitis, pneumonia, pleural empyema, peritonitis, sepsis, meningitis, purulent skin and soft tissue infections, infected wounds, burns, and so on, which are caused by microorganisms that are sensitive to the drug. Gentamicin is the drug of choice for severe bacterial infections caused by undetermined stimuli. Synonyms of this drug are garamycin, gentacylin, ribomycin, and many others.

Amikacin: Amikacin, *O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1→4)-O-[6-amino-6-deoxy-α-D-glucopyranosyl-(1→6)]-N^3-(4-amino-L-2-hydroxybutyryl)-2-deoxy-L-streptamine (3.4.10), is a semisynthetic antibiotic that is synthesized from kanamycin (3.4.6). The primary amino group in this molecule is previously protected by acylating it with *N*-(benzoyloxycarbonyloxy) succinimide in dimethylformamide, after which the resulting product (32.4.9) is treated with an ester synthesized from *N*-hydroxysuccinimide and benzyloxycarbonylamino-α-l-(–) hydroxybutyric acid, and as a result the 4-amino group of the streptamine region of the molecule is selectively acylated. Further removal of two benzyloxycarbonylamine protective groups in the traditional manner, via hydrogen reduction using a palladium on carbon catalyst, forms the desired amikacin (32.4.10) [279–286].

Amikacin is highly effective with respect to Gram-negative microorganisms (blue-pus and gastric bacilli, rabbit fever, serratia, providencia, enterobacteria, proteus, salmonella, shigella), as well as Gram-positive microorganisms (staphylococci, including those that are resistant to penicillin and some cephalosporins), and a few strains of streptococci.



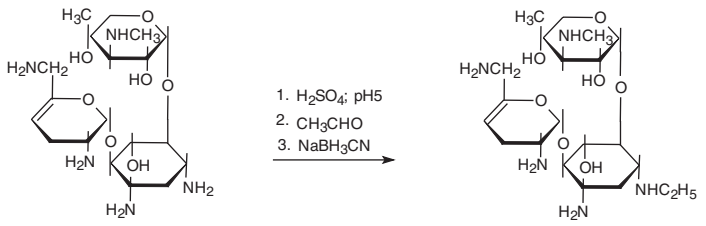
32.4.6 32.4.9



32.4.10

It is used for severe bacterial infections: peritonitis, sepsis, meningitis, osteomyelitis, endocarditis, pneumonia, pleural empyema, pulmonary abscess, purulent skin and soft tissue infections, and infections of the urinary tract that are caused by microorganisms sensitive to the drug. Synonyms of this drug are amikin, biklin, novamin, and others.

Netilmicin: Netilmicin, *O*-3-deoxy-4-*C*-methyl-3-(methylamino)-β-L-arabinopyranosyl (1→4)-O-[2,6-diamino-2,3,4,6-tetradeoxy-α-D-*glycero*-hex-4-enopyranosyl]-(1→6)-2-deoxy-N^3-ethyl-L-streptamine (3.4.10), is also a semisynthetic antibiotic that is synthesized in two stages from another known antibiotic, sisomicin (3.4.11), which is produced by a culture of *M. inyoensis*. In the first stage of synthesis, reacting sisomicin with acetaldehyde in a specific acidic medium of pH 5 is successful in selectively giving an imine at the 3-amino group of the 2-deoxystreptamine region of the molecule. The resulting imine is then hydrogenated by sodium cyanoborohydride to an ethylamino derivative —netilmicin (32.4.12) [287–291].



32.4.11 32.4.12

Netilmicin is also highly effective with respect to Gram-negative microorganisms (blue-pus and colon bacilli, rabbit fever, serratia, providencia, enterobacteria, proteus, salmonella,

shigella), as well as a few Gram-positive microorganisms (staphylococci and a few strains of streptococci).

It is used for severe bacterial infections that are caused by microorganisms sensitive to the drug. Synonyms of this drug are netillin, zetamycin, and others.

32.5 LINCOSAMIDES

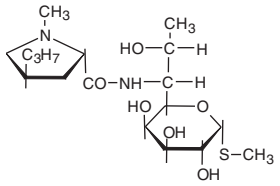
Lincosamides (lincomycin and clindamycin) are representatives of a very small group of drugs synthesized up of an amino acid bound to an amino sugar. Lincosamides bind with the 50 S ribosomal subunit of bacteria and inhibit protein synthesis. They also inhibit peptidyltransferase action. Lincosamides are bacteriostatic antibiotics; however, when they reach a certain level in the plasma, they also exhibit bactericidal action against some bacteria. Lincosamides are highly active against anaerobic infections such as *Peptococcus*, *Peptostreptococcus*, *Actinomyces*, *Propionibacterium*, and *Clostridium fringens*, a few types of *Peptococcus* and *Clostridium.*

Practically all anaerobic Gram-negative bacteria are resistant to lincosamides. Resistance to lincosamides can occur because of the inability of drugs to permeate through the cellular membrane of bacteria, or because of changes in the ribosomal-binding regions.

Lincosamides are most often used for treating anaerobic infections such as intraabdominal and female infections.

Lincosamides are a good alternative to beta-lactam antibiotics for treating infections caused by *S. aureus* or streptococci. It is useful in treating osteomyelitis and septic arthritis because of the large concentration attainable in the bones.

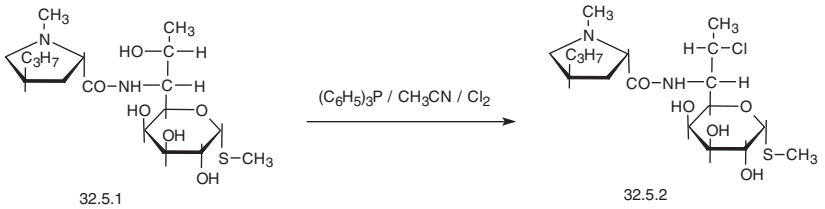
Lincomycin: Lincomycin, 6,8-dideoxy-6-*trans*-(1-methyl-4-propyl-L-2-pyrrolidincarboxamido)-1-methylthio-D-*erythro*-α-D-*galacto*-octopyranoside (32.5.1), is the first lincosamide that has found use in clinical practice, and which was isolated in 1962 from the culture liquid of the activity of the actinomycete *Streptomyces lincolnensis* [292–295].



32.5.1

Lincomycin has an antibacterial effect with respect to Gram-positive microorganisms (staphylococci, streptococci, pneumococci, diphtheria bacillus, and clostridia). It is used for serious bacterial infections: sepsis, osteomyelitis, septic endocarditis, pneumonia, pulmonary abscess, infected wounds, and purulent meningitis. Lincomycin is a reserve drug for infections caused by strains of staphylococci and other Gram-positive microorganisms that are resistant to penicillin and other antibiotics. Synonyms of this drug are lincocin, mycivin, albiotic, and others.

Clindamycin: Clindamycin, methyl-[7-chloro-6,7,8-trideoxy-6-*trans*-(1-methyl-4-propyl-L-2-pyrrollidin-carboxamido)-1-thio-L-*threo*-α-D-*galacto*-octapyranoside] (32.5.2), which is a 7(*S*)-chloro-7-deoxy derivative of lincomycin, is synthesized by replacing the hydroxyl group of lincomycin (32.5.1) at C_7 by treating it with triphenyl phophine in acetonitrile (Raydon reagent), in which a configuration transformation takes place in the given carbohydrate [296–303].

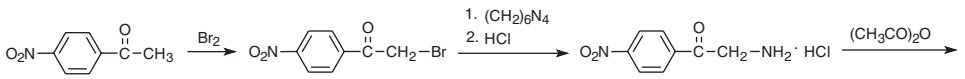


32.5.1 32.5.2

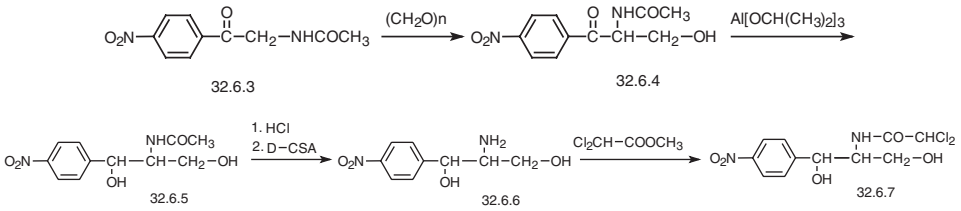
This drug exceeds lincomycin in all positive respects, including absorption into the gastrointestinal tract, antibacterial activity, and antimicrobial spectrum. Synonyms of this drug are cleocin, clinimycin, dalacin, and others.

32.6 CHLORAMPHENICOL

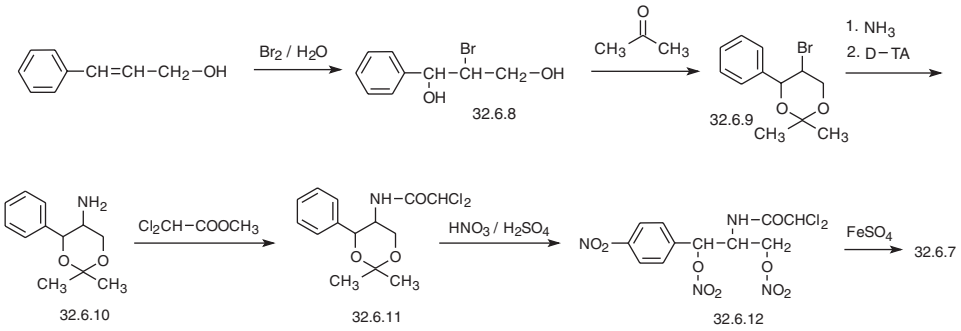
Chloramphenicol, D-*threo*-2,2-dichloro-*N*-[β-hydroxy-α-(hydroxymethyl)]-*n*-nitrophenylacetamide (32.6.7), was first isolated in 1947 from a culture fluid of the actinomycete *Streptomyces venezuelae*; however, it is only currently produced synthetically. When using a synthetic racemic mixture without having previously separated it into D- and L-threo forms, it is called sintomycin. Two ways of synthesizing chloramphenicol are suggested. The first begins with 4-nitroacetophenone, which is brominated with molecular bromine to make ω-bromo-4-nitroacetophenone (32.6.1). This is transformed to ω-amino-4-nitroacetophenone (32.6.2) by successive production of a quaternary salt with urotropine and subsequent break up to an amine using hydrogen chloride. The resulting aminoketone is acylated with acetic anhydride to make ω-acetamido-4-nitroacetophenone (32.6.3), and the product undergoes acylmethylation with paraform aldehyde to give α-acetamido-β-hydroxy-4-nitropropiophenone (32.6.4). Reducing the carbonyl group in the resulting compound with aluminum isopropoxide in isopropyl alcohol gives D,L-threo-2-acetamido-1-(4-nitrophenyl)-1,3-propandiol (32.6.5). The acetyl group is hydrolyzed in hydrochloric acid to form D,L-threo-2-amino-1(4-nitrophenyl)-1,3-propandiol. The resulting racemic mixture of amines is treated with camphor-D-sulfonic acid, and the resulting enantiomeric salts are separated. After alkaline hydrolysis of the selected salt, the product D, (–)-*threo*-2-amino-1-(4-nitrophenyl)-1,3-propandiol (32.6.6) is synthesized. Acylating the aminogroup of this compound with the methyl ester of dichloroacetic acid gives the desired chloramphenicol (32.6.7) [304–312].



32.6.1 32.6.2



The other synthesis begins with cinnamic alcohol, which is reacted with hypobromous acid to make 2-bromo-1-phenyl-1,3-propandiol (32.6.8), the hydroxyl group of which is protected as a ketal by reacting it with acetone, giving 5-bromo-2,2-dimethyl-4-phenyl-1,3-dioxane (32.6.9). Reacting the resulting bromide with ammonia gives an isomeric mixture of D,L-*threo*-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane, which upon treatment with D-tartaric acid, separation of the resulting salts, and subsequent alkaline hydrolysis of the selected salt gives D-(–)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (32.6.10). Acylating this with the methyl ester of dichloroacetic acid gives D-(–)-*threo*-5-dichloroacetamido-2,2-dimethyl-4-phenyl-1,3-dioxane (32.6.11). The phenyl ring is then nitrated, during which the 1,3-dioxane ring is cleaved off, giving dinitrate of D-(–)-*threo*-2-dichloroacetamido-1-(4-nitrophenyl)-1,3-propandiol (32.6.12). Reducing the nitro group in this compound with bivalent iron sulfate gives the desired chloramphenicol (32.6.7) [313–315].



Chloramphenicol inhibits protein synthesis in bacteria, and to a lesser degree in eukaryotic cells. It easily diffuses into the bacterial cell, where it reversibly binds with the 50 S ribosomal subunit. This prevents amino acid ending of tRNA from binding with the binding regions of the 50 S ribosome. The binding of aminoacyl tRNA with the 30 S subunit is not disturbed. Mammalian cells containing 80 S ribosomes are not affected by chloramphenicol. However, this drug inhibits synthesis of mitochondiral proteins in mammalian cells, possibly because of the similarty between mitochondrial and bacterial ribosomes.

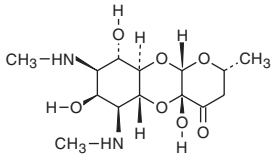
Chloramphenicol has a broad spectrum of antimicrobial activity, including Gram-positive, Gram-negative, aerobic, and anaerobic bacteria, spirochaeta, mycoplasma, chlamydia, and so on; however, it can cause pronounced suppression of blood flow, which is accompanied by reticulocytopenia, granulocytopenia, and in severe cases, aplastic anemia.

Resistance to chloramphenicol is usually explained by the presence of a plasmid that determines the production of chloramphenicol acetyltransferase. This enzyme acetylates the drug, giving it unable to bind with 50 S subunits of bacterial ribosomes. Chloramphenicol is a potentially toxic drug and has a few indications for use. It is the drug of choice for treating typhoid fever, and it is used for treating brain abscesses. Until recently, it was the drug of choice for therapy of bacterial meningitis in children (in combination with ampicillin). However, third-generation cephalosporins are currently preferred for such purposes. Chloramphenicol is an effective alternative for a number of infections in situations, where drugs of choice cannot be used for one reason or another.

However, it should never be used for infections that can readily be treated with other antimicrobial drugs. Synonyms of this drug are levomycetin, amindan, aquamycetin, chloromycetin, ophthoclor, opulets, leukomycin, and many others.

32.7 OTHER ANTIBIOTICS

Spectinomycin: Spectinomycin, 4a,7,9-trihydroxy-2-methyl-6,8-*bis*-(methylamino)-perhydroxypyrano-[2,3-b]benzodioxan-4-one (32.7.1), which is isolated from products of the actinomycete *Streptomyces spectabilis*, is an aminocyclitol, yet it is not an aminoglycoside antibiotic since it does not contain either an amino sugar region or a glycoside bond [316–324].

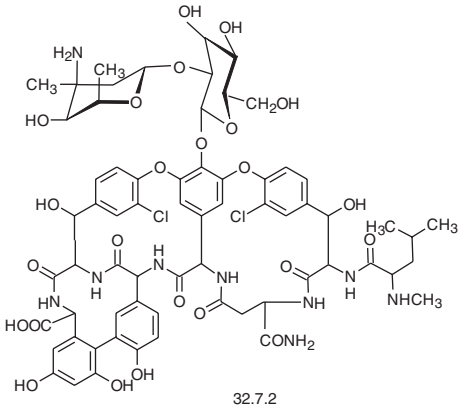


32.7.1

Analogous to streptomycin, spectinomycin binds with ribosomal 30 S subunits of microorganisms and inhibits protein synthesis; however, incorrect reading of the genetic code does not take place. Despite the broad spectrum of activity, spectinomycin is used only for gonococci infections. Other Gram-negative bacteria begin to display resistance during treatment. It is effective with respect to most strains of gonococci, as well as a number of other Gram-negative microorganisms.

It is used for treating severe gonorrheal urethritis and proctitis in men, and severe gonorrheal proctitis in women, which is caused by strains of gonococci that are sensitive to the drug. Synonyms of this drug are actinospectocin, spectam, togamicin, and others.

Vancomycin: Vancomycin (32.7.2) was isolated in 1956 from the products of the functional activity of actinomycetes *Streptomyces orientalis* (currently *Nocardia orientalis*). Based on its chemical structure and contents, vancomycin is classified as a glycopeptide antibiotic. Its molecular mass is significantly more than practically any other used antibiotics [325–330].



32.7.2

Vancomycin inhibits synthesis of bacterial cell membranes. Unlike beta-lactam antibiotics, which inhibit the third stage of peptidoglycan synthesis, vancomycin affects the second stage of creating bacterial cell membranes. Vancomycin inhibits the reaction in which the repeating unit of the cell membrane is separated from the cytoplasmic membrane-bound phospholipids, and binds with the already existing peptidoglycan. It also damages protoplasts by affecting the cytoplasmic membrane through the inhibition of RNA synthesis. Vancomycin is active only with respect to Gram-positive bacteria. It is the most powerful of all of the known antibiotics with respect to *S. aureus* and *Staphylococcus epidermidus*, including methicillin- and cephalosporin-resistant strains.

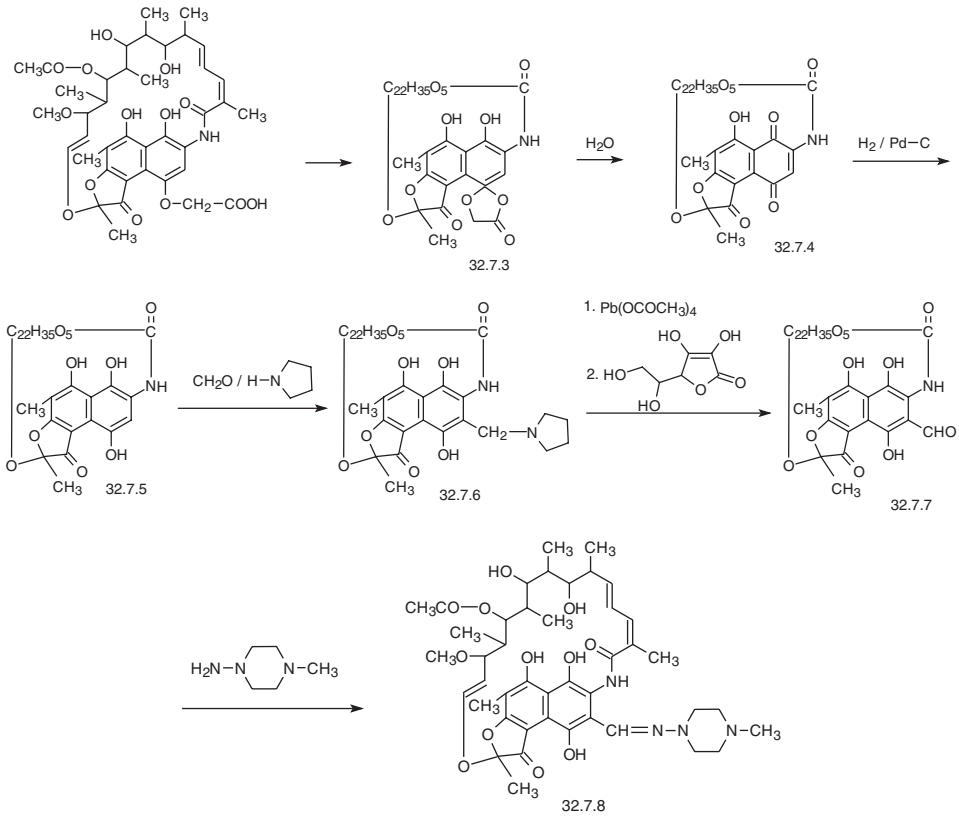
Resistance of Gram-negative organisms (such as mycobacteria), fungi, virii, and protazoans to vancomycin occurs because the barrier is impermeable to the drug, which is ensured by the outer membrane. Resistance of Gram-positive organisms to vancomycin is rarely observed.

Vancomycin is used for serious bacterial infections caused by microorganisms sensitive to this drug when penicillins and cephalosporins are ineffective for diseases such as sepsis, endocarditis, pneumonia, pulmonary abscess, osteomyelitis, meningitis, and enterocolitis, or when penicillins and cephalosporins cannot be tolerated by patients. Vancomycin is the drug of choice for infections caused by methicillin-resistant forms of *S. aureus*, *S. epidermidus*, and other coagulase-negative staphylococci, as well as for endocarditis, diphtherioid infections, and for patients very sick with colitis caused by *C. difficile.* A synonym of this drug is vancocin.

Rifampicin: Rifampicin, 5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[*N*-(4-methyl-1-piperazinyl)-formimidoyl]-2,7-(epoxypentadeca-1,11,13-trienimino)-naphtho-[2,1-b] furan-1,11(2*H*)dion-21-acetate (32.7.8).

Rifampicin is a semisynthetic derivative of rifamicin B, a macrolactam antibiotic and one of more than five antibiotics from a mixture of rifamicins A, B, C, D, and E, which is called a rifamicin complex, which is produced by actinomycetes *Streptomyces mediteranei (Nocardia mediteranei)*. It was introduced into medical practice in 1968. Synthesis of rifampicin begins with an aqueous solution of rifamicin, which under the reaction conditions is oxidized to a new derivative of rifamicin S (32.7.4), with the intermediate formation of

rifamicin O (32.7.3). Reducing the quinone structure of this product with hydrogen using a palladium on carbon catalyst gives rifamicin SV (32.7.5). The resulting product undergoes aminomethylation by a mixture of formaldehyde and pyrrolidine, giving 3-pyrrolidinomethylrifamicin SV (32.7.6). Oxidizing the resulting product with lead tetracetate to an enamine and subsequent hydrolysis with an aqueous solution of ascorbic acid gives 3-formylrifamicin SV (32.7.7). Reacting this with 1-amino-4-methylpiperazine gives the desired rifampicin (32.7.8) [331–334].



Rifampicin is an antibiotic with a broad spectrum of use that differs from rifamicin SV (32.7.5), which is also used in medicine as an independent drug showing high efficacy when taken internally and having a broad antibacterial spectrum of activities.

Rifampicin exhibits an antibacterial effect by inhibiting RNA synthesis. It inhibits DNA-dependent RNA polymerase by preventing the initial development of the chain, not by removing it. Rifampicin does not bind with the RNA polymerase nucleus of mammaliam cells, and does not have an effect on corresponding RNA synthesis. It can inhibit mitochondrial RNA synthesis; however, concentrations required for this exceed those necessary for synthesizing RNA by several hundred times.

Rifampicin is highly active with respect to *Mycobacterium tuberculosis.* Among atypical mycobacteria, it is active with respect to *M. kansasii*, *M. marinum*, and to most types

of *M. scrofulaceum* and *M. xenopi*. The sensitivity of other mycobacteria varies. Rifampicin exhibits activity with respect to *M. lepare*.

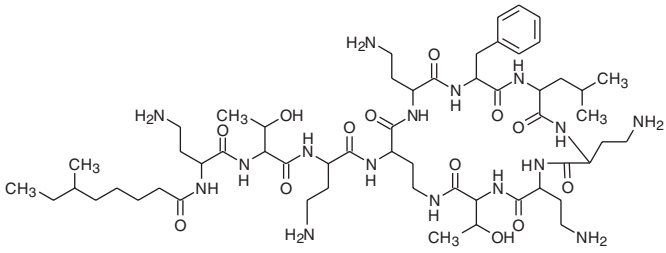
Besides mycobacteria, rifampicin also exhibits activity with respect to a large number of organisms. It is highly active with respect to *S. aureus,* nonenterococci forms of *Streptococcus* and *L. monocytogenes.* Among Gram-negative forms, *Neisseria meningitides*, *H. influenzae*, and *Legionella* are very sensitive to rifampin. *E. coli* and *P. mirabilis* are resistant to it. Anaerobic cocci, forms of *Clostridium*, and *Bacteroids* are frequently sensitive to rifampicin.

Rifampicin is the most effective drug for treating pulmonary and non-pulmonary forms of tuberculosis, including tuberculosis meningitis. It should always be used in combination with other drugs. Synonyms of this drug are rifadin, rimactan, rifapiam, rimactazide, and others.

Polymyxines: Polymyxines are a group of related polypeptide antibiotics that are produced by sporo-forming soil bacteria *Bacillus polymyxa* and *B. circulans*, and they differ in amino acid content. Five different polymyxines have been identified—polymyxines A, B, C, D, and E, which differ in the amino acid content and are differentiated by additional letter notations and names—polymyxine B (aerosporin) and polymyxine E (colistin). It is known that in the process of development, some strains of *B. polymyxa* only form polymyxines A and C, and others synthesize polymyxines B and D. Polymyxine M was later isolated, a sulfomethyl derivative of polymyxine E.

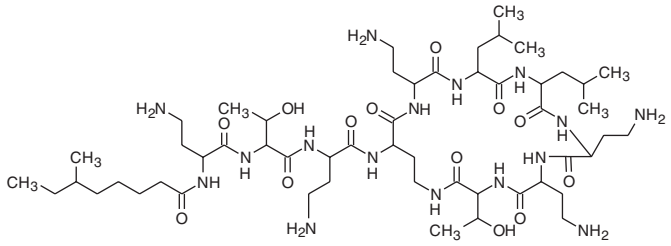
Threonine and α,γ-diaminobutyric acid are present within the structure of these antibiotics. The distinguishing feature of the polymyxine group is in that they contain 4–5 free γ-amine groups of α,γ-diaminobutyric acid, which gives them the property of a cationic detergent able to form complexes with phospholipids of cellular membranes. All polymyxines are similar in term of antibiotic action.

Polymyxine B is *N*-[3-amino-1-[[1-[[3-amino-1-[[6,9,18-*tris*-(2-aminoethyl)-15-benzyl-3-(1-hydroxyethyl)-12-isobutyl-2,5,8,11,14,17,20-hyptaoxo-1,4,7,10,13,16,19-heptaazacyclotris-21-yl]-carbamoyl]-propyl]-carbamoyl]-2-hydroxypropyl]-carbamoyl]-propyl]-6-methyloctanamide (32.7.9) [335–337].



32.7.9

Polymyxine E is *N*-[3-amino-1-[[1-[[3-amino-1-[[6,9,18-*tris*(20 aminoethyl)-3-(1-hydroxyethyl)-12,15-diisobutyl-2,5,8,11,14,17,20-heptaoxo-1,4,7,10,13,16,19-heptaazacyclotris-21-yl]-carbamoyl]-propyl]-carbamoyl]-2-hydroxypropyl]-carbamoyl]-propyl]-6-methyloctanamide (32.7.10) [338].



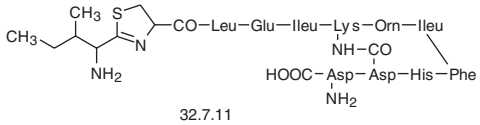
32.7.10

In terms of physiological pH, polymyxines are basically cationic, superficially active compounds, and they exhibit their bactericidal effect by reacting with phospholipid components of the cytoplasmatic membrane of susceptible bacteria, thus destroying the osmotic integrity of their cellular membrane, facilitating the release of many components, including potassium, from the cytoplasm into the surrounding medium. The detailed biochemical mechanism of their action is not yet known. Practically all polymyxines are active exclusively against aerobic Gram-negative microorganisms. In particular, they are active against *P. aeruginosa*, *E. coli*, *K. pneumoniae*, *Enterobacter*, *Salmonella*, *Shigella*, *Haemophilus*, and others. They do not affect coccal aerobic (staphylo-, strepto-, pneumo-, gono-, and meningococci) and anaerobic microorganisms, as well as most strains of *Proteus* bacterias causing tuberculosis and diphtheria.

These drugs are used for gastrointestinal diseases (colitis, enterocolitis, severe and chronic dysentery, sepsis, meningitis, pneumonia, infections of the urinary tract, and others caused by *P. aeruginosa)*, when other antibiotics are ineffective. They are effectively used in the form of ointments for treating a few forms of eczema, boils, hidradenitis, and other skin diseases.

Parenteral use of polymyxines is limited due to their neuro- and nephrotoxic effects. They are the drugs of choice for some specific infections. However, they are used for serious, life-threatening infections such as bacteremia, which are caused by some strains of *P. aeruginosa*, as was already mentioned.

Bacitracin: Bacitracins are polypeptide antibiotics that are isolated from a culture fluid of *B. licheniformis*. Ten individual bacitracins have been isolated: bacitracins A, A_1, B, C, D, E, F_1, F_2, F_3, and G. However, the drug itself, named bacitracin, that is used in medicine is a mixture of polypeptide antibiotics. All bacitracins are polypeptides that contain a thiazole ring. However, bacitracin A, *N*-[[2-(1-amino-2-methylbutyl)-4,5-dihydro-4-thiazolyl] carbonyl]bacitracin F (32.7.11), makes up the main part of the isolated fractions [338–341].



32.7.11

Bacitracin is a bactericidal drug that inhibits the formation of linear peptidoglycan chains, which are the main component of bacterial cell membranes. Most Gram-positive bacteria,

including staphylococci and *C. difficile* are sensitive to this drug. At the same time, it has almost no effect on Gram-negative bacteria. It is used most often externally for local treatment of purulent infections of the eyes and skin. Indications for intramuscular introduction are extremely limited because of its nephrotoxicity. It can be used as a drug for extreme cases of staphylococcus pneumonia in children with emphyemic resistance to all other antibiotics.

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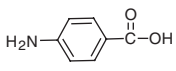
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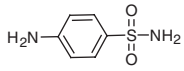
Antimicrobial Drugs

33.1 SULFONAMIDE DRUGS AND TRIMETHOPRIM

Sulfonamide drugs are a group of synthetic antimicrobial drugs that have a broad spectrum of use with respect to Gram-positive as well as Gram-negative microorganisms. They were introduced into medical practice even before the discovery of penicillins. Sulfonamide drugs are derivatives of sulfanilamide (*p*-aminobenzenesulfonamide), which is a structural analog of *p*-aminobenzoic acid (component necessary in bacteria for synthesizing folic acid), the precursor of purine, nucleic acids, and especially DNA.

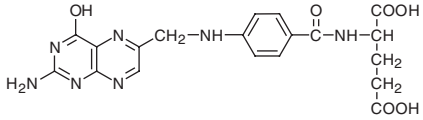


p-aminobenzoic acid



sulfanilamide

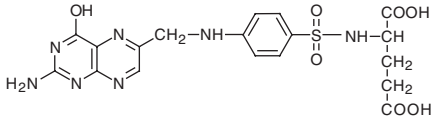
Animal cells are not able to synthesize folic acid by themselves—it must be obtained through the consumption of food.



folic acid

In addition, most bacteria are not able to utilize folic acid of exogen origin, so they synthesize the folic acid necessary for vital functions by themselves. This is the difference between bacterial and animal cells, and it is the reason behind the selective toxicity of sulfonamides.

Sulfanilamide, whose structure is similar to the structure of *p*-aminobenzoic acid, competes with *p*-aminobenzoic acid for inclusion in the folic acid molecule. In short, by taking the place of *p*-aminobenzoic acid, it "interferes" with the biosynthesis of folic acid. As a result, the "misled" enzymes construct a "false" molecule of folic acid, which is not able to carry out the vital function of true folic acid.



"false folic acid"

Thus sulfonamides are bacteriostatic drugs that inhibit bacterial growth by interfering with the microbial synthesis of folic acid. More specifically, sulfonamides block the biosynthetic pathway of folic acid synthesis, thus competitively inhibiting the transformation of *p*-aminobenzoic acid to folic acid (mediated by the enzyme dihydropteroate synthetase), which allows them to be considered as antimetabolites.

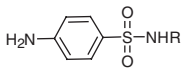
Currently, various sulfanilamide drugs are used in medicine, the choice of which depends on various factors, but above all on the type of stimulant, course of the disease, speed in which the drug is absorbed from the gastrointestinal tract, the speed in which it is excreted, and its ability to diffuse into different organs and tissues.

Sulfonamides have a broad spectrum of antimicrobial activity, including *Staphylococcus aureus,* nonenterococcal types of *Streptococcus*, *Listeria monocytogenes*, *Nocardia*, *Neisseria*, *Haemophilius influenzae*, enteric Gram-negative types of *E. coli*, *Proteus mirabilis*, and a few forms of anaerobic bacteria. Above all, sulfonamides are used for treating uncomplicated infections of the urinary tract, infections caused by *Nocardia asteroids*, streptococcal pharyngitis, menigococcal diseases, toxoplasmosis, and others.

Resistance to such drugs does develop during long-term use. Bacterial resistance to sulfonamides can develop as a result of mutations expressed either in the overproduction of *p*-aminobenzoic acid, or in changes in dehydroproteorate synthetase itself, which becomes more sensitive to the drugs. Resistance can also be mediated by plasmids that code for dehydroproteorate synthetase, or by reduced diffusion of the drug through bacterial cell membranes.

Sulfanilamide drugs do not currently have a clear classification. However, they are grouped as systemic (absorptive action), and local. They are subdivided into short-lasting (sulfacytine, sulfadiazin, sulfamerazine, sulfametazine, sulfametizole, sulfisoxazole); moderate-lasting (sulfamethoxazole, sulfapyridine); and long-lasting (sulfamethoxypiridazine, sulfamter), which, however, are no longer used as independent drugs because of extremely rare, yet nonetheless occurring, hypersensitivity reactions. Drugs for local use include those for ophthalmological use (sulfacetamide, sulfozoxazol); vaginal use (sulfabenzamide, sulfacetamide, sulfathiazole, sulfizoxazol); and external use (maphenid, silver sulfadiazine). Finally, this group includes sulfasalazine and phthalylsulfathiazole, a drug that acts in the lumen of the intestines, but which is poorly absorbed from the gastrointestinal tract.

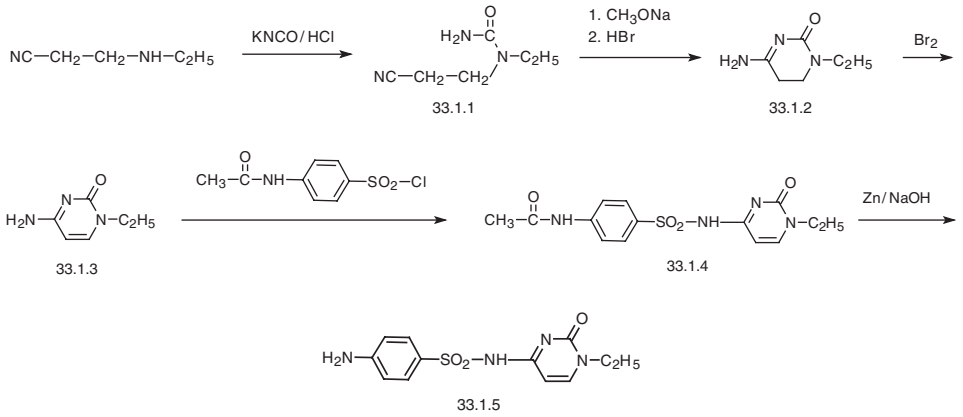
In terms of chemistry, sulfanilamide drugs can be represented by the following simple formula (except for rare exceptions, such as phthalazol):



A huge number of compounds of this type have been synthesized, primarily by reacting 4-acetylaminobenzenesulfonyl chloride with various amines (predominantly aromatic and heteroaromatic), followed by a removal of the protective acetyl group from the amine region of the molecule, or by reacting 4-aminobenzenesulfonamide with an appropriate aromatic or heteroaromatic halogen derivative. The first method is predominantly used because it is easy to do. In terms of determining a correlation between structure and activity, it was shown that the free *p*-amino group in the benzene ring is necessary for the exhibition of antibacterial activity, and it can only be replaced by those groups that permit its transformation to a free

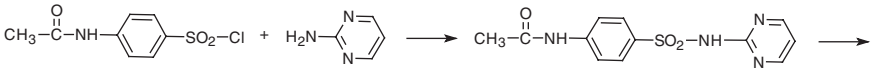
amino group. The presence of an additional substituent in the *o*- and *m*-positions of the benzene ring reduces the activity of the given series of compounds as antibacterial agents. Replacing one of the hydrogen atoms on the nitrogen atom in the sulfonamide region of the molecule leads to a significant change in the activity and solubility of the compounds. Moreover, the nature of the substituent in the sulfonyl radical determines the antimicrobial activity and the pharmacokinetic features of each of the individual compound. Thus the presence of this easily obtained and high volume product, 4-acetylaminobenzenesulfonyl chloride, which is made by reacting acetylaniline with chlorosulfonic acid, or the presence of 4-aminobenzenesulfonamide, which is made from a further reaction of 4-acetylaminobenzenesulfonyl chloride with ammonia and subsequent hydrolysis, the task of synthesizing new, potential sulfonamides has practically resorted to making new heteroaromatic amines. The most widely used sulfonamides examined below are made using these methods.

Sulfacytine: Sulfacytine, N^1-(1-ethyl-1,2-dihydro-2-oxo-4-pyrimidinyl)-sulfanilamide (33.1.5), is synthesized by reacting 4-acetylaminobenzenesulfonyl chloride with 1-ethyl-cytosine (33.1.3) followed by reductive deacylation of the acetanilide part of the molecule (33.1.4) using a system of zinc – sodium hydroxide, which gives the desired sulfacytine. 1-Ethylcytosine (33.1.3) is in turn synthesized from 3-ethylaminopropionitrile, which is reacted with cyanic acid (potassium cyanate–hydrochloric acid) in the first stage of synthesis to give 1-(2-cyanoethyl)-1-ethylurea (33.1.1). This easily cyclizes to 1-ethyl-5,6-dihydrocytosine in the presence of sodium methoxide, and is isolated in the form of a hydrobromide (33.1.2) for subsequent oxidation of the ordinary C_5–C_6 bond. Bromine turns out to be the optimal oxidant for this purpose, and using nitrobenzene as the solvent gives a heteroaromatic amine, 1-ethylcytosine (33.1.3), which was transformed to the desired sulfacytine in the aforementioned manner— by reacting it with 4-acetylaminobenzenesulfonyl chloride and subsequent removal of the protecting acetyl group from the amine part of the molecule [1–4].

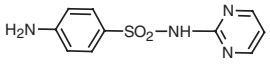


This drug is effective for infections caused by streptococci, gonococci, pneumococci, staphylococci, and also colon bacillus. Sulfacytine is used for pneumonia, cerebral meningitis, staphylococcal and streptococcal sepsis, and other infectious diseases. A synonym of this drug is renoquid.

Sulfadiazine: Sulfadiazine, N^1-2-pyrimidinylsulfanilamide (33.1.7), is synthesized by reacting 4-acetylaminobenzenesulfonyl chloride with 2-aminopyrimidine, which gives an acetanilide derivative (33.1.6). The subsequent hydrolysis of this product with a base leads to the formation of the desired sulfadiazine [5–8].



33.1.6

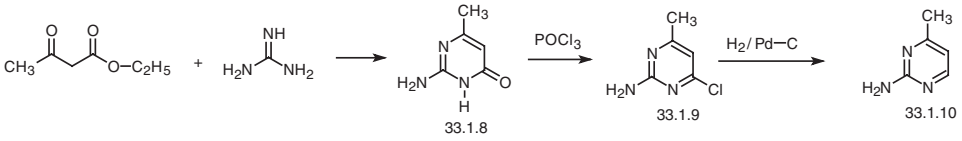


33.1.7

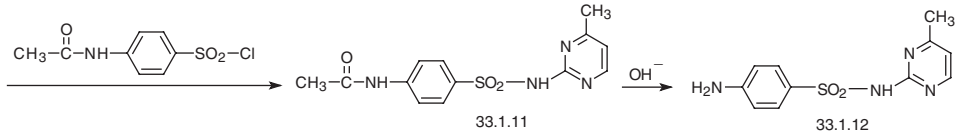
Like sulfacytine, this drug is effective for infections caused by streptococci, gonococci, pneumococci, staphylococci as well as colon bacillus. Sulfadiazine is used for pneumonia, cerebral meningitis, staphylococcal and streptococcal sepsis, and other infectious diseases, although it is the drug of choice for nocardiosis. This drug is not recommended for urinary tract infections because of its low solubility and certain nephrotoxicity. Synonyms of this drug are flammazine, sterinor, terfonil, and others.

It is used in the form of silver salts (sulfadiazine silver) as an external antibacterial agent, primarily for treating burns. It is believed that the presence of the silver ion in the molecule facilitates increased antimicrobial and wound-healing action.

Sulfamerazine: Sulfamerazine, N^1-(4-methyl-2-pyrimidinyl)sulfanilamide (33.1.12), is also synthesized in the manner described above, which is by reacting 4-acetylaminobenzenesulfonyl chloride with 2-amino-4-methylpyrimidine (33.1.10), which is in turn synthesized by the traditional scheme of synthesizing derivatives of pyrimidine. Acetoacetic ester is condensed with guanidine to give 4-methyl-2-aminopyrimidin-6-one (33.1.8). Reacting this with phosphorous oxychloride gives 4-methyl-2-amino-6-chloropyrimidine (33.1.9). The chlorine atom at C_6 of the pyrimidine ring is then removed by reduction with hydrogen using a palladium on carbon catalyst. The resulting 4-methyl-2-aminopyrimidine (33.1.10) is then reacted with 4-acetylaminobenzenesulfonyl chloride to make an acetanilide derivative (33.1.11), the subsequent hydrolysis of which with base leads to the formation of the desired sulfamerazine [8–10].



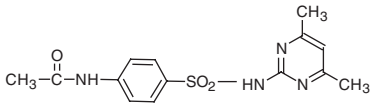
33.1.8 33.1.9 33.1.10



33.1.11 33.1.12

Like all examined sulfanilamides, this drug is effective in treating infections caused by streptococci, gonococci, pneumococci, staphylococci, and also colon bacillus. Synonyms of this drug are dosulfin, polagin, romezin, and others.

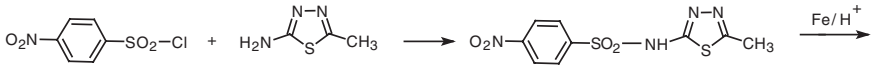
Sulfamethazine: Sulfamethazine, N^1-(4,6-dimethyl-2-pyrimidinyl)sulfanilamide (33.1.13), is also synthesized in the aforementioned manner by reacting 4-acetylaminobenzenesulfonyl chloride with 2-amino-4,6-dimethylpyrimidine, which is in turn synthesized by condensing acetylacetone with guanidine followed by hydrolysis of the acetylamino group using a base [11–15].



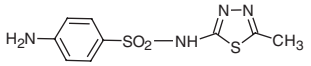
33.1.13

This drug is used for pneumococcal, staphylococcal, and streptococcal infections as well as for sepsis, gonorrhea, and other infectious diseases. Synonyms of this drug are sulfadiamezin and sulfadimidin.

Sulfamethizole: Sulfamethizole, N^1-(5-methyl-1,3,4-thiadiazole-2-yl)sulfanilamide (33.1.15), is synthesized in two ways. According to the first, 5-amino-2-methyl-1,3,4-thiadiazole is reacted with 4-nitrobenzenesulfonyl chloride to make a nitro derivative (33.1.14), which is then reduced using iron filings in acetic acid to give the desired sulfamethizole.

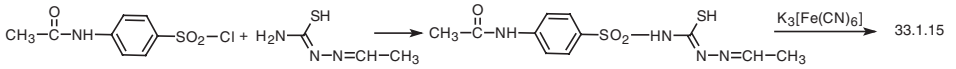


33.1.14



33.1.15

The second method of making sulfamethizole consists of reacting 4-acetylaminobenzenesulfonyl chloride with thiosemicarbazone of acetaldehyde, and subsequent oxidative cyclization of the product (33.1.16) to the substituted 1,3,4-thiadiazole in the presence of potassium ferricyanide in base, along with the simultaneous removal of the protective acetyl group [16,17].

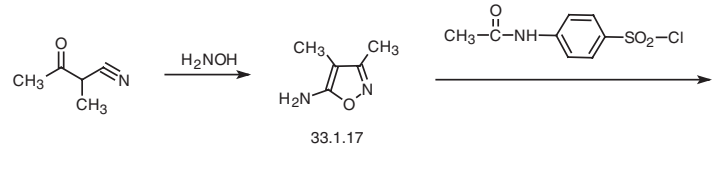


33.1.16

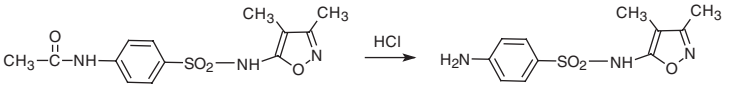
This drug has antibacterial activity with respect to streptococci, pneumococci, staphylococci, meningococci, gonococci, colon bacillus, pathogenic dysentery, and others. It is not very toxic. It is generally used for acute, uncomplicated infections of the urinary tract that

are caused by sensitive organisms. Because it is removed quickly from the organism by the kidneys, the level of drug in the plasma remains low, and therefore it is not used for treating infections that are localized in the urinary tract. Sulfisoxazole is the more preferred drug. Synonyms of this drug are urosol, rufol, thiosulfil, and others.

Sulfisoxazole: Sulfisoxazole, N^1-(3,4-dimethyl-5-isoxazolyl)sulfanilamide (33.1.19), is synthesized by reacting 4-acetylaminobenzenesulfonyl chloride with 5-amino-3, 4-dimethylisoxazol (33.1.17), which is in turn synthesized by heterocyclization of 2-methylacetylacetonitrile with hydroxylamine, and subsequent acidic hydrolysis (hydrochloric acid) of the protective acetyl group in the resulting product (33.1.18) [18,19].



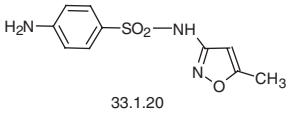
33.1.17



33.1.18 33.1.19

Like all examined sulfanilamides, this drug is effective in treating infections caused by streptococci, gonococci, pneumococci, staphylococci, and also colon bacillus. However, about 90% of it binds with proteins in the plasma after oral administration, and it diffuses mostly to tissues and tissue fluids, which makes it the drug of choice for many systemic infections. Synonyms of this drug are gantrisin, fultrxin, sulfazin, sulfolar, and others.

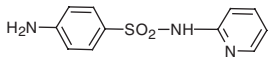
Sulfamethoxazole: Sulfamethoxazole, N^1-(5-methyl-3-isoxazolyl)sulfanilamide (33.1.20), is synthesized by a completely analogous scheme, except by using 3-amino-5-methylisoxazol as the heterocyclic component [20].



33.1.20

Like sulfisoxazole, this drug is effective in treating infections caused by streptococci, gonococci, pneumococci, staphylococci as well as colon bacillus. Unlike sulfisoxazole, only about 70% of it binds with proteins in the plasma after oral administration, and it diffuses mostly to tissues and tissue fluids. However, since it is removed much slower than sulfisoxazole, it does not require frequent administration and is also the drug of choice for many systemic infections. Moreover, it is an ingredient of a combined drug named bactrim, biseptol, and so on (which will be examined later on), which has a fixed correlation with trimethoprim. Synonyms of this drug are gantanol, sinomin, sulfisomezole, and others.

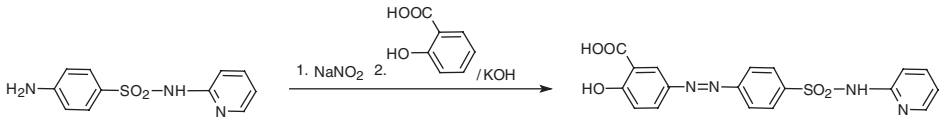
Sulfapyridine: Sulfapyridine, N^1-(2-pyridyl)-sulfanilamide (33.1.21), is also synthesized by an analogous scheme from 4-acetylaminobenzenesulfonyl chloride and 2-aminopyridine [21–23].



33.1.21

Like all sulfanilamides, this drug possesses antibacterial activity with respect to streptococci, pneumococci, staphylococci, meningococci, gonococci, colon bacillus, pathogenic dysentery, and so on. It is a long-lasting drug. Synonyms of this drug are bacillopirin, plurazol, sulfidin, and thiaseptol.

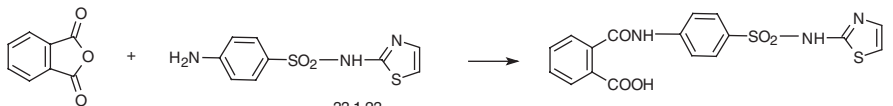
Sulfasalazine: Sulfasalazine, 5-[*p*-[(4,6-dimethyl-2-pyridinyl)sulfamoyl]phenylazo]salicylic acid (33.1.22), is a derivative of sulfapyridine drug described above and one of the few sulfanilamides in which the free amino group in the benzene ring is modified, and it is synthesized by an azo-coupling reaction of a diazo salt, which is synthesized by reacting sulfapyridine (33.1.21) with nitrous acid and salicylic acid alkaline media [24,25].



33.1.21 33.1.22

This drug possesses antibacterial activity with respect to a few cocci and colon bacillus. It exhibits a simultaneous, pronounced healing effect in patients with nonspecific ulcerative colitis, which is explained by the degradation in the body of 5-aminosalicylic acid and sulfapyridine, which possess anti-inflammatory and antibacterial properties. It is used for ulcerative colitis, chronic rheumatoid arthritis as well as acute and subacute inflammatory diseases. Synonyms of this drug are slazopyrin, salazosulfapyridine, and others.

Phthalylsulfathiazolee: Phthalylsulfathiazolee, (N^4-phthaloylsulfanilamido)-thiazole (33.1.24), is also one of the sulfanilamides in which the free amino group in the benzene ring is modified, which can evidently be explained by the localization of the place of its action. It is synthesized by reacting sulfathiazolee (33.1.23), which is synthesized by the standard scheme from 4-acetylaminobenzenesulfonyl chloride and 2-aminothiazole, with phthalic anhydride [26,27].

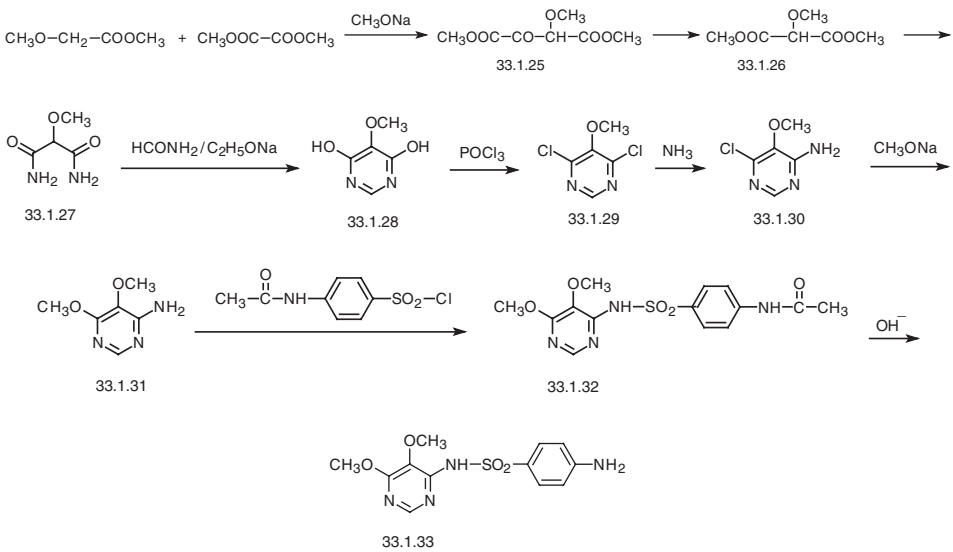


33.1.23 33.1.24

Like other sulfanilamides, this drug possesses antibacterial activity with respect to streptococci, pneumococci, staphylococci, meningococci, gonococci, colon bacillus, pathogenic dysentery, and others. Phthalylsulfathiazolee is slowly absorbed from the gastrointestinal tract, and its initial mass upon oral administration is retained in the intestines, where it is slowly broken down. As is the case with sulfasalazinee, a large concentration of sulfanilamide is created in the intestine, which explains its high activity with respect to intestinal infections. It is used for dysentery, colitis, gastroenteritis, and operational interventions on the intestines in order to prevent purulent complications.

Synonyms of this drug are phthalazol, enterozol, sulfazole, talazol, and many others.

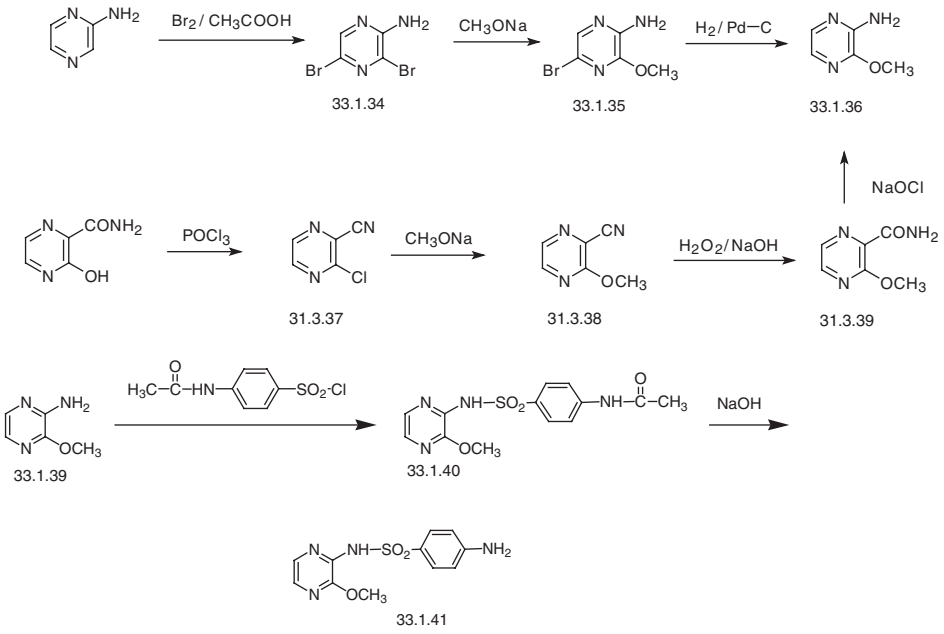
Sulfadoxine: Sulfadoxine, 4,5-dimethoxy-6-sulfanilamidopyrimidine (33.1.33), is synthesized by the standard scheme from 4-acetylaminobenzenesulfonyl chloride and 4-amino-5,6-dimethoxypyrimidine. However, the synthesis of 4-amino-5,6-dimethoxypyrimidine (33.1.31) is itself curious—it is synthesized from methyl ester of methoxyacetic acid. Interacting this with dimethyloxalate in the presence of sodium methoxide gives the methoxy derivative (33.1.25), and the pyrolysis of this compound gives the dimethyl ester of methoxymalonic acid (33.1.26). Reacting this with ammonia gives the diamide of methoxymalonic acid (33.1.27). Heterocyclization of the resulting product by a reaction with formamide in the presence of sodium ethoxide gives 4,6-dioxy-5-methoxypyrimidine (33.1.28), which is then transformed to 4,6-dichloro-5-methoxypyrimidine (33.1.29). The resulting 4,6-dichloro-5-methoxypyrimidine (33.1.29) undergoes a reaction with ammonia to make 4-amino-6-chloro-5-methoxypyrimidine (33.1.30), and the resulting compound is then reacted with sodium methoxide to make the desired 5,6-dimethoxy-5-aminopyrimidine (33.1.31). Reacting this with 4-acetylaminobenzenesulfonyl chloride and subsequent hydrolysis of the acetyl group in (33.1.32) gives sulfadoxine [28–31].



In terms of antibacterial action, this drug is analogous to other sulfanilamides; however, it possesses very prolonged action. Its half-life is from 120 to 200 h. Sulfadoxine is used for infectious diseases caused by microorganisms that are sensitive to the sulfanilamide drugs, such as infections of respiratory organs, gastric and urinary tracts; purulent infections of various localization, osteomyelitis, sinusitis, and other infections. It is used in combination with antimalarial drugs. Synonyms of this drug are sulfarmethoxine, fanasil, and fansidar.

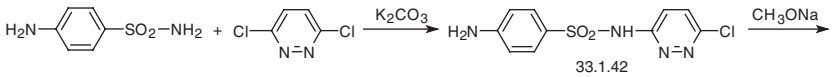
Sulfalene: Sulfalene, 3-methoxy-2-sulfanilamidopyrazine (33.1.41), like other sulfanilamides, is synthesized by the standard scheme from 4-acetylaminobenzenesulfonyl chloride, which is reacted with 3-amino-2-methoxypyrazine, which is synthesized by two technologically available methods. The first of these methods consists of direct bromination of 2-aminopyrazine using acetic acid as a solvent, which gives 3,5-dibromo-2-aminopyrazine (33.1.34). Reacting this with sodium methoxide gives 3-methoxy-5-bromo-2-aminopyrazine (33.1.35). Hydrogen reduction using a palladium on carbon catalyst replaces the bromine atom at C_5 of the product with a hydrogen atom, giving 3-methoxy-2-aminopyrazine (33.1.36).

This same 3-methoxy-2-aminopyrazine (33.1.36) is synthesized from 3-hydroxypyrazin-2-carboxamide. Reacting this with phosphorous oxychloride replaces the hydroxyl group with a chlorine atom while the carboxamide group simultaneously undergoes dehydration to form 3-chloro-2-cyanopyrazine (33.1.37). Next, reacting this with sodium methoxide gives 3-methoxy-2-cyanopyrazine (33.1.38). The cyano group in this compound is hydrolyzed by a base in the presence of hydrogen peroxide to a carboxamide group, giving 3-methoxy-2-carboxamideopyrazine (33.1.39). The resulting product undergoes a Hofmann rearrangement when reacted with sodium hypochlorite, giving the desired 3-methoxy-2 aminopyrazine (33.1.36). Reacting this with 4-acetylaminobenzenesulfonyl chloride and subsequent hydrolysis of the acetyl group with a base to (33.1.40) gives sulfalene [32–34].

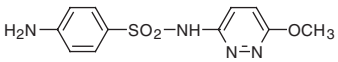


Sulfalene is also a very long-lasting bacteriostatic sulfanilamide with a broad spectrum of antimicrobial activity. It is used for the same indications as sulfadoxine. Its half-life is about 150–200 h. This drug binds to proteins in the plasma to a lesser degree than other sulfanilamides, which ensures its high concentration in the blood in a free form. Therefore, only one dose of sulfalene needs to be taken one time per week. Synonyms of this drug are celfizin, sulfamethopyrazine, sulfamethoxypyrazine, and others.

Sulfamethoxypyridazine: Sulfamethoxypyridazine, N^1-(6-methoxy-3-pyridazinyl)sulfanilamide (33.1.43), is synthesized by replacing the chlorine atom in 6-chloro-3-(4-aminobenzenesulfonilamido)pyridazine with a methoxy group in 33.1.42 using sodium methoxide. The initial 6-chloro-3-(4-aminobenzenesulfonylamido)-pyridazine (33.1.42) is in turn synthesized by reacting 4-aminobenzenesulfanilamide with easily accessible 3,6-dichloropyridazine [35,36].



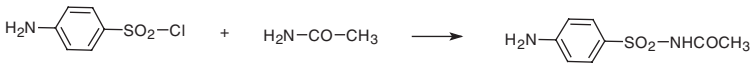
33.1.42



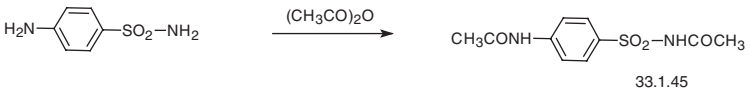
33.1.43

This drug possesses antibacterial activity with respect to a few cocci and colon bacillus. It is a long-lasting drug. It is used for treating pneumonia, bronchitis, tonsillitis, purulent otitis and meningitis, purulent infections of the urinary tract, dysentery, and others. Synonyms of this drug are sulfapyridazine, sufalex, retasulfin, and many others.

Sulfacetamide: Sulfacetamide, N^1-acetylsulfanilamide (33.1.44), is synthesized either by direct alkylation of acetamide with 4-aminobenzenesulfonyl chloride, or by reacting 4-aminobenzenesulfonamide with acetic anhydride and subsequent selective, reductive deacylation of the resulting acetamide 33.1.45 using a system of zinc–sodium hydroxide [37,38].



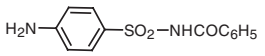
33.1.44



33.1.45

This drug possesses antibacterial activity with respect to streptococci, pneumococci, staphylococci, meningococci, and gonococci. It is used for treating pneumonia, purulent tracheobronchitis, urinary tract infections, gonorrheal diseases of the eyes in newborns and adults, and so on. Synonyms of this drug are albucid, cetamide, prontamide, sebizon, and others.

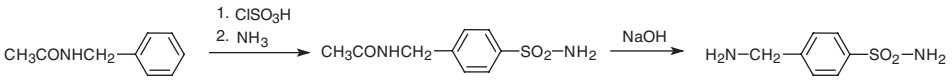
Sulfabenzamide: Sulfabenzamide, N^1-benzoylsulfanilamide (33.1.46), is synthesized just like sulfacetamide [38–41].



33.1.46

It is used for the same indications, primarily in the form of ointments for vaginal infections. A synonym of this drug is sulfabenzide.

Maphenide: Maphenide, n-(aminomethyl)-benzenesulfamide (33.1.48), is structurally somewhat different from all drugs examined above in that the amino group in the p-position to the sulfonamide group is distanced from the benzene ring by one methyl group. This drug is synthesized from N-benzylacetamide, subsequent reaction of which with chlorosulfonic acid and then with ammonia gives 4-(acetamidomethyl)-benzene-sulfonamide (33.1.47). Hydrolyzing this product with a base gives maphenid [42–44].



33.1.47 33.1.48

Synonyms of this drug are marfanil, mezudin, ambamide, septicid, and others.

Currently, the most widely used are sulfisoxazole, sulfamethoxazole, sulfadiazine, sulfamethizole, and trisulfapyrimidine (a mixture of sulfamerazine, sulfamethazine, and sulfadiazine). The first two drugs mentioned are the most widely used. The long-lasting sulfonamide (sulfadioxin) is used only in combination with pyrimethamine (an antagonist of folic acid) for prevention and treatment of tropical fever.

In combination with pyrimethamine or trimethoprim, sulfanilamides are active with respect to a few protozoal infections, including *Toxoplasma*, *Plasmodium falciparum*, and *Pneumocystis carinii.*

33.1.1 Diaminopyrimidines (trimethoprim, pyrimethamine, and trimethoprim-sulfamethoxazole)

The diaminopyrimidines trimethoprim and pyrimethamine are synthetic, antibacterial drugs and inhibitors of dihydrofolate reductase that are used both independently as well as in combination with sulfanilamides, in particular, with sulfamethoxazole (cotrimoxazole, bactrim, biseptol, sulfatrim, and many others).

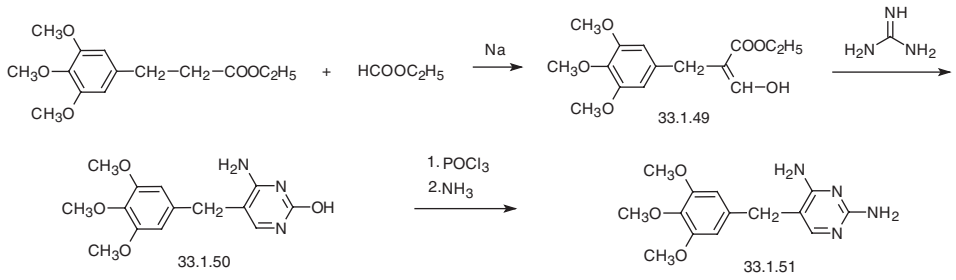
As a matter of fact, diaminopyrimidines (trimethoprim, pyrimethamine) were suggested as medicinal and preventative agents against malarial infections. It was shown that all of the strong dihydrofolate reductase inhibitors could disable the malarial parasite with relatively minor consequences to the host. The closest structural similarity of these drugs (as well as structural similarity between pteridine ring of folic acid and the diaminopyrimide fragment of pyrimethamine) is most likely the reason of the affinity of this compound to receptive regions of dihydrofolate reductase.

All of these compounds are inhibitors of dihydrofolate reductase in bacteria, plasmodia, and humans. Fortunately, they have a significantly higher affinity to bacterial and protozoal dihydrofolate reductase. Pyrimethamine, for example, inhibits dihydrofolate reductase in parasites in concentrations that are a several hundred times lower than that required to inhibit dihydrofolate reductase in humans. This is the basis of their selective toxicity. Selective toxicity can be elevated upon the host organism's production of folic acid, which parasites are not able to use.

Trimethoprim acts in the body by interfering with the action of hydrofolate reductase, an enzyme that reduces dihydrofolic acid to tetrahydrofolic acid. This process is necessary for purine biosynthesis of live organisms and DNA, respectively. Reducing the dihydrofolic acid to tetrahydrofolic acid is also catalyzed in humans by dihydrofolate reductase. However, trimethoprim has thousands of more inhibitory effects with respect to bacterial enzymes than with respect of analogous enzymes of mammals, which is the main benefit of trimethoprim.

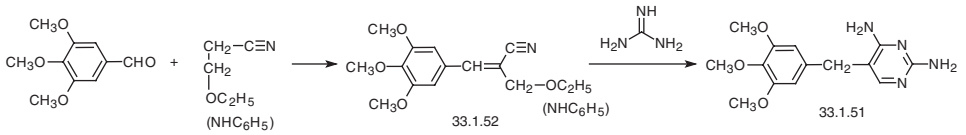
Various sulfonyl amides inhibit one of the stages of this biosynthetic pathway, which is by adding dihydrofolic acid in the place of *n*-aminobenzoic acid in sulfanilamide. Subsequent blockage of one or the other biosynthetic pathways by two drugs (sulfanilamide and trimethoprim at the same time) differs in the high degree of synergism with respect to a broad spectrum of microorganisms. A very strong effect is exhibited with respect to many microorganisms when used in combination with sulfomethoxazole. A ratio of 20:1 sulfamethoxazole/trimethoprim is considered to be optimal. This ratio is obtained in the plasma by taking drugs that have an equal to 5:1 ratio. Of course this ratio can vary widely; however, the presence of trimethoprim in a mixture with sulfanilamide guarantees successful treatment.

Trimethoprim: Trimethoprim, 2,4-diamino-5-(3′,4′,5′-trimethoxybenzyl)pyrimidine (33.1.51), is synthesized in various ways. The first scheme of synthesis begins with ethyl ester of 3,4,5-trimethoxydehydrocinnamic acid, which is formylated with ethyl formate using sodium as a base to make an enol of the semialdehyde 3′,4′,5′-trimethoxybenzylmalonic ester (33.1.49), which undergoes a heterocyclization reaction with guanidine to make 2-amino-4-hydroxy-5-(3′,4′,5′-trimethoxybenzyl)pyrimidine (33.1.50). Subsequent replacement of the hydroxyl group in the resulting product with chlorine using phosphorous oxychloride and then with an amino group using ammonia gives the desired trimethoprim [45–47].

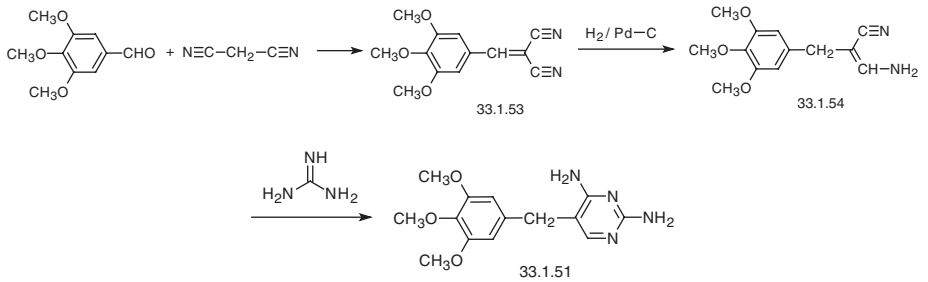


All of the other syntheses begin with 3,4,5-trimethoxybenzaldehyde. According to one of them, condensation of 3,4,5-trimethoxybenzaldehyde with 3-ethoxy- or 3-anilinopropionitrile

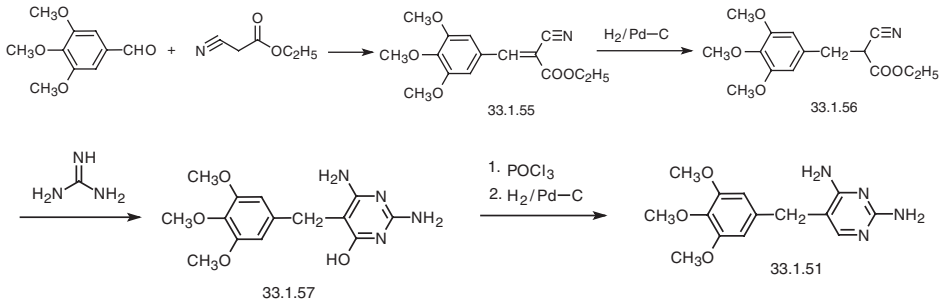
gives the corresponding benzylidene derivative (33.1.52), which upon direct reaction with guanidine gives trimethoprim [48–51].



Trimethoprim has also been synthesized by condensing 3,4,5-trimethoxybenzaldehyde with malonic acid dinitrile in a Knoevenagel reaction, which forms the derivative (33.1.53), which is partially reduced to the enamine (33.1.54) by hydrogen using a palladium on carbon catalyst, which upon being reacted with guanidine is transformed into trimethoprim [52,53].



Finally, trimethoprim can be synthesized in a manner that also uses a Knoevenagel condensation of 3,4,5-trimethoxybenzaldehyde as the first step, but this time with ethyl cyanoacetate, which gives an ylidene derivative (33.1.55). The double bond in this product is reduced by hydrogen over a palladium on carbon catalyst, giving 3′,4′,5′-trimethoxybenzylcyanoacetic ester (33.1.56). Reacting this in a heterocyclization reaction with guanidine gives the desired trimethoprim [54,55].



Trimethoprim has a broad spectrum of antimicrobial activity. It is 20–100 times more active than sulfamethoxazole with respect to most bacterial forms. Trimethoprim is active with respect to Gram-positive, aerobic bacteria such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, and various types of *Streptococcus* and *Listeria monocytogenes*. Trimethoprim is inferior to sulfonamides against forms of *Nocardia*. It is active

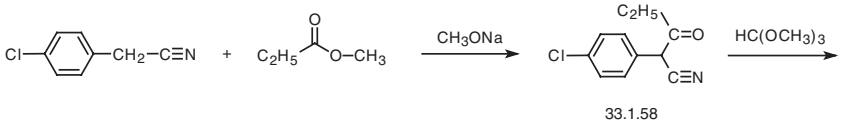
with respect to Gram-negative, aerobic bacteria such as most *E. coli*, *Enterobacter*, *Proteus*, *Klebsiella*, *Providencia*, *Morganella*, *Serratia marcescens*, *Citrobacter*, *Salmonella*, *Shigella*, *Yersinia enterocolitica* that are sensitive to trimethoprim. Trimethoprim is also active with respect to *Legionella*, *Acinetobacter*, *Vibrio*, *Aeromonas*, *Pseudomonas maltophila*, *P. cepacia*, although *P. aeruginosa* is resistant to trimethoprim.

Haemophilus influenzae and *H. ducreyi* are sensitive to trimethoprim. Pathogenic *Neisseria* (meningococci and gonococci) and *Branhamella catarrhalis* are moderately resistant to trimethoprim, although they are very sensitive to a combination of trimethoprim and sulfamethoxazole. Anaerobic bacteria in general are resistant to trimethoprim, although a combination of trimethoprim-sulfamethoxazole does have an effect on them. *Pneumocystis carinii* is also sensitive to that combination.

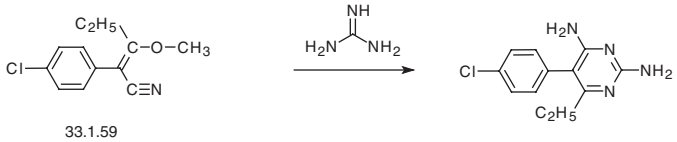
Bacterial resistance to trimethoprim can originate because of a number of reasons: inability of the drug to penetrate through the membrane (*P. aeruginosa*); the presence of dihydrofolate reductase that is not sensitive to inhibition by trimethoprim; overproduction of dihydrofolate reductase and mutation expressed as thyminic dependence, when the organism requires exogenic thymine for synthesizing DNA, i.e. bypassing metabolic blockage caused by trimethoprim.

Resistance to a combination of trimethoprim-sulfamethoxazole is always less frequent than when any of these drugs is used separately. This combination of drugs, which is known by the commercial names cotrimoxazole, bactrim, biseptol, sulfatrim, and many others, is used for treating infections of the respiratory tract, infections of the urinary tract, gastric infections, surgical infections, enteritis, meningitis, and other diseases.

Pyrimethamine: Pyrimethamine, 2,4-diamino-5-(4′-chlorophenyl)-6-ethylpyrimidine (33.1.60), is synthesized from 4-chlorobenzycyanide, which upon condensation with methyl ester of propionic acid in the presence of sodium methoxide gives the β-ketonitrile (33.1.58). Reacting this with ethyl orthoformate gives a methoxymethylene derivative (33.1.59), which upon heterocyclization in pyrimidine using guanidine as the binucleophile forms the desired pyrimethamine (33.1.60) [55–60].



33.1.58



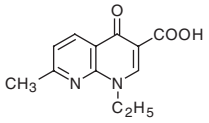
33.1.59 33.1.60

Pyrimethamine, a folic acid antagonist, exhibits antimicrobial action against the causative agent of malaria and possesses sporontocidal action. It is also effective with respect to the causative agent of toxoplasmosis. It is used for preventing malaria and treating toxoplasmosis.

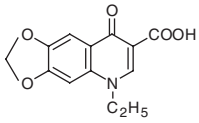
33.2 QUINOLONES

Quinolones are a group of structurally similar antimicrobial drugs that exhibit high activity against many microorganisms.

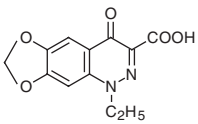
Formally, the first representative of the new class of antimicrobial drugs (called drugs of the quinolone series, which are derivatives of naphthiridine), was nalidixic acid (nevigramon), which was synthesized in 1962 and was suggested for treating urinary tract infections. The main spectrum of its use includes Gram-negative bacteria. It is also effective with respect to colon bacillus, proteus, klebisella, shigella, and salmonella. In recent years a number of chemically similar compounds have been synthesized, such as oxolinic acid (strictly speaking, a derivative of quinolone) and cinoxacin (a derivative of quinolone), although all of them had a relatively narrow antimicrobial spectrum.



nalidixic acid



oxolinic acid



cinoxacin

Enormous progress was made in the 1980s due to the introduction of a fluorine atom to the C_6 position of 4-quinolone and a piperazine fragment to the C_7 position. Introducing a fluorine atom in the indicated position dramatically increased the activity of the drug with respect to Gram-positive microorganisms, which broadened its spectrum of action to include Gram-negative microorganisms. Introducing the piperazine fragment to C_7 ensured activity of this group of drugs with respect to *Pseudomonas aeruginosa.* The substituents at the nitrogen atom of the quinolone structure and in the piperazine ring may vary from drug to drug.

All fluoroquinolones are usable in medical practice: ciprofloxacin, enoxacin, norfloxacin, and ofloxacin have approximately the same antimicrobial spectrum, which includes most aerobic Gram-negative and a few Gram-positive bacteria. Fluoroquinolones are highly active against most enterobacteria, including *E. coli*, *Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Morganella morganii*, *Providencia*, *Citrobacter* and *Serratia.* They are also active with respect to *Pseudomonas aeruginosa*, including strains resistant to other antibacterial drugs. Most strains of *Acinetobacter*, aerobic Gram-negative microorganisms are sensitive to fluoroquinolones. Fluoroquinolones are highly active against most Gram-negative bacterial pathogens of the gastrointestinal tract, such as *Shigella*, *Salmonella*, *Yersinia enterocolitica*, *Aeromonas species*, and *Vibrio species*. Gram-negative coccobacteria *Haemophilus influenzae*, *Haemophilus ducreyi* and Gram-negative cocci *Neisseria meningitides*, *N. gonorrhoeae*, and *Moraxella* are also very sensitive to fluoroquinolones. Fluoroquinolones are also active with respect to most Gram-positive bacteria, *Staphylococcus aureus* and *S. epidermidis*, although the concentrations used must be somewhat higher than for Gram-negative bacterial pathogens.

Fluoroquinolones are powerful bactericidal drugs that change the structure and function of bacterial DNA by affecting the enzyme DNA-gyrase (topoisomerase II). This enzyme is responsible for negative supercoiling twisting (negative supercoiling) to

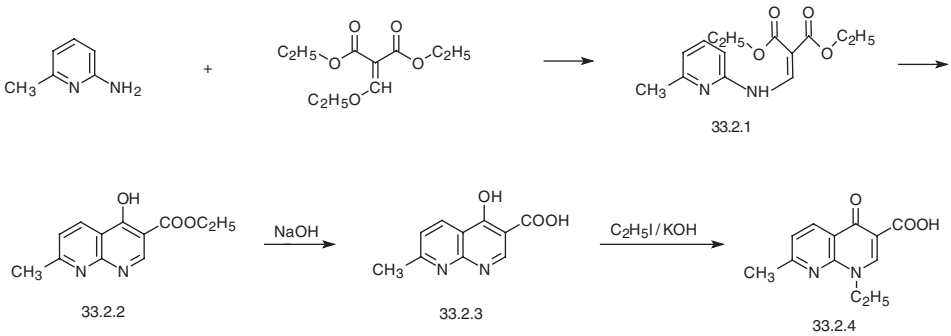
covalently closed, circular DNA as well as breaking up the repeating compounds (catenation, decatenation) of DNA coils linked to the chain. DNA-gyrase is capable of breaking down bacterial DNA that has an approximate length of 1300 μm, such as in *E. coli*, inside a cell whose size ranges from 2 to 3 μm. This enzyme is necessary for replication, restoration, and transcription of certain DNA operons. DNA-gyrase is made up of two A and two B subunits. Quinolones have a direct effect on the function of A subunits.

As was already mentioned, drugs of this series have a similar antimicrobial spectrum, which includes most aerobic Gram-negative and a few Gram-positive bacteria. The specific difference in activity of these drugs is observed with respect to a few specific microorganisms, their relative toxicity, pharmacokinetic features, and so on. For example, ciprofloxacin and norfloxacin have a similar antimicrobial spectrum; however, depending on the type of microorganisms, norfloxacin can turn out to be 2–8 times weaker.

Two mechanisms of resistance have been discovered with respect to fluoroquinolones: a change in subunits A of DNA-gyrase, and reduced permeability of the outer membrane of the bacteria. Resistance is mediated by chromosomes, and not plasmids in the bacteria. The development of resistance while using the drugs is very rarely observed.

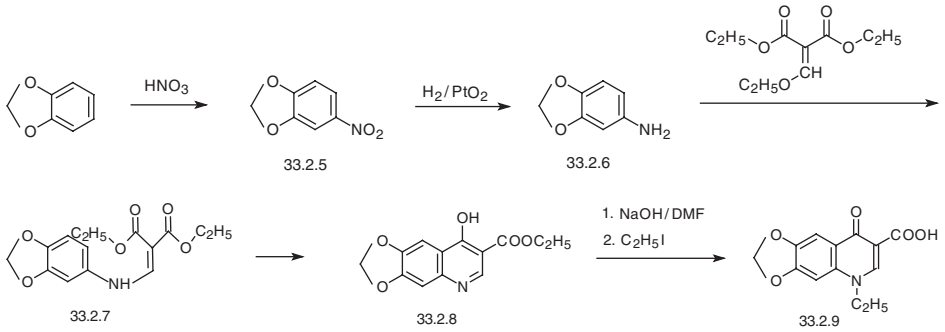
Because of its pharmacokinetic features (pronounced bioaccessability upon oral use, diffusion to tissues and permeation into them, broad spectrum of antibacterial activity, and so on), fluoroquinolones have considerable potential for treating infections of practically any anatomic localization. Fluoroquinolones are very effective in treating infections of the respiratory tract, urinary tract, bones, skin, soft tissues, and so on.

Nalidixic acid: Nalidixic acid, 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthiridin-3-carboxylic acid (33.2.4), is synthesized by the following scheme. In the first stage, the reaction of 2-amino-6-methylpyridine and diethyl ethoxymethylenemalonate forms the substituted product (33.2.1), which when heated cyclizes to ethyl ester of 4-hydroxy -7-methyl-1,8-napthiridin-3-carboxylic acid (33.2.2). Hydrolyzing the resulting product with a base gives the corresponding acid (33.2.3). Alkylating this with ethyl iodide in the presence of potassium hydroxide gives nalidixic acid [60–64].



Nalidixic acid has a bactericidal or bacteriostaic effect depending on the sensitivity of the microorganism and the concentration. It is effective with respect to Gram-negative microorganisms, such as colon bacillus, salmonella, shigella, proteus, and Fridlender's bacillus. It is used for pyeolonephritis, cystitis, urethritis, prostatitis, and gastrointestinal tract infections. Synonyms of this drug are negram, nevigramon, uralgin, urogram, vintron, and many others.

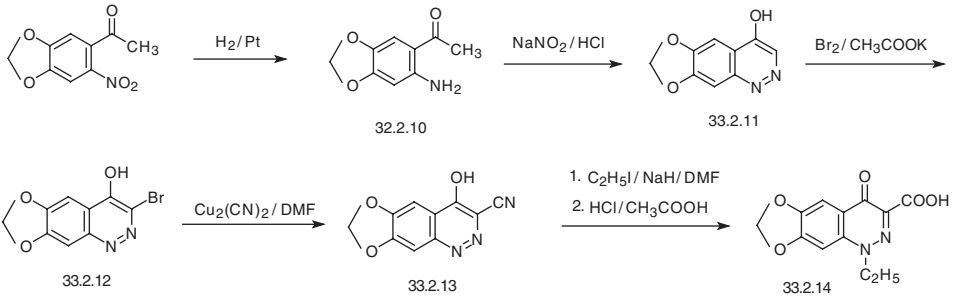
Oxolinic acid: Oxolinic acid, 5-ethyl-5,8-dihydro-8-oxo-1-dioxolo[4,5-g]-quinolin-7-carboxylic acid (33.2.9), is basically synthesized by the same synthetic scheme as nalidixic acid, although it uses 3,4-methylendioxyanyline (33.2.6) as the starting aromatic amine component, and not the 2-amino-6-methylpyridine used to make nalidixic acid. This compound is obtained by hydrogenation to 3,4-methylendioxy-1-nitrobenzene (33.2.5), which is in turn synthesized by nitrating 1,2-methylendioxybenzene with nitric acid. The resulting 3,4-methylendioxyaniline (33.2.6) is then reacted with ethoxymethylenmalonic ester to make the substitution product (33.2.7), which when heated cyclizes to ethyl ester of 4-hydroxy-6,7-methylendioxyquinolin-3-carboxylic acid (33.2.8). Hydrolyzis of this with a base in dimethylformamide and direct treating of the obtained product with ethyl iodide gives the desired oxolinic acid [65–67].



Like nalidixic acid, this drug is effective with respect to Gram-negative microorganisms and is used for the same indications. Synonyms of this drug are nidantin, prodoxol, ocolin, uroxol, and others.

Cinoxacin, Azolinic acid: Cinoxacin, 1-ethyl-1,4-dihydro-4-oxo[1,3]-dioxolo[4,5-g] cinnolin-3-carboxylic acid (33.2.14), is synthesized by a different scheme starting with 2-amino-4,5-methylendioxyacetophenone (33.2.10), which is synthesized by reducing 4,5-methylendioxy-2-nitroacetophenone with hydrogen over a platinum catalyst. In diazotation conditions, this undergoes spontaneous heterocyclization to 4-hydroxy-6, 7-methylendioxycinnoline (33.2.11) obviously due to the presence of a significant amount of the enol form of acetophenone (33.2.10) under the reaction conditions. The resulting cinnoline (33.2.11) then undergoes bromination by molecular bromine in the presence of potassium acetate, giving 3-bromo-4-hydroxy-6,7-methylendioxycinnoline (32.2.12). Upon reacting this with univalent copper cyanide in dimethylformamide, the bromine

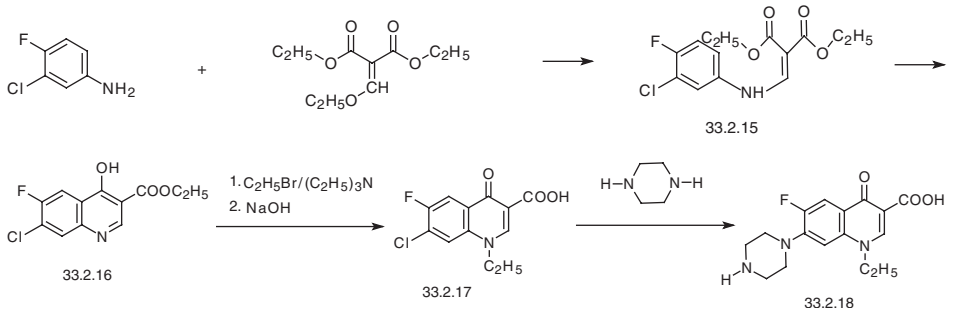
atom is replaced with a cyano group, forming the 3-cyano-4-hydroxy-6,7-methylendioxycinnoline (33.2.13). The resulting product is alkylated at the first position by ethyl iodide using sodium hydride as a base, and the cyano group is hydrolyzed to a carboxyl group using a mixture of hydrochloric and acetic acids, giving the desired cinoxacin [68,69].



This drug is effective with respect to Gram-negative microorganisms and is used for the same indications as nalidixic and oxolinic acids. Synonyms of this drug are cinobactin, nossacin, uronorm, and others.

Norfloxacin: Norfloxacin, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolincarboxylic acid (33.2.18), is the first representative of a series of fluorinated quinolones as well as the first drug of the quinolone derivatives used in medicine that contains a piperazine substituent. The method of synthesis is basically the same as that suggested for synthesizing nalidixic and oxolinic acids.

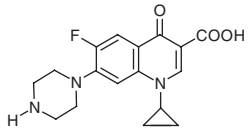
Reacting 3-chloro-4-fluoroaniline and ethyl ethoxymethylenmalonate gives the substitution product (33.2.15), which upon heating in diphenyl ester cyclizes into ethyl ester of 6-fluoro-7-chloro-1,4-dihydro-3-quinolin-4-on-carboxylic acid (33.2.16). Direct treatment of the product with ethyl iodide in the presence of triethylamine and subsequent hydrolysis with a base gives 1-ethyl-6-fluoro-7-chloro-1,4-dihydro-3-quinolin-4-on-carboxylic acid (33.2.17). Reacting this with piperazine gives norfloxacin (33.2.18) [70–75].



Norfloxacin possesses a broad spectrum of bactericidal action. It is highly active with respect to most Gram-negative and a few Gram-positive microorganisms. Anaerobic

bacteria are not sensitive to this drug, while enterococci and akinetobacter are not very sensitive. It is used for bacterial infections of the urinary tract, prostate gland, gastrointestinal tract, gonorrhea, and traveler's diarrhea. Synonyms of this drug are noroxin, barazan, fulgram, bacidal, and others.

Ciprofloxacin: Ciprofloxacin, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolincarboxylic acid (33.2.19), is synthesized in a completely analogous scheme, except that instead of using ethyl iodide in the alkylation stage, cyclopropyl bromide is used [76–78].



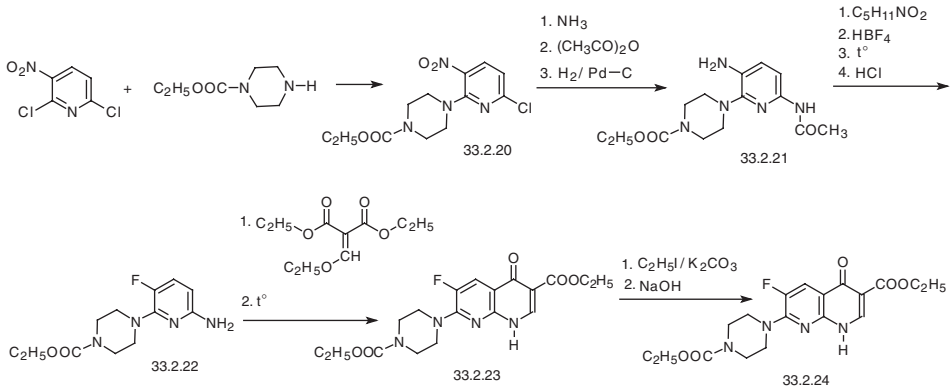
33.2.19

Ciprofloxacin possesses a broad spectrum of antimicrobial action. It is highly effective against Gram-negative microorganisms, such as blue-pus bacillus, hemophilic and colon bacillus, shigella, salmonella, meningococci, gonococci, and a few forms of enterococci. It is also active with respect to many strains of staphylococci, camphylobacter, legionella, mycoplasma, chlamydia, and mycobacteria. *Ureaplasma urealyticum*, *Clostridium difficile*, and *Nocardia asteroids* are resistant to it. It is used for infections of the urinary tract, respiratory tract, biliary tract, infective-inflammatory diseases of the abdominal cavity and organs, pelvis minor, bones, joints, and skin.

Ciprofloxacin is also effective for bacterial prostatitis, noncomplicated gonorrhea, osteomyelitis, and pulmonary infections. It is effective in treating acute infectious diarrhea, including traveler's diarrhea and enteritis. Side effects are rarely seen when taking this drug. Synonyms of this drug are ciproquin, ciprolet, cipropan, ciproxan, ciprocinal, and many others.

Enoxacin: Enoxacin, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-1,8-naphthiridin-3-carboxylic acid (33.2.24), only differs from norfloxacin in that the carbon atom in position 8 of norfloxacin is replaced with a nitrogen atom, i.e. this drug belongs to the napthiridine series and not the quinolone series. It is synthesized from 2,6-dichloro-3-nitropyridine, which is reacted with N-ethoxycarbonylpiperazine, and which leads to substitution of the chlorine atom at the second position of the pyridine ring to give (33.2.20). Subsequent replacement of the chlorine atom at position C_6 with an amino group (using ammonia), acylation of the resulting amino group with acetic anhydride, and finally, reduction of the nitro group at position C_3 of the pyridine ring with hydrogen gives 6-amino-3-acetylamino-2-(4-ethoxycarbonylpiperazinyl)pyridine (33.2.21). In order to introduce a fluorine atom at position C_3, a Schiemann reaction is carried out. To do this, the free amino group is diazotated with amyl nitrite, and the resulting diazonium salt is treated with tetrafluoroboric acid. The resulting diazonium tetrafluoroborate undergoes pyrolysis to give 3-fluoro-6-acetylamino-2-(4-ethoxycarbonylpiperazinyl)pyridine. Finally, removing the

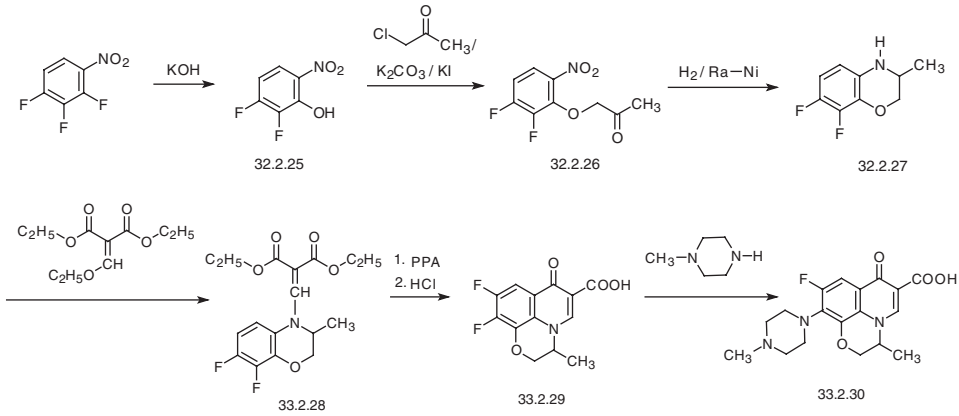
acetyl protection of the amino group at position C_6 gives 3-fluoro-6-amino-2-(4-ethoxycarbonylpiperazinyl)pyridine (33.2.22). The resulting amine (33.2.22) is reacted with ethyl ethoxymethylenmalonate, which results in the formation of a derivative of aminomethylenmalonic ester, which upon heating gives the ethyl ester of 6-fluoro-1,4-dihydro-4-oxo-7-(4-ethoxycarbonyl-1-piperazinyl)-1,8-naphthiridin-3-carboxylic acid (33.2.23). Alkylating this with ethyl iodide followed by hydrolysis of the two carboethoxy groups gives enoxacin [79–82].



In terms of the antibacterial spectrum and region of use, enoxacin basically exhibits the same properties as norfloxacin. However, it is better absorbed from the gastrointestinal tract and has a longer half-life. Synonyms of this drug are bactidan, flumarc, and others.

Ofloxacin: Ofloxacin, (±) 9-3-methyl-10-(4-methyl-1-piperazinyl)-7H-pyrido(1,2,3-de)-1,4-benzoxazin-7-oxo-6-carboxylic acid (32.2.30), has a somewhat more complex structure in comparison with the drugs described above, the main difference being the presence of a methyl-substituted oxyethylene bridge between the nitrogen atom and position C_8 of the quinolone system as well as the presence of a methyl substituent at position C_4 of the piperazine ring. It is synthesized from 2,3,4-trifluoronitrobenzene, which upon reaction with potassium hydroxide gives 2-hydroxy-3,4-difluoronitrobenzene (33.2.25). Reacting this with chloroacetone in the presence of potassium iodide and potassium carbonate gives the corresponding ether of hydroxyacetone (33.2.26). Exhaustive reduction of this compound with hydrogen over Raney nickel in one step gives the desired derivative of difluorobenzoxazine (33.2.27), bypassing, perhaps unnecessary, if not impossible, isolation stages of the amine, then the internal imine, and finally the desired product. According to the schemes of synthesis that have been repeated many times above, the secondary heterocyclic amine (33.2.27) is reacted with ethyl ethoxymethylenmalonate, and the resulting aminomethylmalonic derivative (33.2.28) cyclizes into a pyrido-benzoxazine system. However, unlike any of the cases described above where the reaction was done at high temperatures, this reaction is accomplished using polyphosphoric acid. The resulting ethyl ester of 9,10-difluoro-3-methyl-7H-pyrido (1,2,3-de)-1,4-benzoxazin-7-oxo-6-carboxylic acid undergoes hydrolysis to the

corresponding acid (33.2.29). Finally, reacting this product with N-methylpiperazine replaces the fluorine atom at position C_{10} of the pyridobenzoxazine system, forming orloxacin (32.2.30) [83–86].

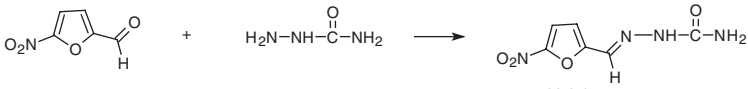


Ofloxacin also possesses a broad spectrum of antimicrobial action. It is highly active with respect to Gram-negative microorganisms, such as blue-pus bacillus, hemophilic and colon bacillus, shigella, salmonella, and chlamydia. It is used for infections of the respiratory tract, ears, throat, nose, skin, soft tissue, bones, joints, infective-inflammatory diseases of the abdominal cavity organs (kidneys, urinary tract), and organs of the pelvis minor (genitalia), and for gonorrhea. Synonyms of this drug are tarivid, flobacin, and others.

33.3 NITROFURANES

A few nitrofurane derivatives possess pronounced antimicrobial activity. All of these compounds are characterized by the fact that they are derivatives of 5-nitrofurfurol, which are synthesized by reacting various compounds that contain a hydrazine functional group. Nitrofuranes are effective with respect to Gram-positive and Gram-negative microorganisms as well as trichomonad and lambliosis. In small concentrations, these drugs act bacteriostatically, while in high concentrations they act bactericidally. They are most effective against a few strains of *E. coli*, *Klebsiella*, *Enterobacter* and *Citrobacter.* It should be noted that they can also be effective against a few microorganisms that are resistant to antibiotics and sulfonamides. Nitrofurazone, furazolidon, and nitrofurantion are the most widely used. Derivatives of nitrofurane are used both orally and as external drugs. Drugs of this series accumulate in the urine and bile. The speed of absorption depends heavily on the crystallized form of the drug. Nitrofuranes are used predominantly as antiseptics for external use (nitrofurazone) as well as for treating infections of the urinary tract and intestines. The exact mechanism of action of these drugs has not been established. However, it seems likely that they inhibit a number of bacterial enzyme systems, most likely by damaging their DNA. It is presumed that the enzyme nitroreductase transforms these drugs to short-lived, intermediate radicals, which react with DNA of bacteria and damage the process of twisting. Resistance, which is rarely observed, can originate as a result of mutations linked to a loss of nitroreductase activity.

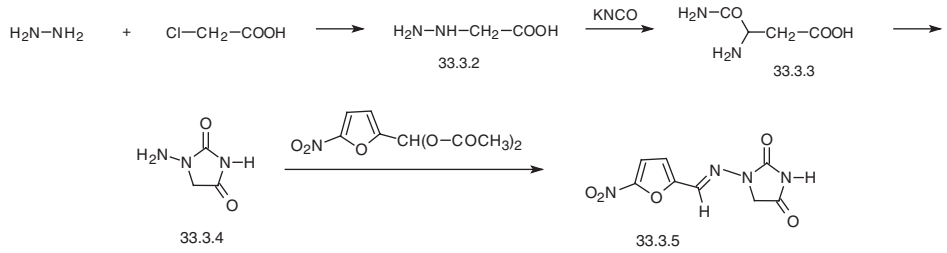
Nitrofurazone: Nitrofurazone is the semicarbazone 5-nitrofurfurol (33.3.1). It is synthesized by reacting 5-nitrofurfurol with semicarbazide [87,88].



33.3.1

Nitrofurazone is an effective drug that acts on a number of Gram-positive and Gram-negative microorganisms (staphylococci, streptococci, dysentery bacillus, colon bacillus, paratyphoid bacillus, and others). It is generally used externally for treating and preventing the pyoinflammatory processes, and internally for treating bacterial dysentery. Wounds are irrigated and wet bandages are synthesized using nitrofurazone. It is used in the form of eye drops for practically all suppurative processes that require use of antibacterial drugs. Synonyms of this drug are furacillin, furacin, antibioptal, vabrocid, and others.

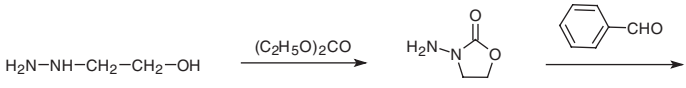
Nitrofurantoin: Nitrofurantoin, 1-(5-nitrofurfurylidenamino)hydantoin (33.3.5), is synthesized from hydrazinoacetic acid (33.3.2), which is synthesized by reacting chloroacetic acid with hydrazine. Reacting hydrazinoacetic acid with potassium cyanate gives the semicarbazidoacetic acid (33.3.3), which upon heating cyclizes into 1-aminoidantoin (33.3.4). Reacting this with diacetylacetal of 5-nitrofurfurol gives the desired nitrofurantoin [89–93].



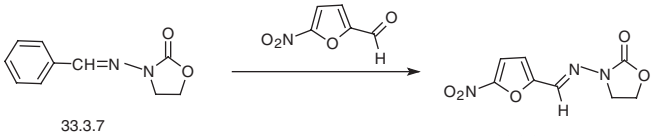
33.3.2 33.3.3 33.3.4 33.3.5

Like nitrofurazone, nitrofurantoin is an effective drug that acts on a number of Gram-positive and Gram-negative microorganisms (staphylococci, streptococci, dysentery bacillus, colon bacillus, paratyphoid bacillus, and others). It is primarily used for treating infectious diseases of the urinary tract (pyelitis, pyelonephritis, cystitis, urethritis). Synonyms of this drug are furadonin, ituran, phenurin, urolong, cistofuran, nitrofurin, and many others.

Furazolidone: Furazolidone, 3-(5-nitrofurfuryliden)amino-2-oxazolidinone (33.7.8), is synthesized from 2-hydroazinoethanol, which is reacted with diethyloxalate to make 3-amino-2-oxazolidone. Reacting this with benzaldehyde gives the corresponding hydrazone (33.3.7). Purifying the resulting product and then reacting it with 5-nitrofurfurol gives furazolidone [94–97].



33.3.6



33.3.7 33.3.8

Furazolidone, like the other nitrofurane derivatives listed above, is effective against Gram-positive and Gram-negative microorganisms. However, it also possesses antitrichomonal activity and is effective in treating lambliosis. In comparison with nitrofurazone and nitrofurantoin, furazolidone is more active with respect to Gram-negative microorganisms, and at the same time it is less toxic. Furazolidone is used internally and locally for the same indications as nitrofurazone and nitrofurantoin. Synonyms of this drug are diafuron, furoxan, itifur, vaginol, medaron, and others.

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– 34 –

Antimycobacterial Drugs

Mycobacteria such as *Mycobacterium tuberculosis, Mycobacterium avium, Myco-bacterium leprae, Mycobacterium kansasii, Mycobacterium fortuitum-M, Mycobacterium chelonae*, and a few others are pathogenic organisms that cause very serious diseases in humans. The characteristic feature of mycobacteria is their high content of lipids (about 40% of their mass), and they are primarily located on the outer bacterial membrane.

As a rule, typical mycobacteria cause tuberculosis, while atypical mycobacteria cause a few other diseases. Mycobacteria of group I (photochromogens) cause diseases associated with pigmentation; mycobacteria of group II (scotochromogens) cause lymphadenitis in children; mycobacterial organisms of group III cause certain pulmonary diseases; and finally, mycobacteria of group IV (*Mycobacterium fortuitum*) cause rare pulmonary and nonpulmonary diseases that do not respond to treatment by the usual selection of antitu-berculosis drugs, and that require treatment with broad-spectrum antibiotics. Apart from these is leprosy (leprosies, Hansen's disease), which is caused by the microorganism *Mycobacterium leprae*.

34.1 ANTITUBERCULOSIS DRUGS

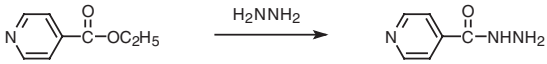
Tuberculosis is an infection caused by the mycobacteria *Mycobacterium tuberculosis*, which most often affects the lungs, and which is characterized by symptoms such as acute inflammation, tissue necrosis, and frequently by the development of open sores. In a few cases, the pathogen penetrates into the lymph or blood and the infection can spread to other body tissues. The modern therapy for tuberculosis is very effective, although it can be long and difficult. The pathogen quickly develops resistance to therapy using a single drug. Moreover, many strains also developed resistance to bi- and even multi-drug therapy, and therefore antituberculosis drugs, as a rule, are used in the form of a combination of two or three drugs.

Drugs used for tuberculosis therapy are very different in terms of activity and toxicity, and they are divided into two groups. Drugs in the first group include those medicinal drugs with a high level of efficacy and relatively low toxicity. Isoniazid, ethambutol, pyraz-inamide as well as the antibiotics rifampicin and streptomycin are included in this group. The majority of patients using these drugs can be successfully healed.

Sometimes it becomes necessary to use a drug of the second group because of microbial resistance and/or depending on the patient. Included in this group of drugs are ethionamide, antibiotics (cycloserine, capreomycin, kanamycin) as well as a very structurally simple drug called *p*-aminosalicylic acid. These drugs are somewhat more toxic than drugs in the first group, and they have certain limitations. Chemotherapy of tuberculosis should include the use of two or more effective drugs for preventing an increase in the number of resistant mutants. Treatment should last long enough to prevent relapses of slow-growing intracellular organisms.

34.1.1 Drugs of the first group

Isoniazid: Isoniazid, isonicotinic acid hydrazide (34.1.1), is synthesized by reacting ethyl ester of isonicotinic acid with hydrazine [1–5].

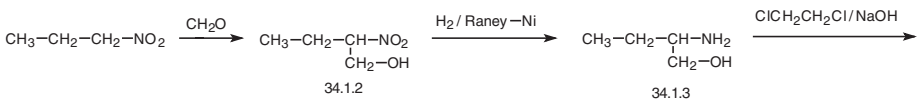


34.1.1

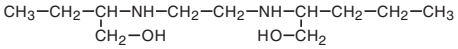
Isoniazid, the hydrazide of isonicotinic acid was introduced into medical practice for treating tuberculosis in 1953. Isoniazid exhibits bactericidal action on *Mycobacterium tuberculosis*. It inhibits the synthesis of mycolic acid, an important component of the cell membrane of mycobacteria. Mycolic acid is specific only to mycobacteria, and it is the cause of the selective toxicity of the drug with respect to these microorganisms.

Mutants that are resistant to isoniazid are rarely seen in nature, and in a spontaneously growing population of tuberculous bacillus there is approximately one mutant in every 10^5–10^6 organisms. Large populations of microorganisms of the order 10^9–10^{10} bacilli in the pulmonary cavities contain a significant number of resistant mutants. If only isoniazid is taken during treatment, an increased number of mutants will be observed and they will eventually become the dominant phenotype. The transformation from sensitive to nonsensitive microorganisms during treatment is called secondary or acquired resistance, which can originate over the course of a few weeks. Isoniazid is the most important drug for treating pulmonary and nonpulmonary forms of tuberculosis. It is active against both intracellular and extracellular organisms. In order to prevent secondary resistance, isoniazid should be used with other effective drugs (usually rifampin). Synonyms of this drug are tubazid, andrazide, niazid, piridizin, and many others.

Ethambutol: Ethambutol, (±)-*N*,*N*′-ethylenbis-(2-aminobutan-1-ol) (34.1.4), is synthesized in several different ways. According to one of them, nitropropane undergoes oxymethylation using formaldehyde, and the nitro group in the resulting 2-nitrobutanol (34.1.2) is reduced by hydrogen to an amino group, making racemic (±) 2-aminobutanol. L (+) tartaric acid is used to separate (+) 2-aminobutanol (34.1.3). Reacting this with 1, 2-dichloroethane in the presence of sodium hydroxide gives ethambutol (34.1.4) [6–15].

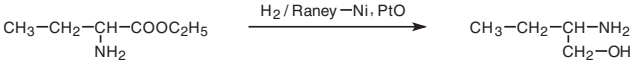


34.1.2 34.1.3



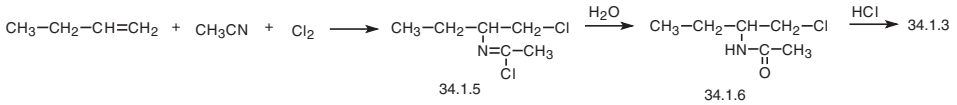
34.1.4

An alternative method of synthesis consists of preparing (+) 2-aminobutanol (34.1.3) by reducing ethyl ester of L-2-aminobutyric acid hydrochloride with hydrogen using simultaneously Raney nickel and platinum oxide catalysts. This gives pure (+) 2-aminobutanol. Reacting this with 1,2-dichloroethane in the presence of sodium hydroxide gives the desired ethambutol (34.1.4) [16,17].



34.1.3

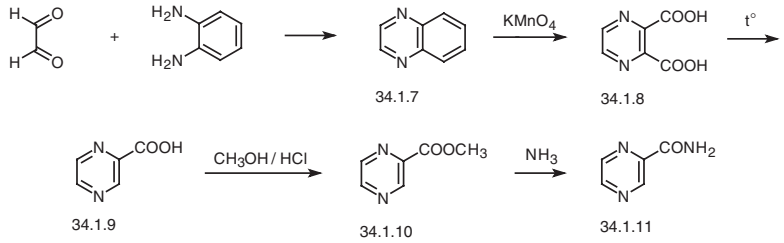
The third way of synthesis is very interesting and resembles of the Ritter reaction, but which takes place in the presence of chlorine. This method consists of reacting 1-butene and acetonitrile in the presence of chlorine, which evidently results in the 1,4-addition of chlorine to the product of the Ritter reaction, forming an intermediate dichloride (33.1.5), which is hydrolyzed with water to make *N*-[1-(chloromethyl)-propyl]-acetamide (33.1.6). Heating this product with hydrochloric acid gives racemic (±) 2-aminobutanol, from which (+) 2-aminobutanol (34.1.3) is isolated as described above using L (+) tartaric acid. Reacting this with 1,2-dichloroethane in the presence of sodium hydroxide gives the desired ethambutol (34.1.4) [18–21].



34.1.5 34.1.6

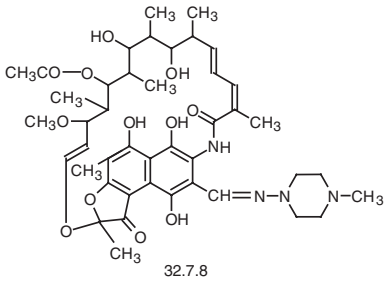
Ethambutol was discovered in 1961. It possesses bacteriostatic action against *Mycobacterium tuberculosis*; however, the exact mechanism of its action is not known. It inhibits the diffusion of mycotic acid into cell membranes of *Mycobacterium smegmatis*, which also explains its selective toxicity. Ethambutol is active only against the mycobacteria *Mycobacterium tuberculosis, Mycobacterium kansasii,* and *Mycobacterium scrofulaceum*. The sensitivity of other mycobacteria to ethambutol differs greatly. Practically, every other type of bacteria are resistant to it. Cases of primary resistance to ethambutol are isolated. Secondary resistance originates when the drug is used independently without simultaneous use of another effective antituberculosis drug, such as isoniazid and rifampin. The mechanism of resistance to this drug is not known. Synonyms of ethambutol are diambutol, chlorbutinol, tibistal, tubetol, and many others.

Pyrazinamide: Pyrazinamide, pyrazincarboxamide (34.1.11), is synthesized from quinoxaline (34.1.7) by reacting *o*-phenylendiamine with glyoxal. Oxidation of this compound with sodium permanganate gives pyrazin-2,3-dicarboxylic acid (34.1.8). Decarboxylation of the resulting product by heating gives pyrazin-2-carboxylic acid (34.1.9). Esterifying the resulting acid with methanol in the presence of hydrogen chloride and further reaction of this ester (34.1.10) with ammonia gives pyrazinamide [22–28].



Pyrazinamide was synthesized in 1952, and it is the nitrogen-analog of nicotinamide. It exhibits hepatotoxicity. Synonyms of this drug are dexambutol, miambutol, esnbutol, ebutol, and others.

Rifampicin: Rifampicin is 5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[*N*-(4-methyl-1-piperazinyl)-formamidoyl]-2,7-(epoxypentadeca-1,11-13-trienimino)-naphtho-[2,1-b] furane-1,11(2H)dion-21 acetate (32.7.8). It is a semisynthetic derivative of rifamicin B, which is synthesized by the actinomycete *Streptomyces mediteranei* (*Nocardia mediteranei*), and was introduced into medical practice in 1968. Rifampicin is described in Chapter 32.



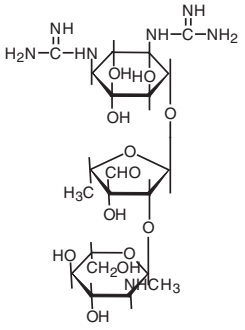
Rifampicin exhibits a bactericidal effect by inhibiting RNA synthesis. It inhibits DNA-dependent RNA polymerase by preventing the initial development of the chain, and not by destroying it. Rifampicin does not bind with RNA polymerase of mammalian cells, and does not have an effect on the corresponding RNA synthesis. It can inhibit mitochondrial RNA synthesis, although the concentrations required for this are several hundred times more than that necessary for RNA synthesis.

Rifampicin is highly active against *Mycobacterium tuberculosis*. Among atypical mycobacteria, it is active against *Mycobacterium kansasii, Mycobacterium marinum,* and most types of *Mycobacterium scrofulaceum* and *Mycobacterium xenopi*. Sensitivity of other mycobacteria varies. Rifampicin also exhibits activity against *Mycobacterium leprae*.

Besides mycobacteria, rifampicin also exhibits activity with respect to a large number of organisms. It is highly active with respect to *Staphylococcus aureus* and nonenterococcal forms of *Streptococcus* and *Listeria monocytogenes.* The Gram-negative bacteria that are very sensitive to rifampin are *Neisseria meningitides, Haemophilus influenzae,* and *Legionella. Escherichia coli* and *Proteus mirabilis* are resistant to it. *Clostridium* and *Bacteroids* forms of Anaerobic cocci frequently turn out to be sensitive to rifampin.

Rifampicin is the most effective drug for treating pulmonary and nonpulmonary forms of tuberculosis, including tuberculous meningitis. It should always be used in combination with other drugs. Synonyms of this drug are rifadin, rimactan, rifapiam, rimactazide and others.

Streptomycin: Streptomycin, *trans*-2,4-diguanidino-3,5,6-trihydroxycyclohexyl-5-deoxy-2-*O*-(2-deoxy-2-methylamino-α-L-glucopyranosyl)-3-*C*-hydroxymethyl-β-L-lyxo-pentofuranoside (32.4.1), is isolated from a cultural liquid of the vital activity of actinomycete Streptomyces griseus. It is described in Chapter 32.

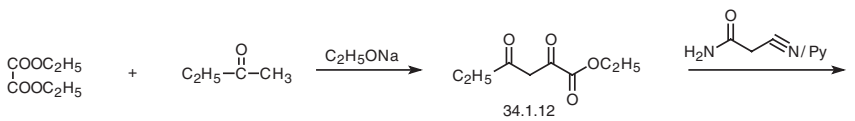


32.4.1

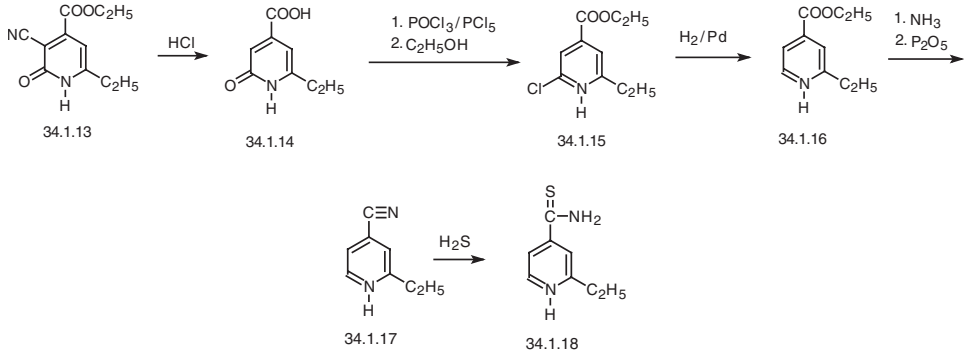
Streptomycin possesses a broad spectrum of antibacterial activity. It is the first clinically effective drug used for treating tuberculosis. Synonyms of this drug are streptan, streptocol, and others.

34.1.2 Drugs of the second group

Ethionamide: Ethionamide, 2-(ethyl)isonicotinthioamide (34.1.18), a derivative of isonicotinic acid, is synthesized by the following scheme. Diethyl oxalate is condensated with methylethylketone in the presence of sodium ethoxide to form the ethyl ester of propionylpyruvic acid (34.1.12). Condensation of this with cyanoacetamide results in heterocyclization, to form 3-cyano-4-carboethoxy-6-ethyl-2-pyridone (34.1.13), which is hydrolyzed with hydrochloric acid to give 4-carboxy-6-ethyl-2-pyridone (34.1.14). Reacting this with a mixture of phosphorous oxychloride and pentachloride gives 6-ethyl-2-chloroisonicotinic acid chloride, which is subsequently treated with ethyl alcohol to obtain the ethyl ester of 6-ethyl-2-chloroisonicotinic acid (34.1.15). Reducing this with hydrogen over a palladium catalyst removes the chlorine atom at position 2 of the pyridine ring, giving the ethyl ester of 6-ethylisonicotinic acid (34.1.15). Interacting this with ammonia, followed by dehydration of the resulting amide of 6-ethylisonicotinic acid using phosphorous pentoxide gives the nitrile of 6-ethylisonicotinic acid (34.1.17). Finally, reacting this with hydrogen sulfide gives ethionamide [29–32].

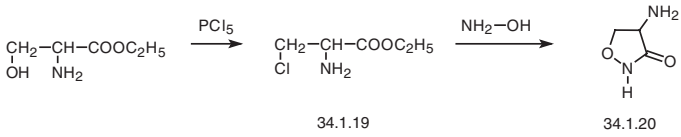


34.1.12



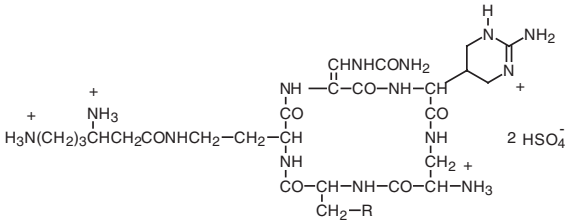
Ethionamide is active with respect to *Mycobacterium tuberculosis* and *Mycobacterium leprae*, but it does not have an effect on other microorganisms. It enhances phagocytosis at the center of tuberculous inflammation, which facilitates its decomposition. However, it frequently causes side effects associated with the gastrointestinal tract as well as a hepatotoxic effect in approximately 5% of patients. Synonyms of this drug are trecatil, ethimide, thiomid, tuberin, tuberoid, and others.

Cycloserine: Cycloserine, 4-amino-3-isoxalidinone (34.1.19), can be synthesized both biosynthetically from the actinomycetes *Streptomyces garyphalus*, *Streptomyces orchidaceus*, and *Streptomyces lavenduale* as well as synthetically from the methyl ester of D-serine, the hydroxyl group of which is replaced with a chlorine atom when reacted with phosphorous pentachloride, and subsequent reaction of the resulting product (34.1.19) with hydroxylamine results in heterocyclization to the desired cycloserine (34.1.20) [33–42].



Cycloserine has a broad spectrum of antibacterial use. It is active against both Gram-positive and Gram-negative bacteria as well as against tuberculosis mycobacteria that are resistant to drugs of the first group. It acts bactericidally, disrupting the synthesis of mycobacterial cell membranes. The accepted explanation behind this is its chemical affinity with D-alanine, which allows it to competitively suppress activity of the enzyme D-alaninracemase and D-alaninesynthetase, which results in the disruption of D-alanyl-D-alanine formation, which is necessary for building cell membranes in bacteria. Cycloserine is used for treating patients with chronic forms of tuberculosis who did not respond to treatment of drugs of the first group. Synonyms of this drug are cyclovaldin, cyclomycin, seromycin, and others.

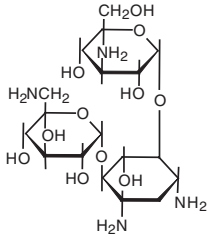
Capreomycin: Capreomycin is a semisynthetic antibiotic (34.1.21) that is isolated from the cultural fluid of *Streptomyces capreolus*, and it is a complex of a minimum of four microbiologically active ingredients that have only partially been characterized. Capreomycins IA and IB are represented below.



34.1.21

Capreomycin IA R = OH
Capreomycin IB R = H
Capreomycin has a pronounced suppressive effect against *Mycobacterium tuberculosis* and *Mycobacterium bovis.* Most strains of *Mycobacterium kansasii* are also sensitive to kanamycin, while other, nontuberculous strains are not sensitive to it. It is often used upon necessity of using parenternal therapy through deep intramuscular injections. Capreomycin is less toxic than kanamycin and has somewhat more of a bacteriostatic effect. Synonyms of this drug are capromycin, capastat, ogostal, and others.

Kanamycin: Kanamycin, *O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)-*O*-[6-deoxy-6-amino-α-D-glucopyranosyl-(1→4)]–2-deoxy-D-streptamine (32.4.6), is isolated from a culture fluid of the actinomycete *Streptomyces kanamyceticus*, which produces three antibiotics—kanamycins A, B, and C. It is described in Chapter 32.

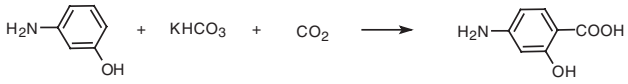


32.4.6

Kanamycin A is similar to streptomycin and neomycines, and it possesses a broad spectrum of antimicrobial action. It is active with respect to most Gram-positive and Gram-negative microorganisms (staphylococci, colon bacillus, klebisella, Fridlender's bacillus, proteus, shigella, salmonella).

It is used to treat sepsis, meningitis, osteomyelitis, peritonitis, pneumonia, pyelonephritis, pyelocystitis, infected wounds, and post-operational, purulent complications that are caused by microorganisms sensitive to this drug. Kanamycin is used to treat tuberculosis of the lungs and other organs upon resistance to other antituberculosis drugs. Synonyms of this drug are karmycin, kamaxin, resistomycin, and many others.

p-Aminosalicylic acid: *p*-Aminosalicylic acid, 5-amino-2-hydroxybenzoic acid (34.1.22), is synthesized in a Kolbe reaction, which consists of direct interaction of *m*-aminophenol with potassium bicarbonate and carbon dioxide while heating at a moderate pressure of 5–10 atm [43–47].



34.1.22

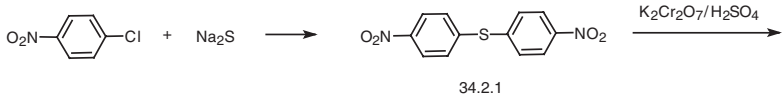
p-Aminosalicylic acid is a bacteriostatic that inhibits most tuberculous mycobacteria. In terms of tuberculostatic activity it is inferior to isoniazid and streptomycin. It is nephro- and hepatotoxic, and is rarely used. A synonym of this drug is apacizin.

34.2 DRUGS FOR TREATING LEPROSY

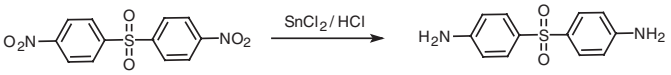
Lesions of the skin, loss of sensitivity to pain, and superficial nerves are the three main signs of leprosy, a disease caused by the mycobacteria *Mycobacterium leprae*. This disease is extremely infectious. Children and men are more susceptible to it than women. The incubation period can last several years, which makes early detection of leprosy difficult. Up until 1982, chemotherapy of leprosy consisted of taking dapsone, which gave good clinical results. However, because of the primary and secondary resistance that originated from prolonged use, it is now necessary to use a certain combination of drugs. Currently, dapsone is used along with rifampin and clofazimine. Ethionamide is also prescribed.

Dapsone: Dapsone, 4,4′-diaminodiphenylsulfone (34.2.3), is synthesized from either 4-chloronitrobenzene or from the sodium salt of 4-acetamidobenzenesulfonic acid. Reacting 4-chloronitrobenzene with sodium sulfide gives 4,4′-dinitrodiphenylthioester (34.2.1), and oxidation of the sulfur atom in this compound using potassium dichromate in sulfuric acid gives 4,4′-dinitrodiphenylsulfone (34.2.2). Reduction of the nitro group in the resulting compound using tin dichloride in hydrochloric acid makes the desired dapsone.

It has also been suggested to reduce the nitro group to an amino group, protect it with an acetyl protection, oxidize the sulfur atom to a sulfone using potassium dichromate, and then remove the protective acetyl group by hydrolysis [48–50].

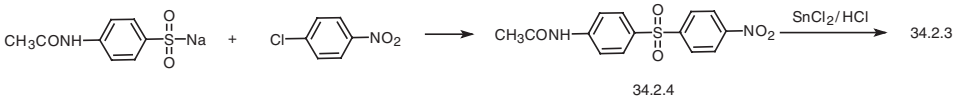


34.2.1



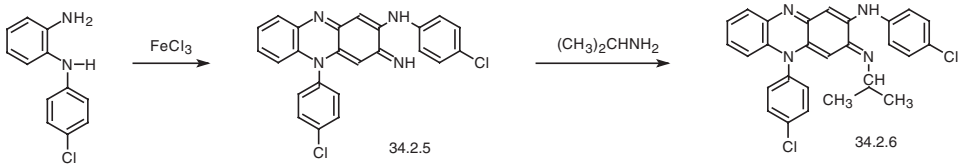
34.2.2 34.2.3

Another way of the synthesis of dapsone begins with 4-acetamidobenzenesulfonic acid, which is reacted with 4-chloronitrobenzene at high temperatures to give 4-acetamido-4′-nitrodiphenylsulfone (34.2.4). Reducing the nitro group in this compound with tin dichloride in hydrochloric acid along with the simultaneous hydrolysis of the acetyl group under the reaction conditions gives the desired dapsone [51–53].



Dapsone, which was first proposed in 1941, possesses both bactericidal as well as bacteriostatic activity with respect to *Mycobacterium leprae* and *Mycobacterium tuberculosis.* It is used to treat patients with herpetiform dermatitis. It is believed that the mechanism of its action consists of competitive inhibition of the enzyme dihydroprotease synthetase, which blocks synthesis of folic acid in microorganisms, allowing it to also be viewed as an analog of *p*-aminobenzoic acid. Synonyms of this drug are avosulfon, croysulfon and others.

Clofazimine: Clofazimine, 2-(*p*-chloroanilino)-5-(*p*-chlorophenyl)-3,5-dihydro-3-(isopropylimino)-phenazine (34.2.6), is synthesized by oxidizing 2-(*p*-chloroanilino)aniline using a solution of iron (III) chloride in water, which leads to the formation of 2-(*p*-chloroanilino)-5-(*p*-chlorophenyl)-3,5-dihydro-3-iminophenazine (34.2.5). Upon reacting this with a primary amine, in particular isopropylamine, the hydrogen atom in the imine region of the molecule is formally replaced with an alkyl group of the introduced amino group (in this case with an isopropyl group), forming the desired drug—clofazimine [54–56].



Clofazimine is a substituted iminophenazine that was first proposed for treating leprosy in 1962; however, it entered into medical practice toward the end of the 1980s. The mechanisms of its action is not definitively known, although there is the assumption that it can inhibit the formation of matrixes with DNA, which leads to a delay in the growth of mycobacteria. Clofazimine exhibits a bactericidal effect between that of dapsone and rifampicin. Synonym of this drug is lamprene.

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– 35 –

Antifungal Drugs

In comparison with bacteria or viruses, fungi are more complex organisms. They have ribosomes, cellular membrane components, and a nuclear membrane. Therefore, antibacterial antibiotics are, as a rule, ineffective against pathogenic fungi.

Fungal infections (mycoses) occur less than bacterial or viral infections. However, that statement may be untrue for a few geographical regions that are favorable for the existence and growth of specific fungal pathogens. A few fungal infections can spread to the surface of the body and cause local disturbances, while others can be systemic and life threatening. Some of these organisms (for example, *Candida*) can spread from a superficial location to internal organs, leading to systemic diseases with serious complications. Fungal (mycotic) infections cause a lot of discomfort, and as a rule, are difficult to cure. Fungal infections are conventionally divided into three categories: dermatophylic, mucocutaneous, and systemic.

The most widespread are dermatophytic fungal infections, which include skin, hair, and nails. Most infections can be cured by using topical drugs, such as tolnaftate, undecylenic acid, haloprogin, clotrimazole, and miconazole. Griseofulvin is used orally for deep infections, in particular for infections of the nail bed. Currently, ketoconazole is widely used for treating chronic dermatophytes.

Mucocutaneous infections caused primarily by the fungus *Candida albicans* occur in regions of moist skin and mucous membranes (i.e. gastrointestinal tract, perianal, and vulvovaginal areas). Amphotericin B, miconazole, clotrimazole, and nystatin are used topically to treat such infections. For chronic infections, ketoconazole is taken orally.

Systemic fungal infections are very rare, although they do present a serious problem since they are naturally chronic and difficult to diagnose and treat. So, antifungal drugs are medications used to treat fungal infections such as athlete's foot, ringworm, and candidiasis (thrush) as well as serious systemic infections like cryptococcal meningitis. Antifungals work by exploiting differences between mammalian and fungal cells to kill the fungal organism and without significantly harming the host.

From the chemical point of view, antifungal drugs can be divided into polyenes, imidazole and triazole derivatives, allylamines, and others. The polyenes (nystatin, amphotericin B, natamycin) bind with sterols in the fungal cell wall, principally ergosterol. This causes the cell's contents to leak out and the cell dies. Human (and other animal) cells contain cholesterol rather than ergosterol so are much less susceptible. The imidazole and triazole groups of antifungal drugs (imidazoles: miconazole, ketoconazole, clotrimazole, econazole, mebendazole, butoconazole, fluconazole) inhibit the enzyme cytochrome P450

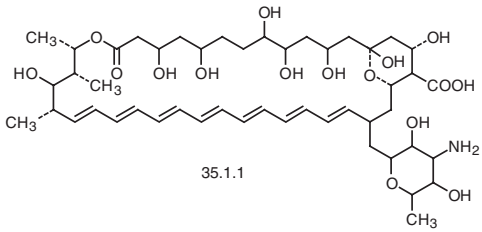
14α-demethylase. This enzyme converts lanosterol to ergosterol, and is required in fungal cell-wall synthesis. These drugs also block steroid synthesis in humans. Allylamines (naftifine, terbinalfine, butenafine, amorolfine) inhibit the enzyme squalene epoxidase, another enzyme required for ergosterol synthesis.

Others: Griseofulvin binds to polymerized microtubules and inhibits fungal mitosis. Flucytosine is an antimetabolite. From the medical point of view, antifungal drugs are considered dermatophytic, mucocutaneous, and systemic.

35.1 POLYENE ANTIFUNGAL DRUGS

Drugs included in this group—amphotericin B, nystatin, natamycin, are used for treating systemic and superficial infections. Natamycin is used only for ophthalmologic superficial infection purposes.

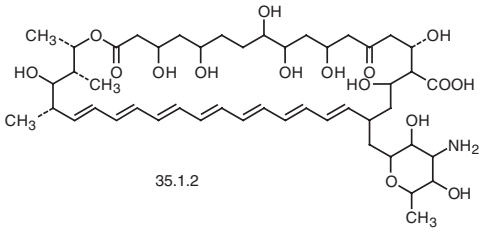
Amphotericin B: Amphotericin B, [1R(1R*,3S*,5R*,6R*,9R*,11R*,15S*,16R*,17R*,18S*,19E*,21E*,23*,25E*,27E*,29E*,31E*,33R*,35S*,36R*,37S*)]-33-[3-amino-3,6-dideoxy-β-D-mannopyranosyl)-oxy]-1,3,5,6,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo [33.3.1]nonatraconta-19,21,23,25,27,29,31-hepten-36-carboxylic acid (35.1.1), is a large polyene antibiotic made from the cultural fluid of the actinomycete *Streptomyces nodosus* [1–5].



35.1.1

This compound has a broad spectrum of antifungal activity, including *Candida albicans*, *Leishmania brasiliensis*, *Mycobacterium leprae*, *Histoplasma capsulatum*, *Blastomyces dermatitidus*, and *Coccidioides immitis*. It possesses fungistatic and fungicidal activity depending on the dose used. The antifungal activity of amphotericin B is exhibited because it binds with sterols, in particular with ergosterol in the cellular membrane of sensitive fungi. This reaction makes pores in the membrane and increases the permeability of the membrane to small molecules, thus reducing the function of the membrane as an osmotic barrier and making the cells more sensitive to being destroyed. Amphotericin B is active against growing cells and cells that are dormant. However, this compound is not highly selective and reacts with host mammalian cells. Despite the many side effects, amphotericin B remains the primary drug for treating severe, acute systemic fungal infections. It is used for generalized fungal infections, such as candidomycosis, aspergillosis, histoplasmosis, cryptococcosis, coccidioidomycosis, blastomycosis, and pulmonary mycoses. Synonyms of this drug are amphocyclin, fungisone, fungilin, and others.

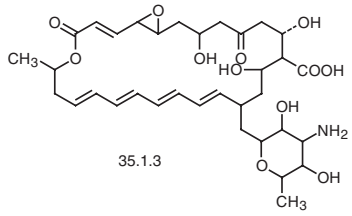
Nystatin: Nystatin is stereoisomeric 33-[(3-amino-3,6-dideoxy-β-D-mannopyranosyl) oxy]-1,3,4,7,9,11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo [33.3.1] nonatriaconta-19,21,25,27,29,31-hexaen-36-carboxylic acid (35.1.2) [6–14].



35.1.2

Nystatin was isolated in 1949 from the products of the vital activity of the actinomycete *Streptomyces noursei*, and it was the first antifungal antibiotic to be discovered. This polyene antibiotic is structurally similar to amphotericin B. It has a broad spectrum of activity. The mechanism of antifungal activity is similar to the mechanism of action of amphotericin B. It is used for preventing and treating candida infections of the skin and mucous membranes. In terms of preventative action, it is used for preventing the development of candidomycosis during prolonged treatment with penicillin drugs and antibiotics of other group, especially during oral use of tetracycline antibiotics, levomecytin, and others. Synonyms of this drug are biofanal, moronal, nicporil, fazigin, candex, and others.

Natamycin: Natamycin, a mixture of stereoisomeric 22-[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-1,3,26-trihydroxy-12-methyl-10-oxo-6,11,28-trioxatricyclo[22.3.1.0.^{5,7}]-octacosa-8,14,16,18,20,penten-25-carboxylic acid (35.1.3), like amphotericin and nystatin, is a polyene antibiotic that is isolated from the products of the vital activity of the actinomycete Streptomyces natalensis [15–17].



35.1.3

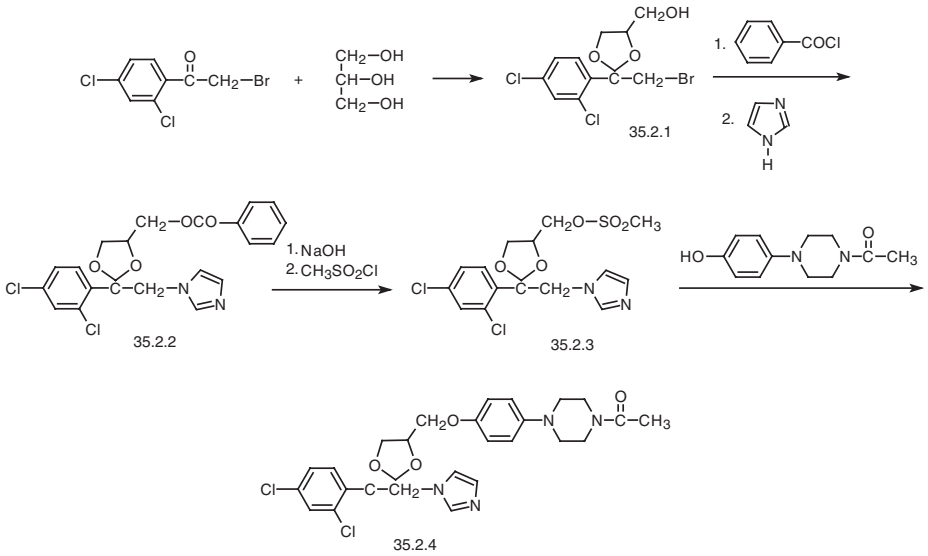
The spectrum of its activity is somewhat narrower than that of amphotericin and nystatin, but at the same time, it is less toxic. It exhibits especially pronounced activity against a few strains of *Fusarium* and *Cefalosporium*. Natamycin is a drug for treating superficial fungal infections, and it is used only for ophthalmologic purposes. Synonyms of this drug are pimafucin, pimaricin, tennecetin, and others.

35.2 IMIDAZOLES (TRIAZOLES)

Some imidazole derivatives have turned out to be extremely beneficial for treating fungal infections. They are ketoconazole, miconazole, clotrimazole, econazole, butoconazole, and others.

The antifungal activity of imidazole derivatives is currently explained by their ability to selectively raise the permeability of the membrane of fungal cells by interfering with the biosynthesis of sterins, in particular ergosterin, by inhibiting its synthesis and by changing the lipid content of the membrane. However, unlike amphotericin B, benzimidazole derivatives are active only against growing cells. This drug does not affect host cells because mammals use exogenic sterols for their vital functions.

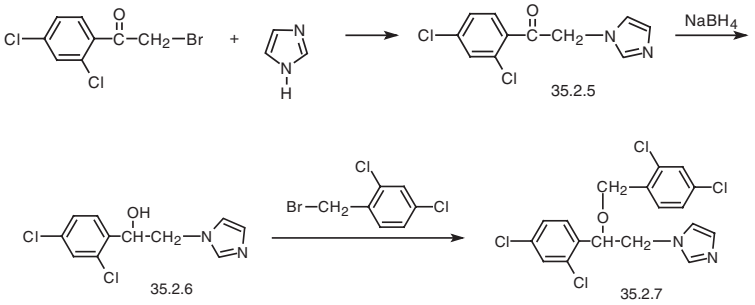
Ketoconazole: Ketoconazole, cis-1-acetyl-4-[4-[2-(2,4-dichlorophenyl)-2-(1H-imidazole-1-ylmethyl)-1,3-dioxolan-4-ylmethyl]phenyl]piperazine (35.2.4), is synthesized from 2,4-dichlorophenacyl bromide, the ketalization of which using glycerol gives cis-2-(2,4-dichlorophenyl)-2-bromoethyl-4-hydroxymethyl-1,3-dioxolane (35.2.1). Acylating the hydroxyl group of this compound with benzoyl chloride, and then alkylating the resulting compound with imidazole gives the derivative (35.2.2). Next, alkaline hydrolysis removes the benzoyl group, and a reaction with methanesulfonyl chloride gives a mesylate (35.2.3). Finally, alkylating the resulting 1-acetyl-4-(4-hydroxyphenyl)piperazine gives ketoconazole (35.2.4) [18–21].



Ketoconazole has a broad spectrum of antifungal activity, including many candida infections. It possesses fungicidal and fungistatic activity with respect to dermatophytes, yeast fungus, dimorphous fungi, and eumycetes. It is also active with respect to staphylococci and streptococci. It is effective for chronic diseases, treating fungal infections of the gastrointestinal tract, sex organs, skin, hair, and nails. It is used in combination with shampoo for treating and preventing mycelial fungi, seborrheic dermatitis, and dandruff. Synonyms of this drug are nizoral and others.

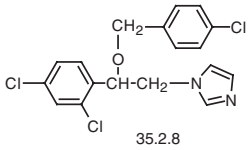
Miconazole: Miconazole, 1-[2,4-dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl]-imidazole (35.2.7), like ketoconazol, is synthesized from 2,4-dichlorophenacylbromide, which is reacted

with imidazole to make 1-(2,4-dichlorobenzoylmethyl)-imidazole[2,4-dichloro-ω-(1-imidazolyl)-acetophenone] (35.2.5). Reducing the carbonyl group in this molecule with sodium borohydride gives 1-(2,4-dichlorophenyl)-3-(1-imidazolyl)-ethanol (35.2.6), and the hydroxyl group is alkylated by 2,4-dichlorobenzylbromide using a powerful base such as sodium hydride to make miconazole (35.2.7) [22–24].



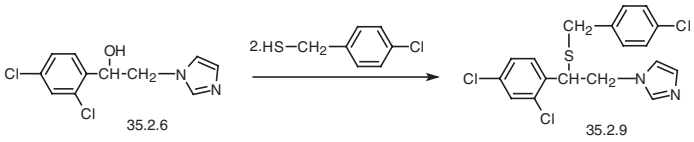
Miconazole is primarily used externally for candida and dermatophyte infections of the skin and vaginal candidosis as well as for acute internal mycoses. Synonyms of this drug are acnidazil, dactar, dermonistate, and others.

Econazole: Econazole, 1-[2,4-dichloro-β-[(4-chlorobenzyl)oxy]phenethyl]-imidazole (35.2.8), is an analog of myconazole. It differs in the presence of a single chlorine atom in the benzyl part of the molecule, and it is synthesized in the same manner, except that it uses 4-chlorobenzylchloride in the last stage instead of 2,4-dichlorobenzylbromide [22–24].



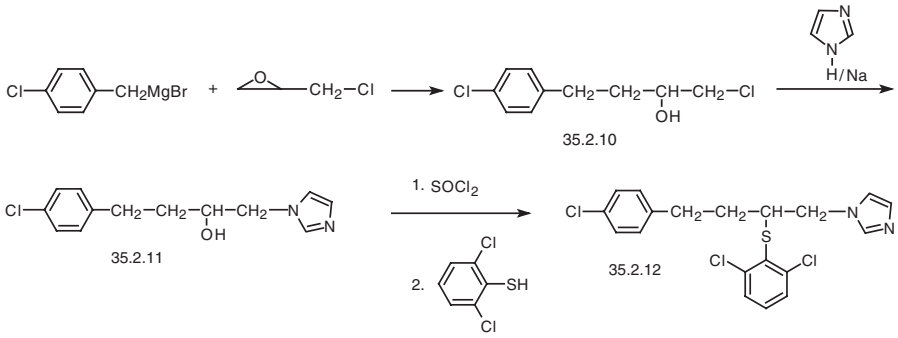
Econazole is also used externally (only superficially) to treat ringworm and candidoses caused by flora that are sensitive to this drug (*Trichophiton rubrum, Trichophiton menta-grophytes, Trichophiton tonsurans, Microsporum canis, Microsporum audouini, Microsporum gypseum, Candida albicans*). When used locally, it kills fungi in three days. Synonyms of this drug are pevaryl, exostatin, dermazol, and others.

Sulconazole: Sulconazole, 1-[2,4-dichloro-β-[(4-chlorobenzyl)thio]phenethyl]-imidazole (35.2.9), is an analog of exonazole. It differs in the replacement of the etheral oxygen bridge (which connects the 4-chlorobenzyl part of the molecule with phenethylimidazole) for a thioether bond. The corresponding changes in the synthesis of this drug are the replacement of the hydroxyl group in 1-(2,4-dichlorophenyl)-2-(1-imidazolyl)-ethanol (35.2.6) with a chlorine atom using thionyl chloride, followed by a reaction of the resulting chloride with 4-chlorobenzylmercaptane to make sulconazole [25,26].



Like econazole, sulconazole is used externally (only superficially) for the same indications as econazole. Synonyms of this drug are exelderm, sulcosyn, and others.

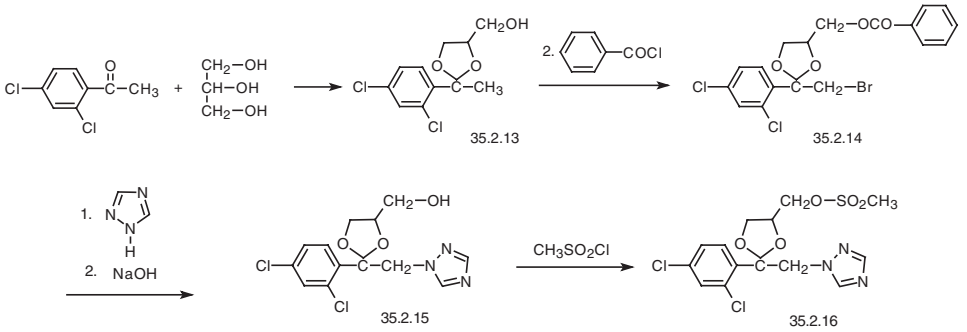
Butoconazole: Butoconazole, 1-[4-(4-chlorophenyl)-2-[(2,6-dichlorophenyl)thio]butyl]-1H-imidazole (35.2.12), is synthesized from 4-chlorobenzylmagnesium bromide, which is reacted with epichloridrine to make 4-(4′-chlorophenyl)-1-chlorobutan-2-ol (35.2.10), which is reacted with imidazole in the presence of sodium to make 4-(4′-chlorophenyl)-1-(1H-imidazolyl)butanol-2 (35.2.11). The hydroxyl group in the last is replaced with a chlorine atom upon reaction with thionyl chloride, which is then by the reaction with 2,6-dichlorothiophenol butoconazole [27,28], is obtained.



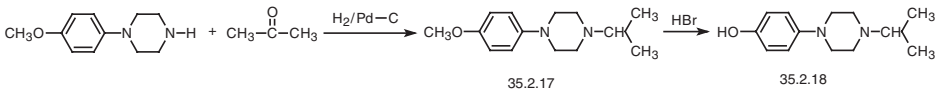
Butoconazole is a fungostatic drug, and it is formally classified as an imidazole, but only because of the presence of an imidazole ring in the structure. It is believed that butoconazole, like miconazole, econazole, and other "pure" representatives of the imidazole class, also inhibits the biosynthesis of estrosterin in the cytoplasmatic membrane of fungi; however, it is very possible that this is not the only mechanism of its action. It is effective for vaginal infections caused by various types of candida. It is also used only externally and vaginally. Synonyms of this drug are femstat, listomin, and others.

Terconazole: Terconazole, 1-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-yl-methyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(1-methylethyl)-piperazine (35.2.19), is chemically very similar to ketoconazole, the only difference being that instead of an imidazole ring it contains a triazole ring and the piperazine ring, instead of an acetyl group is substituted by an isopropyl group. It is synthesized from 2,4-dichloroacetophenone, which is reacted with glycerol in the presence of *p*-toluenesulfonic acid to make a ketal, 2-(2,4-dichlorophenyl)-2-methyl-4-hydroxymethyl-1,3-dioxolane (35.2.13). Brominating this with molecular bromine at the methyl group and then acylating the free hydroxyl group with benzoyl chloride gives 2-(2,4-dichlorophenyl)-2-bromomethyl-4-benzoyloxymethyl-1,3-dioxolane

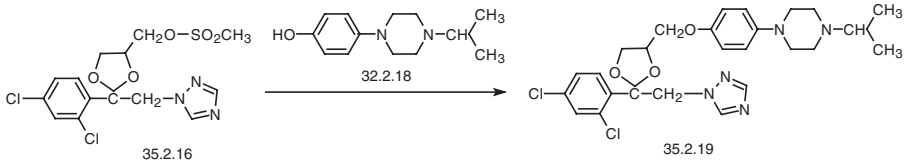
(35.2.14). Reacting this with 1,2,4-triazole in the presence of sodium, followed by the hydrolysis of the protecting benzoyl group with sodium hydroxide gives 2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-4-hydroxymethyl-1,3-dioxolane (35.2.15). Treating this with methanesulfonyl chloride gives the corresponding mesylate 35.2.16.



The way of making the second necessary fragment, 1-isopropyl-4-(4-hydroxyphenyl)-piperazine (35.2.18) is started from 4-(4-methoxyphenylpiperazine). Reducing this with hydrogen in the presence of acetone and using a palladium on carbon catalyst gives 1-isopropyl-4-(4-methoxyphenyl)piperazine (35.2.17). Treating of the resulting product with concentrated hydrobromic acid removes the protection from the phenol hydroxyl, making 1-isopropyl-4-(4-hydroxyphenyl)piperazine (35.2.18).

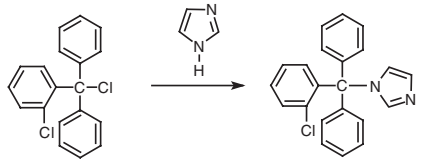


Finally, reacting the mesylate (35.2.16) with the resulting 1-isopropyl-4-(4-hydroxyphenyl)piperazine (35.2.18) gives the desired terconazole [29–32].



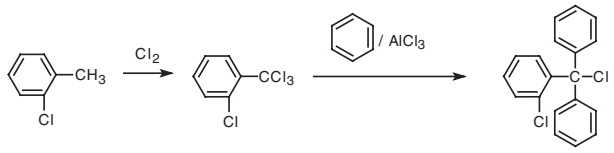
Terconazole is effective for fungistatic action for many strains of *Candida* and dermatophytes. The exact mechanism of its action is unknown, although it inhibits the action of the enzyme lanosterol 1-demethylase of cytochrome P-450 of sensitive fungi (similar to other azols described above), causing a reduction in the amount of ergosterin, which is necessary for the organisms to construct membranes and to retain the appropriate permeability. It is only used externally for treating vulvovaginal candidoses. Synonyms of this drug are terazol, tercospor, and others.

Clotrimazole: Clotrimazole, 1-(*o*-chloro-α,α-diphenylbenzyl)imidazole (35.2.21), is synthesized by reacting 2-chlorotriphenylmethylchloride (35.2.20) with imidazole in the presence of triethylamine [33–37].



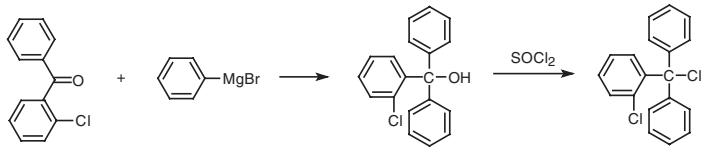
35.2.20 35.2.21

The starting substance 2-chlorotriphenylmethylchloride is made in various ways. In particular, chlorinating 2-chlorotoluene under light makes 2-chlorotrichloromethylbenzene (35.2.22), which is reacted with benzene in the presence of aluminum chloride to give 2-chlorotriphenylmethylchloride (35.2.20).



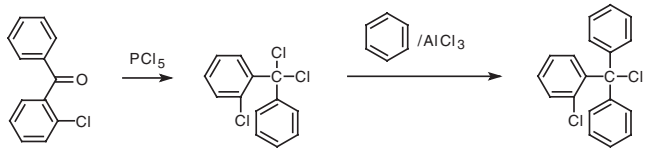
35.2.22 35.2.20

An alternative way of making 2-chlorotriphenylmethylchloride is a Grignard reaction between 2-chlorobenzolphenone and phenylmagnesium bromide, followed by substitution of the hydroxyl group in the resulting 2-chlorotriphenylmethylcarbinol (35.2.23) with a chlorine using thionyl chloride.



35.2.23 35.2.20

And finally, reacting phosphorous pentachloride with 2-chlorobenzophenone gives 2′-chloro-1,1-dichlorodiphenylmethane (35.2.24), which is used for the alkylation of benzene in the presence of aluminum chloride and gives 2-chlorotriphenylmethylchloride (35.2.20).



35.2.24 35.2.20

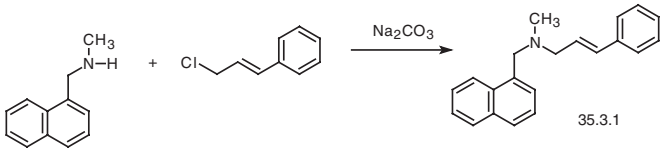
Clotrimazole formally also is an imidazole derivative because of the presence of an imidazole ring in its structure. It is believed that, like miconazole, econazole, and other "pure" representatives of the imidazole class, it also inhibits the biosynthesis of ergosterin in the cytoplasmatic membrane of fungi.

In terms of pharmacological action, clotrimazole is very similar to miconazole. It has a broad spectrum of antifungal activity. It is effective with respect to dermatophytes, and it also has an antimicrobial effect against streptococci and staphylococci. It is also effective with respect to trichomonases. It is very widely used, both externally and vaginally for treating superficial infections. Synonyms of this drug are canesten, empecid, lotrimin, micosporin, and others.

35.3 ALLYLAMINES

Naftifine is the first representative of a new class of antifungal drugs (naftifine, terbinafine (lamisil), amorolfine, butenafine) classified as allylamines.

Naftifine: Naftifine, (E)-N-methyl-N-(3-phenyl-2-propenyl)-1-naphthalinmethanamine (35.3.1), is synthesized by alkylating N-methyl-(1-naphthylmethyl)-amine with cinnamyl chloride in the presence of sodium carbonate [38–43].

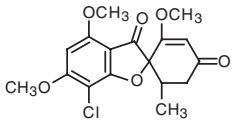


35.3.1

Naftifine is only permitted to be used externally and only superficially as a drug with a broad spectrum of action against dermatophytes and candida infections. According to the initial data, it exceeds the activity of econazole. Moreover, it does not have a locally irritating effect. It is believed that the fungicide activity of this drug is based on its ability to inhibit the fungal enzyme squalene epoxidase, thus lowering the concentration of ergosterol. The corresponding enzyme in mammals is inhibited significantly less. Synonyms of this drug are exoderil, naftin, and others.

35.4 OTHERS

Griseofulvin: Griseofulvin, 7-chloro-2′,4,6-trimethoxy-6′-methylspiro[benzofuran-2(3H),1′-[2]-cyclohexen]-3′,4-dione (35.4.1), is an antibiotic produced by the mycelial fungus Penicillium patulum [44–51].

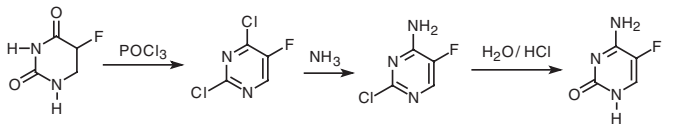


35.4.1

Griseofulvin is an antifungal drug used to treat superficial infections. It has a fungistatic effect on various types of dermatophytes (trichophytes, microsporums, achoriones, epidermophytones). The antifungal activity is explained by its ability to inhibit cell mitosis in fungi, causing the formation of multiple-nuclei, defective cells. The spectrum of antifungal activity of griseofulvin includes dermatophyte infections of the skin, nails, and scalp. It is ineffective against deep systemic mycotic infection. It is also ineffective for candidomycoses. It is possible to develop resistance to it.

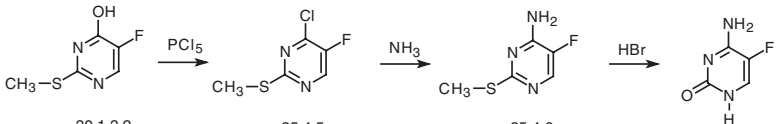
It is primarily used for treating those suffering from favus, trichophytosis, mycrosporia of the hairy region of the head and smooth muscle, nail beds, and red epidermophyton. It is only used orally. Griseofulvin is only used in the oral, medicinal form. Synonyms of this drug are fulcin, licuden, grifulvin, and others.

Flucytosine: Flucytosine, 5-fluorocytosine (35.4.4), is synthesized from fluorouracil (30.1.3.3). Fluorouracil is reacted with phosphorous oxychloride in dimethylaniline to make 2,4-dichloro-5-fluoropyrimidine (35.4.2), which is reacted with ammonia to make a product substituted with chlorine at the fourth position of the pyrimidine ring—4-amino-2-chloro-5-fluoropyrimidine (35.4.3). Hydrolysis of the chlorovinyl fragment of this compound in a solution of hydrochloric acid gives the desired flucytosine [52–55].



30.1.3.3 35.4.2 35.4.3 35.4.4

An alternative way of synthesis consists of making flucytosine from a precursor of fluorouracil—5-fluoro-2-methylthiouracil (30.1.3.2) using a somewhat analogous scheme. Treating 5-fluoro-2-methylthiouracil (30.1.3.2) with phosphorous pentachloride gives 4-chloro-5-fluoro-2-methylthiopyrimidine (35.4.5), which upon being reacted with ammonium is transformed into 4-amino-5-fluoro-2-methylthiopyrimidine (35.4.6). Hydrolysis of the methylthiovinyl fragment using concentrated hydrobromic acid gives the desired flucytosine [56–58].

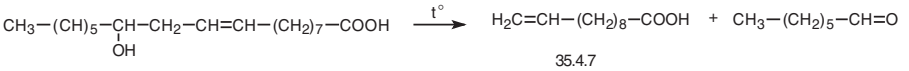


30.1.3.2 35.4.5 35.4.6 35.4.4

Flucytosine is a fluorinated derivative of pyrimidine. Its spectrum of activity is narrower than that of amphotericin B. However, it exhibits a synergetic effect when used in combination with amphotericin B. In sensitive fungi, flucytosine is transformed into 5-fluorouracil, which in turn is turned into 5-fluorodeoxyuracilic acid, an inhibitor of thymidylate synthetase, and correspondingly, DNA synthesis. 5-Fluorouracil triphosphate, which causes the formation of defective RNA, may also be involved in this process. The mechanism is highly selective because mammalian cells are not able to turn a large amount of flucytosine into 5-fluorouracil.

Flucytosine is used with amphotericin for treating certain systemic fungal infections, in particular for treating subcutaneous chromobastomycosis. It is used intensively for treating systemic infections of the urinary tract that are caused by various strains of *Candida*. Synonyms of this drug are ancobon, ancotil, and others.

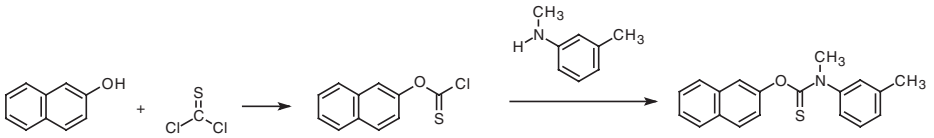
Undecylenic acid: Undecylenic acid, 10-undecylenic acid (35.4.7), is synthesized by pyrolysis at 400°C and low pressure (50 mm) an oxyderivative of oleic acid—ricinoleic acid—the glyceride of which is the main ingredient of castor oil [59,60].



35.4.7

Undecylenic acid, like zinc undecylenate, is very effective as an external drug for treating moderate dermatophyte infections and yeast dermatitis, but it is not effective for shingles and for candida infections. Synonyms of this drug are benzevrine, micocid, undetin, and others.

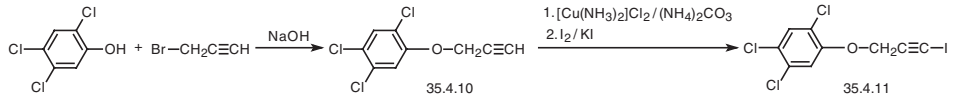
Tolnaftate: Tolnaftate, O-(2-naphthyl)-N-methyl-N-(3-tolyl)-thiocarbamate (35.4.9), is synthesized by reacting equimolar amounts of 2-naphthol and thiophosgene to make a monosubstituted product of thiophosgene (35.4.8), which is then reacted with N-methyl-3-toluidine to give the desired tolnaftate [61–64].



35.4.8 35.4.9

Tolnaftate is used as an external drug for moderate dermatophyte infections (shingles), and it is not effective for treating candida infections. Synonyms of this drug are tinatox, tonoftal, timoped, tinaderm, tinactin, and others.

Haloprogin: Haloprogin, 3-iodo-2-propinyl-2,4,5-trichlorophenyl ether (35.4.11), is synthesized by an iodide substitution using a mixture of iodine and potassium iodide and a cupric derivative of 2,4,5-trichlorophenylpropargyl ether (35.4.10), which is synthesized by a standard method from propargyl bromide and 2,4,5-trichlorophenol in the presence of sodium hydroxide [65–67].



35.4.10 35.4.11

Haloprogin is used as an external drug for moderate dermatophyte infections (shingles), and it is effective for superficial candida infections. Synonyms of this drug are halotex, mycilan, micanden, and others.

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– 36 –

Antiviral Drugs

Antiviral drugs are a class of medication used specifically for treating viral infections. Like antibiotics, specific antivirals are used for specific viruses. Viruses cause more diseases than any other group of parasites. They can cause blindness, deafness, paralysis, mental retardation, various birth defects, and in at least a few plants and animals, cancer. Of all the most well-known viral diseases, the ones that should be stated are measles, mumps, smallpox, chicken pox, influenza, poliomyelitis, and yellow fever. There is suspicion that viruses are the cause of multiple sclerosis, Hodgkin's disease, Down's syndrome, and possibly even schizophrenia. However, along with the significant progress made in the area of treating bacterial infections, the development of chemotherapy of viral diseases has been relatively modest. There is only a small selection of attainable drugs for treating a very limited number of viral infections.

Viruses are one of the great mysteries of biology. It is very hard to differentiate it as a living or nonliving entity. Viruses occupy a place somewhere in between a molecule and a live organism. At the same time, they also can be considered the most minute organism and the largest molecule. No signs of life are observed in viruses for a long time, and they can remain in this state for years. However, at any moment they can be "resurrected"—the only thing they need is a receptive cell. Each virus is only able to attack a limited assortment of cells. This allows them to be divided into three main groups: viruses that attack plants, viruses that attack animals (including humans), and viruses that attack single-cell organisms (microbes and bacteria).

Viruses are much simpler organisms than bacteria, and they are made from protein substances and nucleic acid. A single nucleoprotein molecule formed from molecules of nucleic acid that are chemically bound to a bulky protein molecule can be considered a simple viral particle. The protein molecule plays the role of a protective membrane. Thus the virus can be schematically described as a nucleic acid insert that is protected by a protein covering. A virus can contain either ribonucleic acid or deoxyribonucleic acid, but it never contains both of them together. The type of nucleic acid is the basis of one of the classifications of viruses. Viruses are obligatory intracellular parasites, which, upon entering a cell (i.e. after being infected) use many biochemical systems of the host cell.

On one hand, entering a live cell with relative ease and being involved in its complex mechanisms as if it were a part of its chromosomal apparatus creates a huge problem for finding selective toxicity of drugs against viruses. On the other, it makes the virus a

powerful instrument for research. In particular, in the viral process of multiplying, it generally uses the host cells' apparatus of biosynthesis by modifying it in some way. Therefore, it is very hard to select compounds for clinical use that have beneficial antiviral activity that do not damage the normal cell metabolism of uninfected host cells (not having a toxic effect on them). Nevertheless, there are certain antiviral drugs that have a certain selective action against cells infected by viruses, and which suppress the replicating cycle of the virus.

Despite the fact that the exact mechanism of infection is extremely specific to each type of virus, the general scheme of infection can be represented in the following manner. A virus is absorbed at the surface of a host cell, most likely by an electrostatic or hydrophilic interaction. It is possible that many viruses bind to certain virus-specific receptors. Then the virus permeates through the membrane of the host cell, where it releases nucleic acid from its protein protection, thus losing its individuality as a virus. Then the viral nucleic acid begins to act as if it was a functional part of the "host" cell. It begins to replicate, and transcription of the viral genome takes place either in the cytoplasm, or in the nucleus of the host cell. As a result of these events, a large amount of viral nucleic acid and protein are made to make new generations of virions. During this process, the replication mechanism of the host cell is turned off, and thus the described cycle is repeated over and over again.

Chemotherapy of viral infections is achieved by three different approaches, including preventative immunization; use of endogenic antiviral substances, for example an interferon that is believed to bind with specific receptors on the surface of the cellular membrane and activate RNA and protein synthesis inside the cell, which exhibits an antiviral effect; and finally, use of antiviral drugs. One approach for creation af antiviral drugs is to interfere with the ability of a virus to get into a target cell. A number of "entry-inhibiting" or "entry-blocking" drugs are being developed.

Two entry-blockers, amantadine and rimantidine, have been introduced into medicinal practice. A second approach is to target the processes that synthesize virus components after a virus invades a cell. One way of doing this is to develop "nucleotide or nucleoside analogs" that look like the building blocks of RNA or DNA, but jam the enzymes that synthesize the RNA or DNA once the analog is incorporated.

The first successful antiviral, acyclovir, is a nucleoside analog, and is effective against herpesvirus infections. The first antiviral drug to be approved for treating HIV, zidovudine (AZT), is also a nucleoside analog.

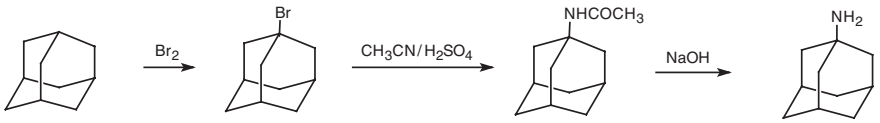
The first drugs on pharmaceutical market proposed as antiviral agents were idoxuridine and citarabine, and a while later, vidarabine, which is a first-generation antiviral drug. They have limited clinical use because of their narrow therapeutic index (ratio of effective and lethal doses). These drugs have a direct effect on viral replication; however, they also inhibit certain host cell functions. Later, amantadine, acyclovir, ribavirin, and zidovudine were suggested. Currently, a number of new drugs have been suggested for treating acquired immunodeficiency syndrome (AIDS)—ribavirin, ampligen, dideoxycytidine, and foscarnet.

Research in the area of antiviral drug synthesis has only recently allowed a significant step to be made in the area of treating diseases caused by herpes simplex virus, and just recently for treating AIDS. These drugs act by inhibiting the process of virus cell multiplication.

Currently, amantadine, vidarabine, trifluridine, idoxuridine, sciclovir, ribavirin, and zidovudine are used as antiviral drugs. An analysis of the mechanisms of action of existing and used viral drugs permits the conclusion to be made that they can increase resistance of

the cell to a virus (interferons), suppress adsorption of the virus in the cell or its diffusion into the cell, and the process of its "deproteinization" in the cell (amantadine); as well as antimetabolites that inhibit the synthesis of nucleic acids. The clinical "usefulness" of these pyrimidine and purine drugs depends directly on their ability to selectively block synthesis of viral nucleic acids while not stopping the synthesis of "host" cell nucleic acid.

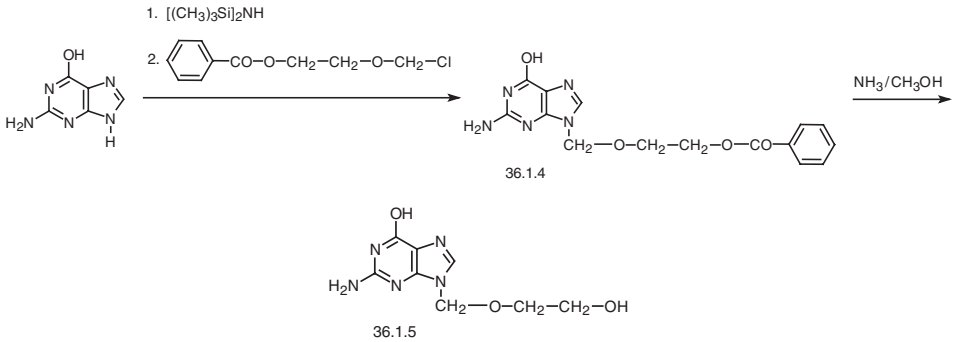
Amantadine: Amantadine, 1-adamantylamine (36.1.3), is synthesized from adamantane, which is first brominated with molecular bromine to make 1-bromoadamantane (36.1.1). Interacting this with acetonitrile in a Ritter reaction conditions gives 1-acetylaminoadamantane (36.1.2). Hydrolysis of the last with sodium hydroxide gives amantadine [1–6].



36.1.1 36.1.2 36.1.3

Amantadine is a primary amine derivative of adamantane. It has an effect on mycoviruses, which are RNA-containing viruses. It has a very narrow spectrum of action and is used only for treating and preventing influenza A. It is also used for treating Parkinsonism. The exact mechanism of antiviral action of amantadine is not completely understood. It is believed that it is an ion channel blocker. It has also been suggested that amantadine inhibits absorption of viral particles into the host cell, which is expressed in the breakdown of diffusion of the virus into the cell, or inhibition of the "stripping process" of the virus. The main use is for the prevention of type A2 influenza. Synonyms of this drug are simmetrel, viregit, mantadan, and others.

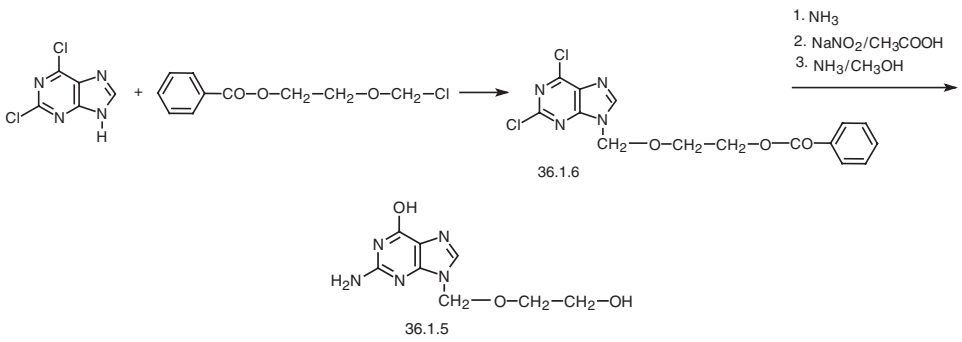
Acyclovir: Acyclovir, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one (36.1.5), is synthesized by alkylating guanine with 1-benzoyloxy-2-chloromethoxyethane in triethylamine. The hydroxyl and amino groups of guanine are previously protected with a trimethylsilyl group by being treated with hexamethyldisilazane. After hydrolysis the resulting product with water, 9-(2-benzoyloxymethoxymethyl)guanine (36.1.4) is isolated. Treating this with a methanol solution of ammonia removes the benzoyl protecting group from the hydroxyethoxymethyl fragment, giving acyclovir.



36.1.4

36.1.5

Another way of preparing acyclovir begins with 2,6-dichloropurine, which is alkylated with the same 1-benzoyloxy-2-chloromethoxyethane, but in a triethylamine—dimethylformamide system to make 2,6-dichloro-9-(2-benzoyloxyethoxymethyl)purine (36.1.6). Treating this with a methanol solution of ammonia replaces both chlorine atoms with amino groups, and subsequent diazotization using sodium nitrite in dilute acetic acid selectively replaces one of the two amino groups for a hydroxyl group, in particular the amino group at position C_6 of the purine system. Finally, treating the product with a methanol solution of ammonia removes the benzoyl protection from the synthesized 9-(2-benzoyloxyethoxymethyl)guanine (36.1.4) to make acyclovir [7–11].

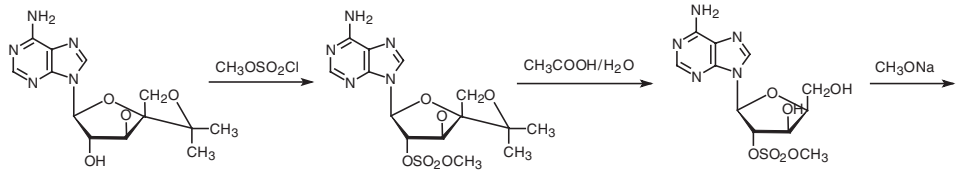


As it is evident from the chemical structure, acyclovir looks like a nucleoside analog of guanosine in side chain of which, instead of the traditional cyclic sugar residue a 2-hydroxyethoxymethyl acyclic side chain is present. Acyclovir possesses antiviral activity with respect to types 1 and 2 of herpes simplex, shingles virus, Epstein–Barr virus, and cytomegalovirus.

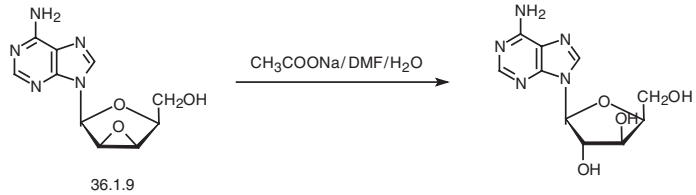
The mechanism of antiviral activity consists of its transformation to triphosphate and subsequent inhibition of viral DNA synthesis. Its action is highly selective. Acyclovir diffuses into the cell infected by a virus and phosphorylates thymidine kinase of herpes simplex to a monophosphate. Uninfected cells do not use acyclovir as a substrate. The monophosphate is subsequently transformed to a diphosphate, and then a triphosphate, which inhibits viral DNA polymerase, as well as viral DNA, where it acts in the process of breaking the chain, thus preventing further elongation of the DNA chains and correspondingly, replication of the DNA virus. Acyclovir is used for herpes simplex that has attacked the eyes and genetilia, for herpes in other locations, shingles, and chicken pox. Synonyms of this drug are aovirax, cycloviran, sifiviral, and others.

Vidarabine: Vidarabine, 9-*B*-arabinofuranosyl-6-amino-9-*H*-pyrine (36.1.10), is synthesized both microbiologically from the culture fluid of the actinomycete Streptomyces antibioticus NRRL 3238, as well as synthetically. It is synthesized from the acetonide-β-D–xylofuranoside of adenine—9-(3′,5′-*O*-isopropyliden-β-D–xylofuranoside)adenine, which is reacted with methanesulfonyl chloride to make the mesylate 9-(3′,5′-*O*-isopropyliden-2′-*O*-methansulfonyl-β-D-xydlofuranoside)adenine (36.1.7). Prolonged heating in 90% acetic acid removes the acetonyl protective group from the resulting compound, giving the product (36.1.8).

Reacting this with sodium methoxide leads to the formation of an epoxide—9-(2′,3′-anhydro-β-luxofuranosyl)adenine (36.1.9). Finally, heating this epoxide with sodium acetate or benzoate opens the epoxide ring in the dimethylformamide–water system to make the corresponding dihydroxy derivative, vidarabine [12,13].

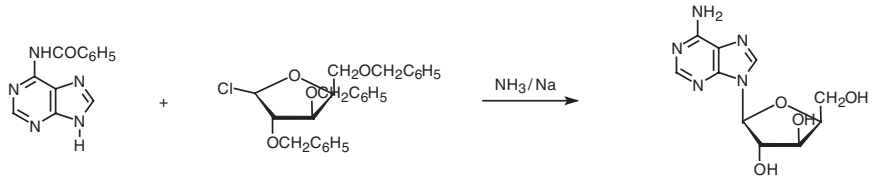


36.1.7 36.1.8



36.1.9 36.1.10

Another way of synthesis of vidarabine that was developed later consists of alkylating of 6-benzamidopurine with 2,3,5-*tri*-*O*-benzyl-D-arabinofuranosyl chloride using sodium in liquid ammonia. This simultaneously *N*-debenzylates the sixth position of the purine system and fulfil O-debenzylation of hydroxyl groups of the furanosyl fragment of the molucule, giving vidarabine [14].

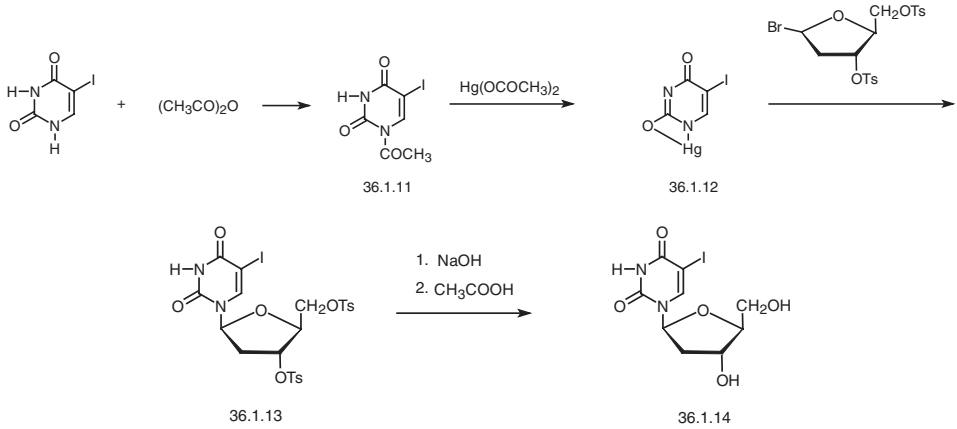


36.1.10

Vidarabine (adenine arabinoside) is the stereoisomer of adenosine. This analog of a purine nucleoside exhibits selective activity against the herpes virus. The ribose residue is replaced with an arabinose residue. Like acyclovir, it turns into mono-, di-, and triphosphate in cells infected by a virus, thus inhibiting DNA polymerase, and correspondingly preventing DNA synthesis of the virus approximately 20–40 times more than in "host" cells. It is easily metabolized to a less active, yet nonetheless antiviral compound—arabinosylhypoxanthine. It has been successfully used for herpetic encephalitis, and for complicated shingles. It is used in the form of eye drops for herpetic keratoconjuctivitis. A synonym of this drug is Vira-A.

Idoxuridine: Idoxuridine, 5-iodo-1-(2-deoxyyribofuranosyl)pyrimidin-2,4-(1*H*.3*H*)-dione (36.1.14), is synthesized by the following scheme. 5-Iodouracil is acylated with acetic anhydride to make 1-acetyl-5-iodouracil (36.1.11). Treating this with mercury(II) acetate gives

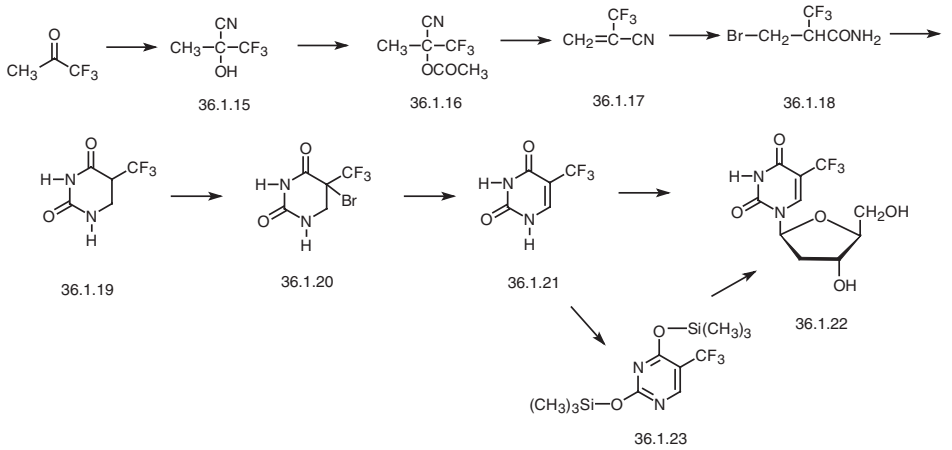
5-iodomonomercury uracil (36.1.12), which is reacted with 1-bromodidesoxy-D-ribofuranosyl-3,5-*bis*-(*p*-toluenesulfonate) to make a ditosyl derivative (36.1.13). Hydrolysis of the tosyl groups using sodium hydroxide and subsequent treatment of the resulting substance with acetic acid gives the desired product idoxuridine [15–19].



Idoxuridine is an analog of timidin—and iodinated derivative of deoxyuridin. Idoxuridine has an effect on viral DNA, and does not have an effect on viral RNA. The primary action of idoxuridine consists of inhibiting viral DNA replication by incorporating right in the DNA itself. Upon systemic introduction, this nucleoside is phosphorylated by both viral, as well as cellular thymidine kinase to an active triphosphorylated compound, which inhibits synthesis of both viral and cellular DNA. Since this drug also affects mammalian cells and also possess theratogenic, mutagenic, and immunosuppressive action, its use is limited to external use. It is used primarily for ophthalmology for herpetic infections of the eye (keratitis). Synonyms of this drug are herplex, stoxil, iduviran, and others.

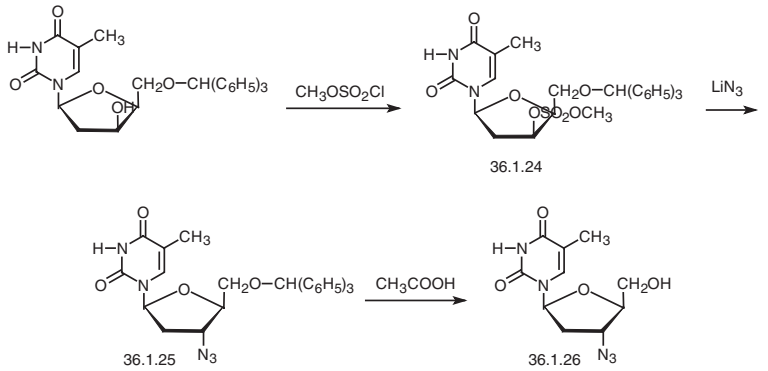
Trifluridine: Trifluridine, 5-trifluoromethyl-1-(2-deoxyribofuranosyl)pyrimidin-2, 4-(1*H*.3*H*)-dione (36.1.22), is synthesized from 5-trifluoromethyluracil. This is synthesized by the following scheme. It begins with trifluoroacetone, from which the oxynitrile (36.1.16) is synthesized. Acetylation of this product gives the corresponding trifluoroacetate (36.1.16). Pyrrolysis of this compound gives trifluoromethylacrylonitrile (36.1.17). Adding to this dry hydrogen bromide in methanol solution in a process of which methanolysis of the nitrile group takes place the bromide 36.1.19 is obtained, which upon acidic hydrolysis undergoes heterocyclization to the dihydropyrimidine 36.1.20. Brominating of the obtained dihydropyrimidine with molecular bromine and subsequent dehydrobromination of the resulting product 36.1.21 on heating in dimethylformamide gives 5-trifluoromethyluracil (36.1.22). This is reacted with 2-deoxy-D-ribos-1-phosphate using the nucleoside phosphorylase enzyme, or by treating it with hyxamethyldisylazane and then with trichloromethylsilane to make 2,4-trimethylsilyloxy-5-trifluoromethyl pyrimidine (36.1.23). Hexamethyldisilazane, which itself does not form trimethylsilyl ethers, is used because using a combination of two reagents leads to optimal yield of trimethylsilyl ethers. Reacting the resulting pyrimidine

derivative with 3,5-*bis*-(4-nitrobenzoate)-2-deoxyribofuranosyl chloride in the presence of mercury (II) acetate makes the corresponding ditrimethylsilyloxy nucleoside, which when treated with an aqueous solution of potassium iodide to remove the protecting groups. The resulting product undergoes preliminary purification by chromatography, and then is treated with a methanol solution of diisopropylamine to remove the 4-nitrobenzoyl protection from the furanosyl part, giving the desired trifluridine [20–23].



Trifluridine is also a halogenated derivative of timidin and is used for keratoconjuctivitis. In terms of action and region of use it is analogous to idoxuridine. It is also (like idoxuridine) turned into triphosphate, which inhibits DNA polymerase. A synonym of this drug is viroptic.

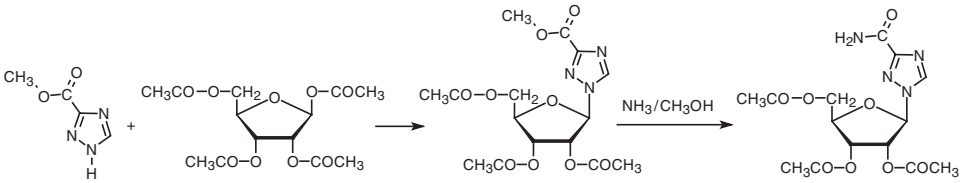
Zidovudine: Zidovudine is 3′-azido-3′-deoxytimidine (36.1.26), is synthesized from 1-(2′-deoxy-5′-O-trityl-β-D-lyxosyl)thymine, which is treated with methansulfonyl chloride in pyridine to make the corresponding mesylate 36.1.24. Replacing the methyl group with an azide group using lithium azide in dimethylformamaide makes the product 36.1.25 with inverted configuration at C_3 of the furanosyl ring. Heating this in 80% acetic acid removes the trityl protection, giving zidovudine [24–28].



Zidovudine is an antiretroviral drug that is clinically active against HIV-1 and is intended to treat HIV-infected patients. Zidovudine is an analog of thymidine that inhibits replication of the AIDS virus. It also turned into mono-, di-, and triphosphates by the same cellular enzymes that catalyze phosphorylation of thymidine and thymidine nucleosides. Zidovudine-triphosphate is then included in the terminal fragment of the growing chain of viral DNA by viral reverse transcriptase, thus causing the viral DNA chain to break apart in cells infected with the virus.

Zidovudine has been authorized for treating patients with AIDS. It significantly prolongs the life of the patient, although it has a number of toxic effects. Synonyms of this drug are azidothymidine and retrovir.

Ribavirin: Ribavirin, 1-β-D-ribofuranosyl-1*H*-1,2,4-triazol-3-carboxamide (36.1.28), is synthesized by reacting methyl ester of 1,2,4-triazol-3-carboxylic acid with O-1,2,3, 5-tetraacetyl-β-D-ribofuranose to make methyl ester of 1-O-2,3,5-tetraacetyl-β-D-ribofuranosyl-1,2,4-triazol-3-carboxylic acid (36.1.27), which is treated with an ammonia solution of methanol to simultaneously dezacylate the carbohydrate part and amidation of the carboxyl part of the product to give ribavirin [29–37].



36.1.27 36.1.28

Ribavirin is a synthetic analog of nucleosides. It is effective against many DNA and RNA viruses, such as viral influenza and herpes. The mechanism of its action is not completely known. However, it is highly likely that it is not the same for all viruses. It has been tried on a number of AIDS patients with various results. A synonym of this drug is virazoll.

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– 37 –

Drugs for Treating Protozoan Infections

The most widespread protozoan infections caused by pathogenic protozoa are malaria, leishmaniasis, and trypanosoma, as well as trichomonas, amebiasis, giardia, and toxoplasmosis. All types of protozoa are single-cell organisms that can adapt to various conditions. They are much more versatile than bacteria. They have a fairly complex life cycle, and therefore they exist in many forms. These forms require different approaches when treating patients that have protozoan infections. Protozoa are typical parasites that occupy host cells, multiply in them, and then destroy them.

Prevention of protozoan diseases consists of controlling the spread of the disease, improving sanitarial-hygenic conditions of life, receiving vaccinations, and treatment. It should be kept in mind that malaria is spread by mosquitoes, in particular by the bite of (female) *Anopheles mosquito*; leishmaniasis is spread through infected gerbils; trypanosome is spread by the tsetse fly; amibiasis and giardia are spread through food and water; and toxoplasmosis is spread through meat products and infected cats. Many different chemotherapeutic drugs are used to combat protozoan parasites.

37.1 ANTIMALARIAL DRUGS

Antimalarial drugs are designed to prevent or treat malaria. Antimalarial drugs currently used for treatment for prophylaxis are mefloquine, primaquine, chloroquine, pyrimethamine, amodiaquin, quinine/quinidine, chloroguanide.

Malaria is the most widely spread of all the diseases caused by protozoa. The causative agents of malaria are plasmodia (*Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae* and *Plasmodium ovale).* Malarial plasmodia have two developmental cycles; an asexual cycle, which takes in the body of an infected person (schizogony); and a sexual cycle, which takes place in the body of the mosquito (sporogony). When a person is bit by a mosquito, sporocytes that were formed in the blood of the mosquito (from male and female hematocytes) enter the body. These enter liver cells, where they form primary tissue schizonts, which grow, divide, and transform into merozoites. Merozoites then enter the blood of the person and diffuse into erythrocytes, where they develop further. After maturing in erythrocytes, schizonts again divide and transform into merozoites. These merozoites are periodically released from the occupied erythrocyte cells and attack a new group of erythrocytes, starting the process over. This process lasts for 3–4 days. The moment when erythrocytes are

destroyed and the merozoites enter the blood is expressed by an onset of malarial fever, which is referred to as the perierythrocytic form of malaria. However, upon being infected by the plasmodia *P. vivax, P. malariae* and *P. ovale*, another pathway of development is possible, which is called the exoerythrocytic form of malaria. This is when parasites in the merozoite stage of development remain in or enter the liver cells again. This restarts the erythrocytic cycle of development of plasmodia and the onset of relapse. In tropical malaria, the paraerythrocytic forms are not present.

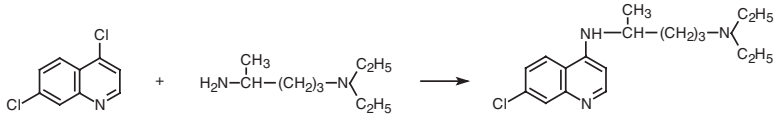
Chemotherapy of malaria consists of affecting various stages of the life cycle of the parasite. Antimalarial drugs are subdivided into three corresponding groups: those that have an effect on erythrocyte stage of the life cycle, those that destroy exoerythrocytic (or hepatic stage), and those that affect both stages simultaneously. The oldest drugs used against malaria are quinine and quinidine. Currently, aminoquinolines such as chloroquine and its analog (primarily for affecting the parasite during the erythrocyte stage), and primaquine (for affecting the parasite during the exoerythrocyte stage) are used to treat malaria. Recently, mefloquine, and a natural compound quinghaosu, as well as various antibiotics in combination with antimalarial drugs have begun to be used.

37.1.1 Drugs effective against the erythrocyte stage of plasmodia infection

4-Aminoquinolines and quinolinmethanols

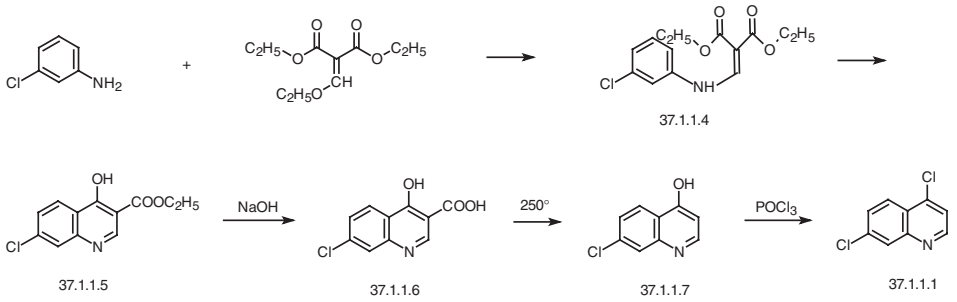
In the erythrocyte stage of plasmodia infection, two classes of drugs are used: 4-aminoquinolines and quinolinmethanols. 4-Aminoquinolines (chloroquine, amodiaquin, and hydroxychloroquine) are synthetic compounds. Their most important structural characteristic is the type of substituent at C_7 and C_4 of the quinoline ring. It has been shown that an amine substituent is necessary at C_4 of the quinoline ring, which can vary while retaining antimalarial activity of the compound; however, the necessary conditions for expression of antimalarial activity is the presence of a chlorine atom at C_7 of the quinoline ring. The prototype of this group of compounds is chloroquine. The second group of drugs used during the erythrocyte stage of malarial infections is quinolinmethanol derivatives. This group includes mefloquine, pyranobenzodioxepin derivative isolated from the plant—quinghaosu, as well as cinchona alkaloids that are made from the bark of the cinchona tree, of which only quinine is still used for treating malaria.

Chloroquine: Chloroquine, 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline (37.1.3), is made by reacting 4,7-dichloroquinoline (37.1.1.1) with 4-diethylamino-1-methylbutylamine (37.1.1.2) at 180 °C [1–3].

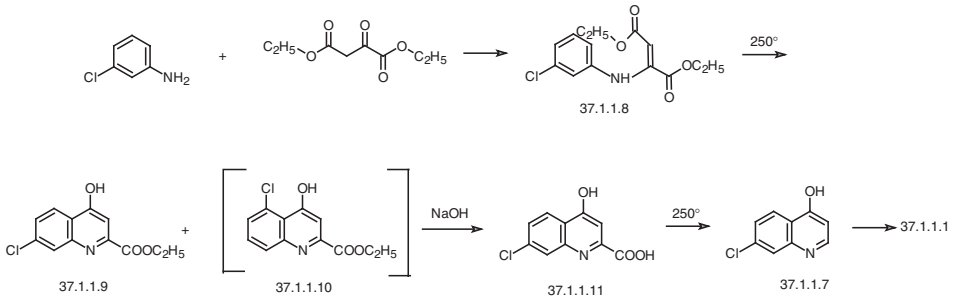


37.1.1.1 37.1.1.2 37.1.1.3

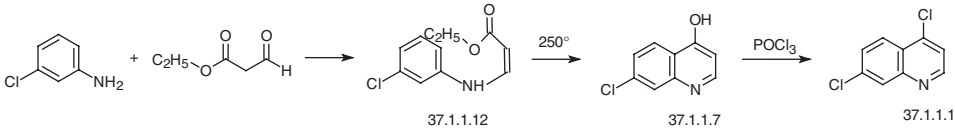
In order to realize the synthesis, the necessary 4,7-dichloroquinoline (37.1.1.1) is prepared in several ways from 3-chloroaniline. One of these ways consists of reacting 3-chloroaniline with ethoxymethylenmalonic ester to make (3-choroanilino)-methylenemalonic ester (37.1.1.4), which then undergoes high-temperature heterocyclization to make the ethyl ester of 7-chloro-4-hydroxyquinolin-3-carboxylic acid (37.1.1.5). Hydrolyzing this with sodium hydroxide gives 7-chloro-4-hydroxyquinolin-3-decarboxylic acid (37.1.1.6), which when heated at 250–270 °C is decarboxylated, forming 7-chloro-4-hydroxyquinoline (37.1.1.7). Treating this with phosphorus oxychloride gives one of the desired components for synthesis of chloroquine – 4,7-dichloroquinoline (37.1.1.1) [4,5].



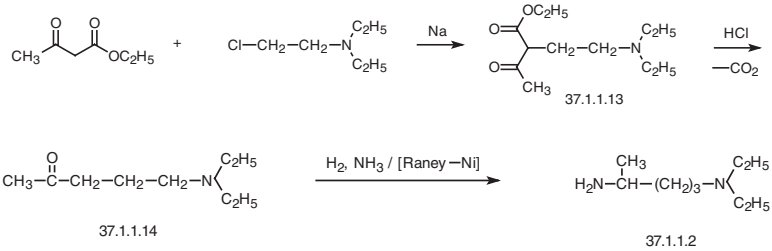
The second method of preparing of 4,7-dichloroquinoline (37.1.1.1) consists of reacting 3-chloroaniline with the diethyl ester of oxaloacetic acid in the presence of acetic acid to give the corresponding enamine (37.1.1.8), which when heated to 250 °C undergoes heterocyclization to the ethyl ester of 7-chloro-4-hydrozyquinolin-2-carboxylic acid (37.1.1.9) accompanied with a small amount of 5-chloro-4-hydroxyquinolin-2-carboxylic acid (37.1.1.10), which is separated from the main product by crystallization from acetic acid. Alkaline hydrolysis of the ethyl ester of the 7-chloro-4-hydroxyquinolin-2-carboxylic acid (37.1.1.9) and subsequent high-temperature decarboxylation of the resulting acid (37.1.1.11) gives 7-chloro-4-hydroxyquinolin (37.1.1.7). Reacting this with phosphorus oxychloride using the scheme described above gives 4,7-dichloroquineoline (37.1.1.1) [6].



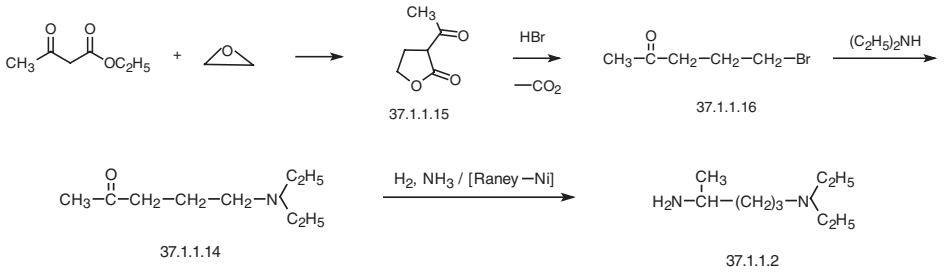
Finally, the third of the suggested variants for making 4,7-dichloroquinoline (37.1.1.1) consists of reacting 3-chloroaniline with the ethyl ester of formylacetic acid to make the enamine (37.1.1.12), which on heating directly cyclizes to 7-chloro-4-hydroxyquinoline (37.1.1.7). Reacting this with phophorus oxychloride according to the scheme already described gives 4,7-dichloroquinoline (37.1.1.1) [7].



The second component necessary for synthesizing of the chloroquine is 4-diethylamino-1-methylbutylamine (37.1.1.2), is also made in various ways. Alkylating acetoacetic ester with 2-diethylaminoethylchloride gives 2-diethylaminoethylacetoacetic acid ester (37.1.1.13), which upon acidic hydrolysis (using hydrochloric acid) and simultaneous decarboxylation makes 1-diethylamino-4-pentanone (37.1.1.14). Reductive amination of this compound with hydrogen and ammonia using Raney nickel as a catalyst gives 4-diethylamino-1-methylbutylamine (37.1.1.2) [8].



Another way suggested for making 4-diethylamino-1-methylbutylamine (37.1.1.2) is by starting with 3-acetylbutyrolactone (37.1.1.15), which is made by reacting acetoacetic acid ester with ethylenoxide. Acidic hydrolysis of the ester group in 3-acetylbutyrolactone (37.1.1.15) along with simultaneous decarboxylation gives 1-bromo-4-pentanone (37.1.1.16). Reacting this with diethylamine gives 1-diethylamino-4-pentanone (37.1.1.14), and reductive amination of this compound using hydrogen and ammonia using Raney nickel as a catalyst gives 4-diethyl-1-methylbutylamine (37.1.1.2) [9].



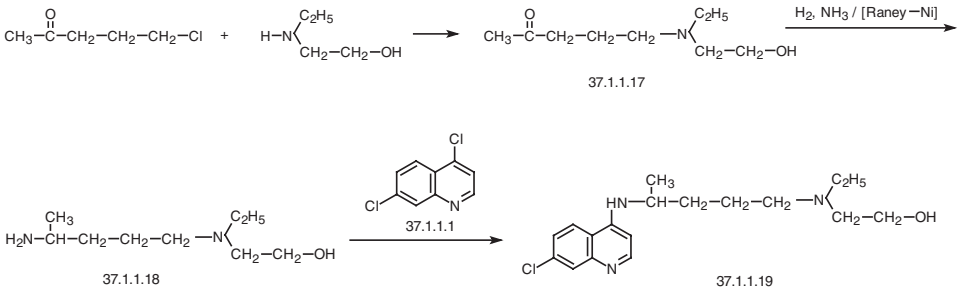
Chloroquine is the drug of choice for preventing and treating acute forms of malaria caused by *P. vivax, P. malariae, P. ovale*, as well as sensitive forms of *P. falciparum*. The mechanism of its action is not completely clear, although there are several hypotheses explaining its antimalarial activity. Chloroquine and its analogs inhibit synthesis of nucleic acids of the parasite by affecting the matrix function of DNA. This happens by preliminary

binding of the drug through hydrogen bonds with the purine fragments, and subsequent introduction of the chloroquine molecule between the orderly arranged base pairs into the spirals of the DNA of the parasite. Thus chloroquine prevents transcription and translation, which significantly limits the synthesis of DNA and RNA in the parasite. The selective toxicity of chloroquine in particular with respect to malarial plasmodia is also attributed to the ability of the parasitized red blood cells to concentrate the drug in amounts approximately 25 times greater than in normal erythrocytes. There is also a different hypothesis. Chloroquine has a high affinity for tissues of the parasite and is concentrated in its cytoplasm. As a weak base, it increases the pH of the intracellular lysosome and endosome. A more acidic medium in these organelles is needed for the parasite to affect mammalian cells. As a result, chloroquine inhibits growth and development of parasites.

Thus the main quality of chloroquine that exceeds all other antimalarial drug is its effect on erythrocytic schizonts (hematoschizotropic action). However, chloroquine also possesses amebicidal action. It has also been observed to have immunodepressive and antiarrhythmic properties.

It is used for all types of malaria, for chemotherapy, as well as for non-gastric amebiasis, and amebic abscesses of the liver. Synonyms of this drug are nivaquine, quingamine, delagil, resoquine, atroquine, and others.

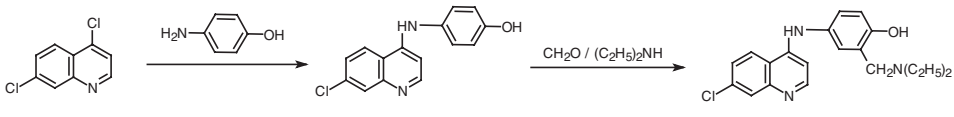
Hydroxychloroquine: Hydroxychloroquine, 7-chloro-4-[4-[ethyl(2-hydroxyethyl)amino]-1-methylbutylamino]quinoline (37.1.1.19), is made by a scheme similar to that of making chloroquine. Reacting 1-chloro-4-pentanone with 2-ethylaminoethanol gives the corresponding aminoketone (37.1.1.17), which undergoes reductive amination in conditions analogous to those described above, making 4-[ethyl(2-hydroxyethyl)amino]-1-methylbutylamine (37.1.1.18). Reacting this with 4,7-dichlroquinoline (37.1.1.1) makes the desired hydroxychloroquine [10,11].



Hydroxychloroquine, like chloroquine, is also used for treating acute forms of malaria caused by *P. vivax, P. malariae, P. ovale*, and also sensitive forms of *P. falciparum.* It is also effective and safe like chloroquine, although it does not have obvious advantages. The only advantage is that it is somewhat better tolerated. Its use is somewhat more limited than chloroquine. Synonyms of this drug are plaquenil, quensyl, toremonil, and others.

Amodiaquin: Amodiaquin, 4-[(7-chloro-4-quinilyl)amino]-α-diethylmaino-*o*-cresol (37.1.1.21), is made by reacting 4,7-dichloroquineoline (37.1.1.1) with 4-aminophenol to

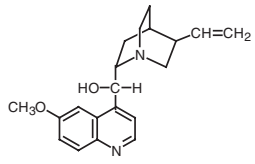
make 7-chloro-4-(4-hydroxyphenylamino)-quiniline (37.1.1.20), which then undergoes an aminomethylation reaction using formaldehyde and diethylamine, giving amodiaquin [12–15].



37.1.1.20 37.1.1.21

Amodiaquin is also a structural analog of chloroquine and hydroxychloroquine, and it does not express any vital differences in terms of activity. Therefore it is used less often than the drugs described above. Synonyms of this drug are flavoquine and camoquin.

Quinine: Quinine, (5-vinyl-2-quinuclidinyl)-(6-methoxy-4-quinolyl)methanol (37.1.1.47), is isolated from the bark of the cinchona tree [16].

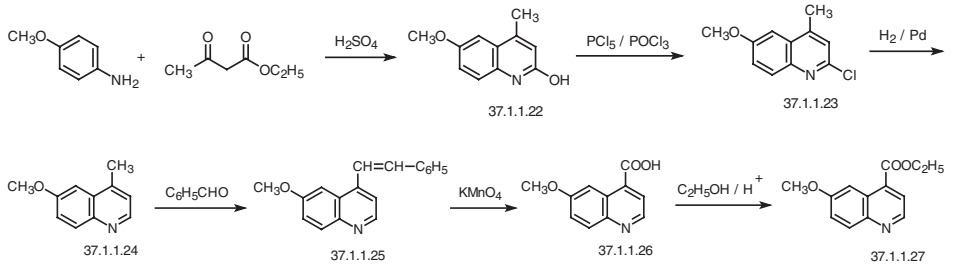


37.1.1.47

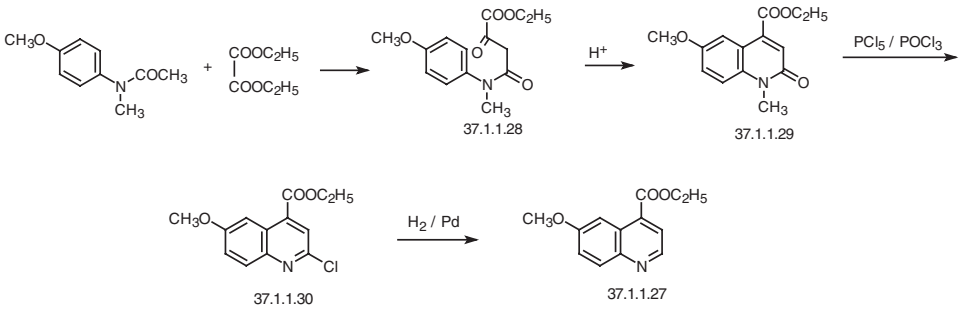
Since the 17th century, cinchona bark was used in Europe as an antifever drug, and then as a drug for treating malaria. Two alkaloids were isolated from the bark of the cinchona tree as far back as the 1820s (quinine and cinchonine) which are noncondensed biheterocycles containing two heterocyclic nucleus, quinoline and quinuclidine. Quinine is a methoxylated derivative of cinchonine. Quinine is the levorototary isomer of quinidine. Its structure consists of a quinoline ring, the fourth position of which is bounded by a hydroxy methylene bridge to a quinuclidine ring. The methoxy group at C_6 of the quinoline ring and the vinyl group in the quinuclidine ring enhance the activity of the compound; however, they are not absolutely necessary for the compounds of this group to express antimalarial activity. Quinine has gained significant importance as a base structure for synthesizing numerous compounds with antimalarial activity. The synthesis of this drug is very complex and has been made in different ways, but it basically comes down to the ester condensation of 6-methoxyquinoline (quininic) acid esters (37.1.1.27) and *N*-benzoylhomomeroquinene (27.1.1.42), which can be made in various ways, and subsequent successive treatment of the resulting product with hypobromite and then with sodium ethoxide in order to create the quinuclidine fragment.

One of the methods of making the ethyl ester of quininic acid (37.1.1.27) that should be mentioned is the method described in the following scheme. Reacting *p*-anisidine and acetoacetic ester in the presence of sulfuric acid gives 6-methoxylepidine (37.1.1.22). The

hydroxyl group of this compound is replaced with a chlorine atom by reacting it with a mixture of phosphorus oxychloride and phosphorus pentachloride, giving 2-chloro-4-methyl-6-methoxyquinoline (37.1.1.23). Reducing this compound with hydrogen using a palladium catalyst removes the chlorine atom at C_2 and gives 4-methyl-6-methoxyquinoline (37.1.1.24). Condensing this with benzaldehyde gives 2-(6-methoxy quinolinyl-4)-styrene (37.1.1.25), the double bond in which is oxidized using potassium permanganate to make 6-methoxyquinolinic acid—cinchonine (37.1.1.26), which is then converted into an ester (37.1.1.27) in the usual manner.

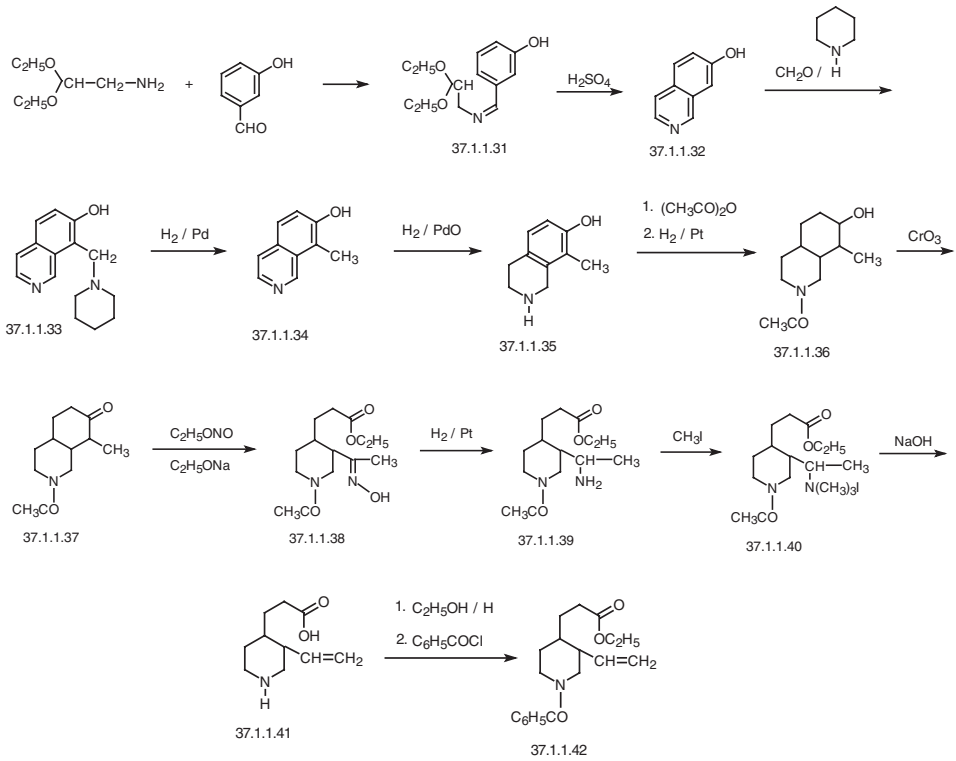


Another convenient way for preparation of quininic acid ethyl ester (37.1.1.27) is by using *p-N*-methylacetanisidine and diethyloxalate, which are reacted to form the *p-N*-methylacetaniside of oxalacetic acid (37.1.1.28). Heterocyclization of the product under acidic conditions leads to the formation of *N*-methyl-2-keto-4-carbethoxy-6-methoxyquinoline (37.1.1.29), which is reacted with a mixture of phosphorus oxychloride and phosphorus pentachloride to make 2-chloro-4-carboethoxy-6-methoxyquiniline (37.1.1.30). Reducing this with hydrogen using a palladium catalyst gives ethyl ester of 6-methoxyquinolinic acid (37.1.1.27).



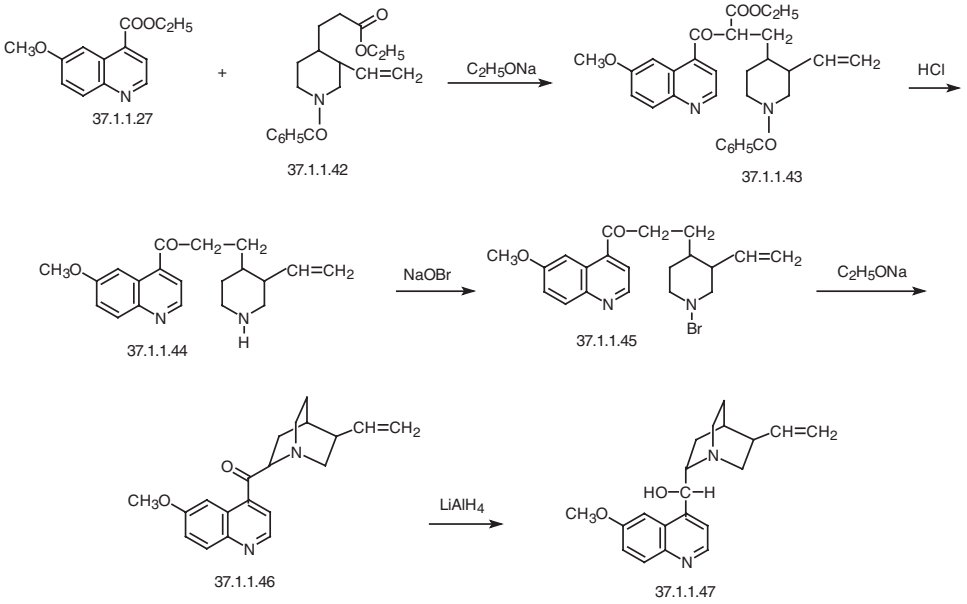
Synthesis of *N*-benzoylhomomeroquinene (37.1.1.42) is carried out using 7-oxyisoquinoline (37.1.1.32), which is made by reacting of aminoacetal with *m*-hydroxybenzaldehyde with isolation of the intermediate imine (37.1.1.31), which then cyclizes in the presence of sulfuric acid to the starting substance—7-oxyisoquinoline (37.1.1.32). The resulting 7-oxyisoquinoline is aminomethoxided with a mixture of formaldehyde and piperidine to make 7-oxy-8-piperidinomethylisoquinoline (37.1.1.33). Reducing this with hydrogen using a palladium catalyst removes the piperidine fragment, giving 7-oxy-8-methylisoquinoline

(37.1.1.34). This is again reduced with hydrogen in order to hydrogenate the pyridine fragment, except this time a palladium oxide catalyst is used. This forms 7-oxy-8-methyltetrahydroisoquinoline (37.1.1.35). *N*-Acylating the resulting compound with acetic anhydride and then hydrogenating it with hydrogen using a platinum catalyst gives a mixture of stereoisomeric *N*-acetyl-7-oxy-8-methyldecahydroisoquinolines, from which the *cis*-isomer (37.1.1.36) is isolated. It is oxidized using chromium(VI) oxide to *N*-acetyl-7-keto-8-methyldecahydroisoquinoline (37.1.1.37). Reacting this with ethyl nitrite in the presence of sodium ethoxide cleaves up the methylcyclohexanone fragment, giving *N*-acetyl-10-oxyminodihydrohomomeroquinene (37.1.1.38), which is then reduced in the presence of a platinum catalyst to the amine (37.1.1.39). This undergoes exhaustive methylation using methyl iodide to make a quaternary salt (37.1.1.40), which is then cleaved on heating in concentrated alkali, giving racemic homomeroquinene (37.1.1.41). Successive esterification and subsequent benzoylation of the product gives the ethyl ester of *N*-benzoylhomomeroquinene (37.1.1.42).



On the next stage, the ethyl ester of *N*-benzoylhomomeroquinene (37.1.1.42) is condensed with the ethyl ester of 6-methoxyquinolinic acid (37.1.1.27) in the presence of sodium ethoxide to make a derivative of quinotoxin (37.1.1.43). Boiling this in hydrochloric acid results in hydrolysis of the carbethoxy and benzoyl groups, and simultaneous decarboxylation gives the compound (37.1.1.44). Treating this with sodium hypobromite makes an

N-bromo derivative (37.1.1.45), which is reacted with sodium ethoxide realizing the key moment of the synthesis—the transformation of the piperidine derivative to a quinuclidine derivative (37.1.1.46). Reducing the keto group in this molecule with lithium aluminum hydride gives the desired quinine (37.1.1.47) [17–22].



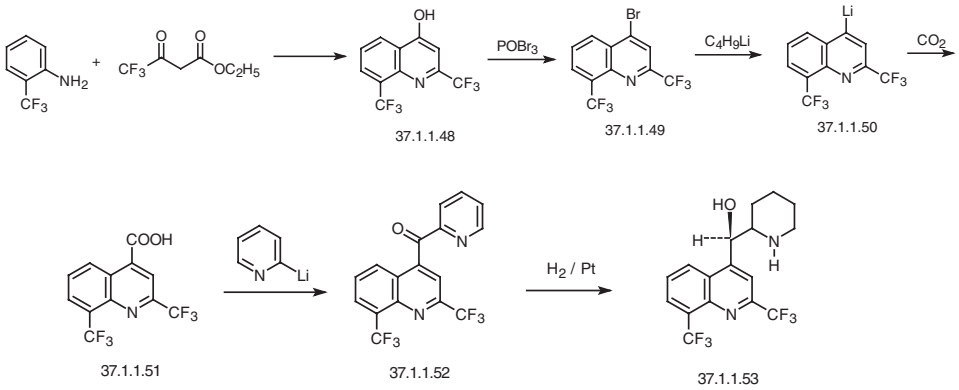
In terms of its type of action, quinine is an antimalarial drug similar to chloroquine, although it is inferior in its activity.

Like chloroquine, quinine binds with plasmodium DNA, thus interfering in the synthesis of nucleic acids and preventing its replication and transcription. Quinine also suppresses a large portion of the enzymatic system and therefore it is characterized as a general protoplasmid toxin. This fact agrees well with the action of quinine on membranes, its local anesthetizing and its cardiodepressive effects.

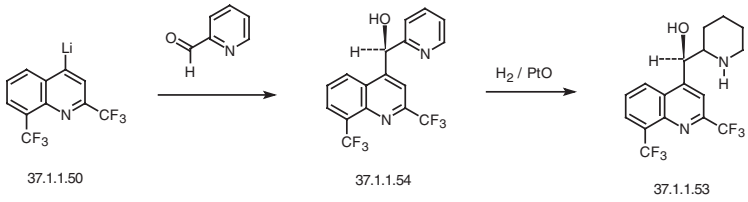
Upon oral administration, quinine effectively acts in combination with pyrimethamine, sulfadiazine, and/or tetracycline for treating uncomplicated incidents of chloroquine-resistant forms of *P. falciparum*. Because of the many associated side effects, its use is extremely limited. Currently, the only indication for use is for forms of malaria that are resistant to other synthetic drugs. Synonyms of this drug are bronchopulmin, nicopriv, quinnam, and others.

Mefloquine: Mefloquine, D,L-erythro-α-2-piperidyl-2,8-*bis*-(trifluoromethyl)-4-quinolinmethanol (37.1.1.53), is made in various ways from 2-trifluoromethylaniline. According to the first method, heterocyclization of the reaction product 2-trifluoromethylaniline with trifluoroacetoacetic ester gives 2,8-*bis*-(trifluoromethyl)-4-hydroxyquinoline (37.1.1.48). Reacting the product with phosphorus tribromide replaces the hydroxyl group in the fourth position of the quinoline ring with a bromine atom, giving 2,8-*bis*-(trifluoromethyl)-4-bromoquinoline

(37.1.1.49). Reaction of the last with butyllithium gives a organolithium derivative—2,8-*bis*-(trifluoromethyl)-4-lithiumquinoline (37.1.1.50). Reacting this with carbon dioxide makes 2,8-*bis*-(trifluoromethyl)-4-quinolincarboxylic acid (37.1.1.51). Interaction of the resulting acid with 2-lithiumpyridine gives the ketone (37.1.1.52). Reducing both the keto group and the pyridine ring with hydrogen using a platinum catalyst gives the desired mefloquine [23].

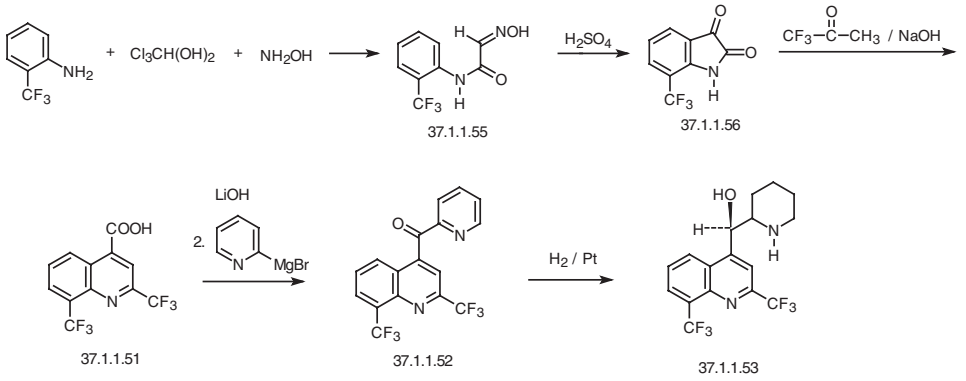


The second way of making mefloquine is from 2,8-*bis*-(trifluoromethyl)-4-lithiumquiniline described above (37.1.1.50), which is reacted with 2-formylpyridine to make α-2-pyridyl-2,8-*bis*-(trifluoromethyl)-4-methanolquinoline (37.1.1.54). The pyridiyl group in this compound is also reduced as described above, resulting in the formation of the desired mefloquine [24].



Finally, the third way of making mefloquine also begins with 2-trifluoromethylaniline, except in this case it is reacted with chloralhydrate and hydroxylamine to make isonitrosoacetyl(2-trifluoromethyl)anilide (37.1.1.55), which when heated in the presence of sulfuric acid cyclizes to 7-trifluoromethylisatine (37.1.1.56) (Sandmeyer reaction). The resulting 7-trifluoromethylisatine (37.1.1.56) is then reacted with 1,1,1-trifluoroacetone in the presence of a base in a Friedlaender reaction conditions to make 2,8-*bis*-(trifluoromethyl)-4-quinoline carboxylic acid described above (37.1.1.51). Reacting this with lithium hydroxide turns it into a lithium salt, which is reacted with a Grignard reagent, 2-magnesiumbromopyridine (made from 2-bromopyridine and magnesium). The resulting

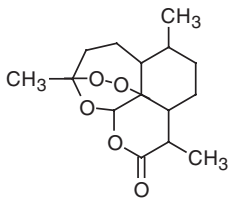
ketone (37.1.1.52) is again reduced with a platinum catalyst to make the desired mefloquine [25].



Mefloquine is an analog of quinine, and it differs from it in that the side chain at C_4 of the quinoline ring contains a piperidine fragment instead of a quinuclidine fragment, and positions C_2 and C_8 are substituted with trifluoromethyl groups. This antimalarial drug was created to treat and prevent chloroquine resistance of malarial forms caused by *P. falciparum.* It is not clinically active against exoerythrocyte forms of *P. vivax,* although it is extremely active against blood schizontosides *P. vivax* and *P. falciparum*. It is intended to be used for treating weak and moderate forms of malaria caused by the indicated plasmodia. A synonym of this drug is lariam.

Quinghaosu (Artemisinine)*:* Quinghaosu, octahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano-(4,3-di)-1,2-benzodioxepin-10-(3*H*)-one (37.1.1.57), is isolated from the plant *Artemisia annua* [26].

It also has been made synthetically [27].



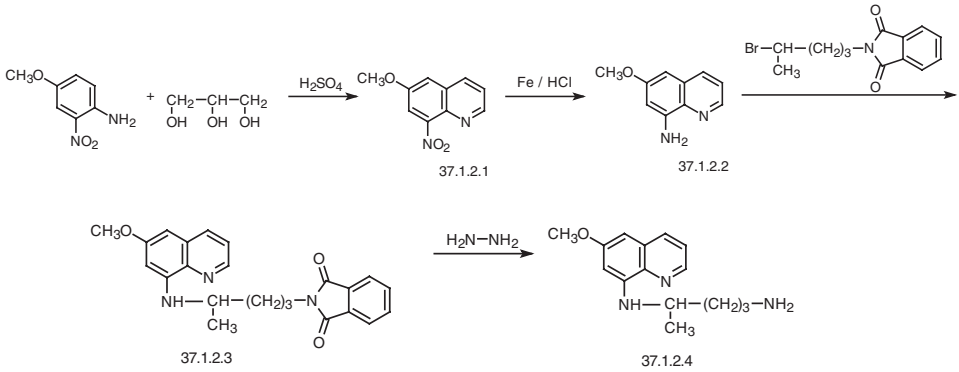
37.1.1.57

Quinghaosu is the latest fundamental discovery in this area and is a heterocyclic compound that does not have a nitrogen atom in its structure. It is taken from a Chinese folk medicine. It is isolated from the plant *Artemisia annua.* It is amazing that this compound, which is completely different than the other drugs described in this chapter in terms of structure, exhibits the exact same therapeutic effect. The main interest in quinoghaosu is based on the fact that it is active against resistant forms of malaria caused by *P. falciparum*, and even its cerebral forms. Synonyms of this drug are artemisine, artemisinin, and others.

37.1.2 Drugs effective against the hepatic (exoerythrocyte) stage of plasmodia infection

8-Aminoquinolines

Primaquine: Primaquine, 8-[(4-amino-1-methylbutyryl)amino]-6-methoxyquinoline (37.1.2.4), is made from 6-methoxy-8-nitroquinoline (37.1.2.1), which is synthesized in a Skraup reaction from 4-methoxy-2-nitroaniline and glycerol in the presence of sulfuric acid. The nitro group in this compound is reduced to make 6-methoxy-8-aminoquinoline (37.1.2.2). Alkylating the amino group with 4-bromo-1-phthalimidopentane gives 8-[(4-phthalimido-1-methylbutyryl)amino]-6-methoxyquinoline (37.1.2.3), the hydrazinolysis of which removes the phthalimide protection, giving primaquine [28,29].



Moving the side chain from the fourth position of the quinoline ring to the eighth position completely changes the compound's spectrum of activity. Unlike the 4-substituted aminoquinolines, primaquine has practically no effect on erythrocyte forms of the malaria parasite. Its activity is limited to tissue forms of the parasite in mammals and in the mosquitoes themselves. This makes primaquine an especially valuable drug, allowing radical recovery and simultaneous prevention, which is usually not achieved by using erythrocyte drugs. The place of action of primaquine is the mitochondria of the malarial parasite. It seems likely that primaquine interferes in the process of electron transfer, causing damage to mitochondrial enzymatic systems. This is expressed in the swelling and vacuolization of the parasite's mitochondria. Host mitochondria are not affected.

Primaquine is the most effective and most toxic drug from the whole series of known 8-aminoquinolines. It is generally used for treating exoerythrocyte forms of malaria caused by *P. vivax* and *P. ovale*. It also acts on the sexual forms of the plasmodia, which die in the human body upon using this drug.

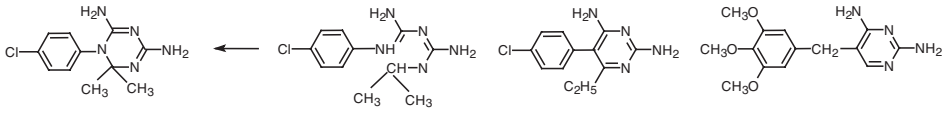
Primaquine is used for treating and preventing late relapses of 3- and 4-day malaria as well as tropic malaria. Synonyms of this drug are avlon and others.

37.1.3 Drugs effective against hepatic and erythrocyte forms of plasmodia infection

Biguanides and diaminopyrimidines turned out to be active compounds against both exoerythrocyte and erythrocyte forms of plasmodia. Chlorguanidine (37.1.2.3) was introduced

into medical practice as an antimalarial drug as a result of work on a large series of guanidine derivatives. It is presumed that this compound transforms into an active dihydrotriazine compound in the body.

A while later, pyrimethamine (33.1.60) was suggested as a result of intensive research of antimetabolites of folic acid. Trimethoprim (33.1.51) is the result of later research. The structural similarity of these drugs with the pteridine fragment of folic acid undoubtedly determines their affinity with binding regions of dihydrofolate reductase.



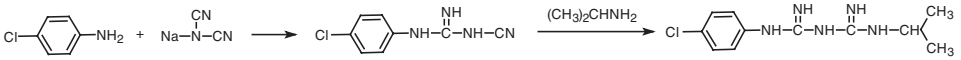
dihydrotriazine metabolite of chlorouanid | 37.1.3.2 chloroguanid | 33.1.60 pyrimethamine | 33.1.51 trimetoprim

All of these compounds are inhibitors of dihydrofolate reductase in bacteria, plasmodia, and humans. Fortunately, they have a significantly high affinity for bacterial and protozoan dihydrofolate reductases. Pyrimethamine, for example, inhibits parasite dihydrofolate reductase at levels several hundred times lower than required to inhibit dihydrofolate reductase in humans. This is the basis of their selective toxicity. The selective toxicity can be increased upon supplying additional folic acid to the host organism, which the parasite cannot use. In fact, diaminopyrimidines (trimetoprim, pyrimethamine) were initially suggested as medicinal and preventative drugs against malarial infections. It was shown that all powerful inhibitors of dihydrofolate reductase can remove the malarial parasite with relatively minor consequences in the host.

As was already stated, biguanides and diaminopyrimidines are active against exoerythrocyte and erythrocyte forms for plasmodia. Each of these drugs can be used individually for prevention; however, the maximal effect is achieved when used in combination with sulfonamides.

It has been shown that a few sulfones and sulfonamides may be of interest as drugs for treating malaria. Experimental research uncovered the pronounced synergism between sulfonamides and chloroguanide and pyrimethamine.

Chloroguanide: Chloroguanide, N^1-(4-chlorophenyl)-N^5-isopropylbiguanide (37.1.3.2), is made from 4-chloroaniline and sodium dicyanoamide, the interaction of which results in the formation of (4-chlorophenyl)dicyanodiamide (37.1.3.1). Reacting this with isopropylamine gives the desired chloroguanide [30–32].

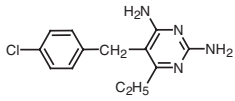


37.1.3.1 37.1.3.2

In *in vitro* conditions, chloroguanide is not active, although in the organism it transforms to an active dihydrotriazine compound.

Chloroguanide is active with respect to exoerythrocyte and erythrocyte forms of plasmodia. It is most beneficial for suppressive therapy. It is used for preventing malaria, and it should be started 2 weeks before entering a malarial zone and should be taken for 8 weeks. Synonyms of this drug are biguanide, bigunal, paludrine, proguanil, and others.

Pyrimethamine: Pyrimethamine, 2,4-diamino-5-(4′-chlorophenyl)-6-ethylpyrimidine (33.1.60), is described in Chapter 33.



33.1.60

This powerful inhibitor of dihydrofolate reductase is used for preventing and treating malaria caused by plasmodia *P. vivax, P. malariae, P. ovale*, including *P. falciparum.*

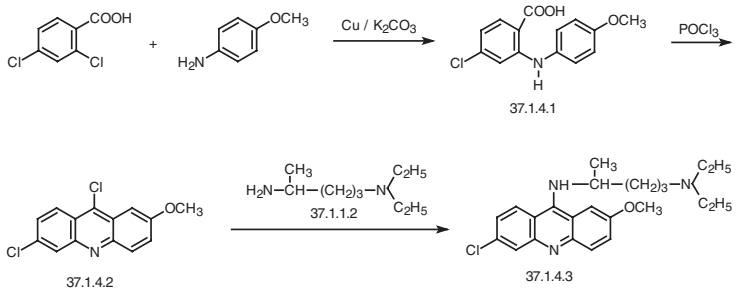
Pyrimethamine, an antagonist of folic acid, exhibits antimicrobial action against causative agents of malaria and simultaneously possesses sporontocide action. It is also effective with respect to the causative agent of toxoplasmosis. It is used for preventing malaria and treating toxoplasmosis. It can only be used for preventative measures; however, because resistance develops quickly and because of the fact that the maximal effect is achieved by using it in combination with sulfadoxine, a combined drug which is prescribed under the name fansidar, which contains a pyrimethamine–sulfadoxine ratio of 1:20.

A combination of pyrimethamine, sulfonamide, and quinine is the drug of choice for acute attacks of malaria and its chloroquine-resistant forms.

Pyrimethamine in combination with sulfadiazine or trisulfapyrimidine is the drug of choice for toxoplasmosis. A synonym of this combined drug is daraprim.

Other antimalarial drugs: The malaria parasite is sensitive to many different groups of drugs, and different combinations of drugs are used depending on each specific case.

Quinacrine: Quinacrine, 6-chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine (37.1.4.3), is synthesized from 6,9-dichloro-2-methoxyacridine (37.1.4.2) and aforementioned 4-diethylamino-1-methylbutylamine (37.1.1.2). The 6,9-dichloro-2-methoxyacridine (37.1.4.2) necessary for the synthesis is made in two stages. The initial reaction of 2,4-dichlorobenzoic acid and *p*-anizidine in the presence of copper dust and potassium carbonate gives 2-(4-methoxyanilino)-4-chlorobenzoic acid (37.1.4.1), which upon reaction with phosphorus oxychloride turns into the necessary 6,9-dichloro-2-methoxyacridine (37.1.4.2) [33–38].



37.1.4.1

37.1.4.2

37.1.1.2

37.1.4.3

Quinacrine is a derivative of acridine that is chemically and clinically very similar to 4-aminoquinolines. It was the primary drug for prevention and therapy of malaria during World War II. Today it is rarely used for treating malaria, although it is used to treat amebiasis. Synonyms of this drug are mepacrine, atabrine, acrisuxin, and others.

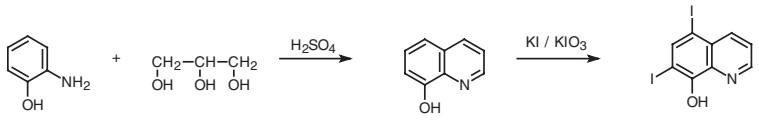
In treating resistant forms of malaria, tetracycline is also used in combination with pyrimethamine, sulfonamides, sulfones, and dapsone, which is widely used for treating leprosy (as a rule, in combination with pyrimethamine).

37.2 DRUGS FOR TREATING AMEBIASIS

Amebiasis is an infection of the body by the protozoa *Entamoeba histolytica,* which most often affects the large intestine, although they can also affect the lungs, liver, brain, and other organs. This disease can attack the gastrointestinal tract without any clinical symptoms, with moderately expressed clinical symptoms (diarrhea, cramps, meteorism), as well as with symptoms of acute ameba dysentery, which is accompanied by bloody diarrhea, vomiting, fever, and dehydration. The presence of the protozoan microorganisms *E. histolytica* in other organs can cause liver death, ameba hepatitis, and lung abscess. Cases of heart damage (causing pericarditis) and brain damage (leading to brain abscess) have been described.

The microorganisms are passed from one person to another by way of amebic cysts, a form of ameba existence in which the protozoa have maximum resistivity to external influences The cysts are not damaged by gastric juices, and therefore, they pass into the intestines where they can develop into trophozoites, which attack the mucous membranes of the intestines, are absorbed, and can penetrate further into other organs. *E. histolytica,* the cause of amebiasis, has a relatively complex life cycle in the host organism. The secreted cysts (in an unchanged form) are the cause of new infections. There are many drugs used for treating amebiasis. However, not one of them can be considered completely effective since this microorganism is very resistant. Drugs used for treating amebiasis can be characterized according to their primary location of action. For example, a few drugs (iodoquinol, diloxanide, paromomycin) are only active against amebas that are localized in the lumen of the intestine and other tissues, and they are used for amebic dysentery and hepatic abscesses. The third group (metronidazole, tinidazole) is active against amebas localized both inside and outside the intestine.

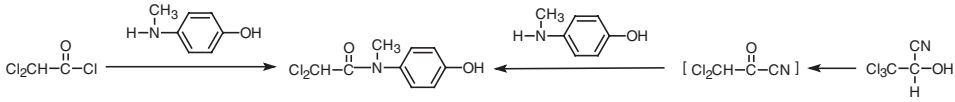
Iodoquinol: Iodoquinol, 5,7-diiodo-8-quinolinol (37.2.2), is made by iodination of 8-oxyquinoline (37.2.1) using a mixture of potassium iodide/potassium iodate. The initial 8-hydroxyquinolin (37.2.1) is made from 2-aminophenol and glycerol in the presence of sulfuric acid and nitrobenzene (Skraup synthesis) [39,40].



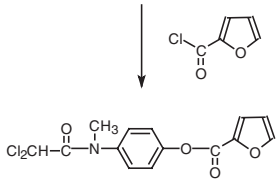
37.2.1 37.2.2

Iodoquinol is an amebocide used against *E. histolytica*, and it is active against both cysts and trophozoites that are localized in the lumen of the intestine. It is considered the drug of choice for treating asymptomatic or moderate forms of amebiasis. The mechanism of action is unknown. Iodoquinol is used for diseases caused by moderate intestinal amebiasis. Synonyms of this drug are diquinol, iodoxin, diiodoquin, amebaquin, and others.

Diloxanide: Diloxanide, 2,2-dichloro-*N*-(4-furoyloxyphenyl)-*N*-methylacetamide (37.2.4), is made by acylating 2,2-dichloro-*N*-(4-hydroxyphenyl)-*N*-methylacetamide (37.2.3) with -2-furoyl chloride. The 2,2-dichloro-*N*-(4-hydroxyphenyl)-*N*-methylacetiamide (37.2.3) is made by *N*-acylating 4-hydroxy-*N*-methylaniline with either dichloroacetyl chloride, or by an extremely original method of using chloral cyanohydrin [41–43].



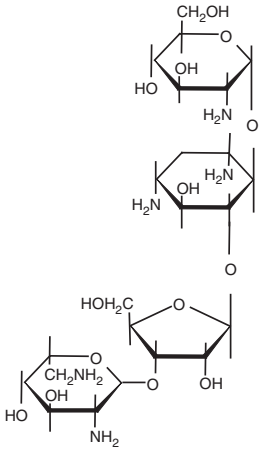
37.2.3



37.2.4

Diloxanide is also active against cysts and trophozoites localized in the lumen of the intestine, and it is used for treating the carrier *E. histolytica*, as well as for treating asymptomatic or moderate forms of amebiasis. In the transition stage to trophozoites, the drug is less active than iodoquinol. A synonym of this drug is furamide.

Paromomycin: Paromomycin (32.4.5) was described in Chapter 32. It is recommended for treatment of acute and chronic forms of intestinal amobiasis, as well as for treating intestinal bacteria *Salmonella* and *Shigella*.

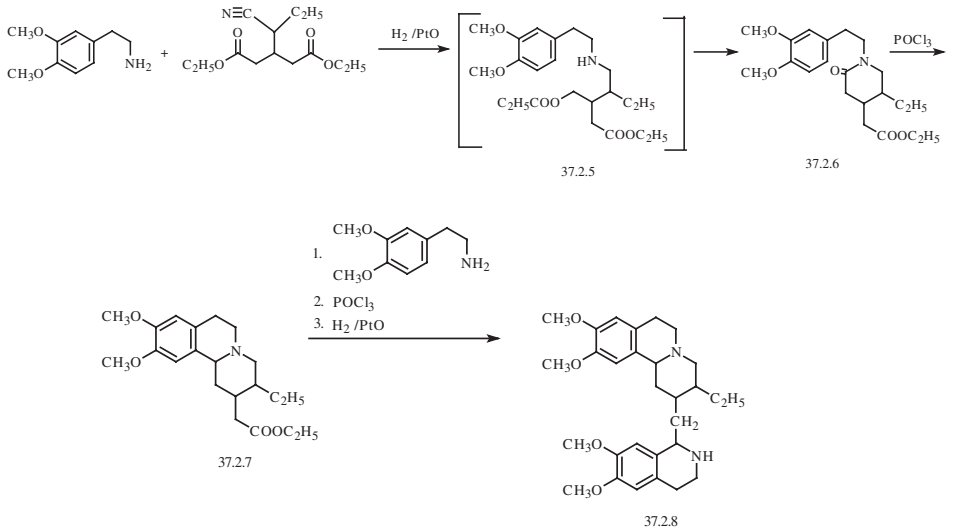


32.4.5

Synonyms of this drug are aminosidine, catenulin, crestomycin, hydroxymycin, monomycin, zygomycyn, and others.

Emetine: Emetine, 3-ethyl-2,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2-(1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolylmethyl)-1*H*-benzo[a]quinolizine (37.2.8), is a natural compound. Traditionally, the alkaloid emetine was extracted from the ipecacuanha plant (*Brazilian root*) and used as the primary drug for treating amebiasis, leishaniasis, and dysentery. Various ways of synthesizing emetine have been suggested, all of which begin with homoveratrylamine – 2-(3,4-dimethoxyphenyl)ethylamine [44–48].

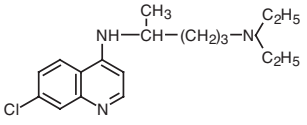
Upon a combined catalytic hydrogenation of the ethyl ester of β–(α'-cyano)propylglutaric acid and homoveratrilamine, a reductive amination reaction takes place, in which ammonia is released and an intermediate amine (37.2.5) is formed, which under the reaction conditions undergoes intramolecular cyclization to give 1-[2-(3,4-dimethoxyphenyl)-ethyl]-4-carbethoxymethyl-6-ethylpiperidone-2 (37.2.6). Reacting the resulting lactam with phosphorus oxychloride causes heterocyclization into the derivative of benzoquinolizine (37.2.7). Subsequent reaction of the product with homoveratrylamine makes the corresponding amide. Upon reaction with phosphorus oxychloride, this compound cyclizes to an isoquinoline derivative, and the pyridine ring is then hydrogenated by hydrogen to a racemic mixture of products, from which the desired emetine is isolated.



This drug has a direct amebicidal effect against trophozoites *E. histolytica* in tissues, and it is not active against cysts in either the lumen or intestinal walls, or in other organs. The mechanism of action of emetine consists of the blockage of protein synthesis in eukaryotic (but not in prokaryotic) cells. It inhibits the process of polypeptide chain formation. Protein synthesis is inhibited in parasite and mammalian cells, but not in bacteria.

Emetine is currently only used as a drug for treating amebiasis in cases of resistance to other drugs. Synonyms of this drug are ipecin and methylcefalin.

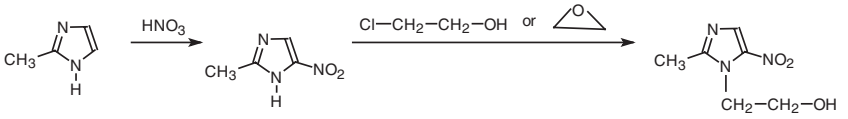
Chloroquine: Chloroquine (37.1.1.3), its synthesis, and its properties are described in Section 37.1 of this chapter.



37.1.1.3

Chloroquine is also widely used for treating amebiasis.

Metronidazole: Metronidazole, 2-methyl-5-nitroimidazol-1-ethanol (37.2.10), is made by nitrating 2-methylimidazole to make 2-methyl-5-nitroimidazole (37.2.9), which is then reacted with 2-chloroethanol or ethylenoxide, which is easily transformed to the desired metronidazole [49,50].



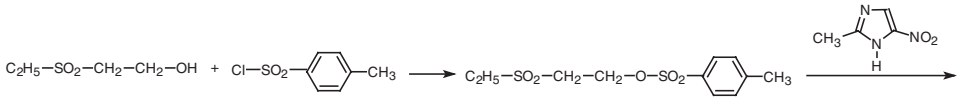
37.2.9 37.2.10

Metronidazole is a synthetic antiprotozoan drug that was first introduced into medical practice in 1960. It suppresses the development of trichmonad, giardia, ameba, lambliosis, bacteriods, fusobacteria, and a few other diseases. It is effective with respect to obligate anaerobic bacteria. It is not active with respect to aerobic microorganisms. Metronidazole easily diffuses through the membrane of both aerobic and anaerobic bacteria. Further activation and effects of the drug require it to pass through certain reductive processes, which exist in anaerobic organisms and a few bacteria in anaerobic conditions. The drug's nitro group is reduced by proteins with a low redox potential. This reaction lowers the concentration of unchanged metronidazole, and makes a gradient that allows a large amount of the drug to pass into the bacteria. The somewhat unstable and unknown intermediate product of the reduction of metronidazole reacts with bacterial DNA, causing the protozoan parasite to die. The mechanism of resistance to metronidazole is not completely understood. Metronidazole exhibits high bactericidal activity with respect to most anaerobes (*Protococcus, Peptostreptococcus, Clostridium Bacteroides* and *Fusobacterium*), as well as a few non-spore forming Gram-positive organisms (*Actinomyces, Eubacterium, Bifidobacterium, Propionibacterium*). It is not active with respect to aerobic infections. It is highly active against anaerobic protozoan infections, including *Trichomonas vaginalis, E. histolytica, Giardia lamblia* and *Balantidium coli*.

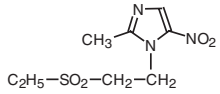
Metronidazole is the drug of choice for amebiases, vaginal trichomonasis and trichlomonadic urethritis in men, lambliosis, amebic dysentery, and anaerobic infections caused by microorganisms that are sensitive to the drug. Synonyms of this drug are flagyl, protostat, trichopol, and vagimid.

Tinidazole: Tinidazole, 1-2-(ethylsulfonyl)ethyl-2-methyl-5-nitroimidazole (37.2.12), is also made from 2-methyl-5-nitroimidazole (37.2.9), which upon being reacted with 2-ethoxysulfonyl-*p*-toluenesulfonate (37.2.11) transformed into the desired tinidazole.

The 2-ethoxysulfonyl-*p*-toluenesulfonate (37.2.11) necessary for this reaction is in turn made by tosylation of 2-ethylsulfonyl ethanol using *p*-toluenesulfonyl chloride [51–53].



37.2.11



37.2.12

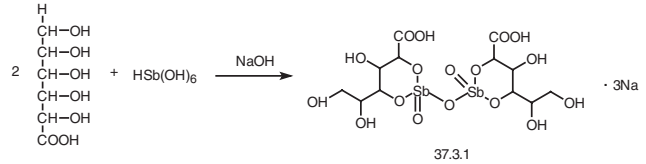
In terms of mechanism of action and indications for use, tinidazole is very similar to metronidazole. It is also effective against amebas, trichomonad, lambliosis, acute ulcerative gingivitis, and post-operational anaerobic infections. It is used for treating practically all protozoan infections. Synonyms of this drug are tinaport, tinimed, and tinisan.

37.3 DRUGS FOR TREATING LEISHMANIASIS

A group of trypanosomic protozoan parasites of the family *Leishmania* cause a number of diseases known as leishmaniasis. This disease is mainly found in the tropics and subtropics, and it is transmitted by specific blood-sucking insects. There is cutaneous leishmaniasis (causative agent—*Leishmania tropica)*, and visceral leishmaniasis (causative agent *Leishmania donovani*). Acriquin and monomicin are used for treating local skin leishmaniasis.

A pentavalent antimony derivative—sodium stibogluconate is widely used to treat visceral leishmaniasis (kala azar). It should be noted that organic salts of trivalent antimony (antiomalin, the lithium salt of antimonylmalic acid; antimosan, a derivative of arylsulfonic acid; stibamin, a derivative of *p*-aminophenylstylbonic acid, and others) have long been the traditional and effective drugs for treating leishmaniasis. It was recently shown that pentavalent antimony salts were more convenient to use. It is believed, however, that pentavalent antimony is reduced to trivalent antimony in the body. Amfotericin B, metronidazole, and pentamidin are also used to treat leishmaniasis.

Sodium stibogluconate:Sodium stibogluconate, D-gluconic acid, 2,4:2′,4′-*O*-[oxybis (oxidostibylidyne)] bis-, trisodium salt, (37.3.1), is made by reacting gluconic acid with freshly precipitated antimony acid and the neutralization of the resulting mixture using sodium hydroxide, after which the desired product—sodium stibiogluconate—is precipitated by alcohol [54].



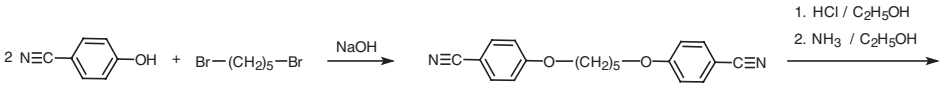
37.3.1

Sodium stibiogluconate is the drug of choice for treating leishmaniasis. It is believed that it inhibits the glycotic enzyme phosphofructokinase (which plays a role in the Kreb's cycle) in parasites of the family *Leishmania*. As a result, the parasitic microorganisms cease to produce the energy necessary to stay alive, and die. Synonyms of this drug are solucurmin and others.

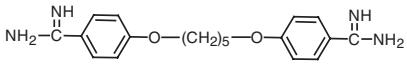
37.4 DRUGS FOR TREATING TRYPANOSOMIASIS

Trypanosomiasis is a disease that is better known by the name sleeping sickness. It is expressed as chronic sleepiness, headaches, impaired motor coordination, apathy, loss of intellect, and when not treated, death. In Africa, trypanosomiasis is transmitted by the tsetse fly that has been infected with trypanosomiasis (*Trypanosoma gambience* and *Trypanosoma rhodesience*). In South America, this disease is also transmitted by blood-sucking insects. There is a group of diamidinic compounds that are active against trypanosoma. The most widely used compound for this purpose is pentamidine. Nifutrifox and an older drug, suramine, also are used quite often.

Pentamidine: Pentamidine, 4-4′-(pentamethylendioxy)dibenzamidine (37.4.2), is made by reacting 4-hydroxybenzonitrile with 1,5-dibromopentane in the presence of sodium hydroxide to make 1,5-*bis*-(4-cyanophenoxy)pentane (37.4.1). Subsequent reaction of this with an ethanol solution of hydrogen chloride with the intermediate formation of an iminoester, and then with an ethanol solution of ammonia gives the desired pentamidine [55–57].



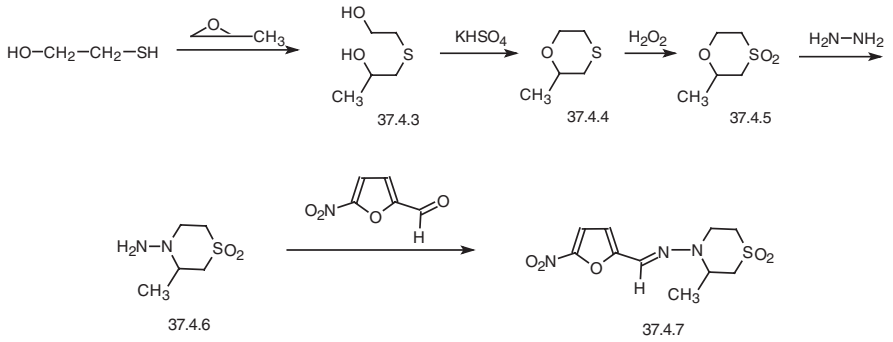
37.4.1



37.4.2

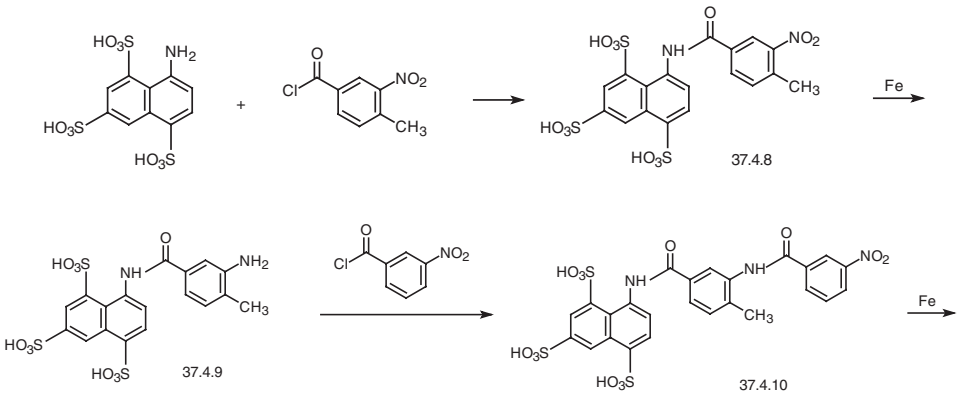
This drug destroys microorganisms that cause trypanosomiasis and leishmaniasis. It is believed that pentamidine can act either by inhibiting the process of oxidative phosphorylation, or by inhibiting the process of glucose metabolism, or by inhibiting the activity of dihydrofolate reductase, or by reacting with DNA or nucleotides of the parasite. Synonyms of this drug are lomidine, nebupent, and others.

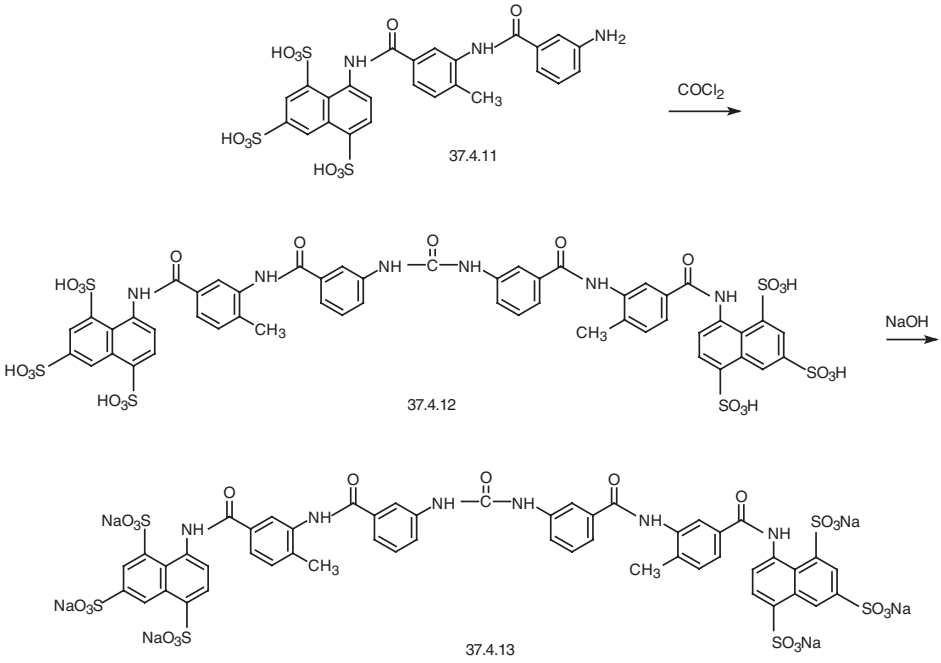
Nifurtimox: Nifurtimox, 1,1-dioxide 4-[(5-nitrofuryliden)amino]-3-methylthiomorpholine (37.4.7), is made by the following scheme. Interaction of 2-mercaptoethanol with propylene oxide in the presence of potassium hydroxide gives (2-hydroxyethyl)-(2-hydroxypropylsulfide) (37.4.3), which undergoes intramolecular dehydration using potassium bisulfate to make 2-methyl-1,4-oxithiane (37.4.4). Oxidation of this using hydrogen peroxide gives 2-methyl-1,4-oxithian-4,4-dioxide (37.4.5), which when reacted with hydrazine transforms to 4-amino-3-methyltetrahydro-1,4-thiazin-1,1-dioxide (37.4.6). Reacting this with 5-nitrofurfurol gives the corresponding hydrazone—the desired nifurtimox [58,59].



Nifurtimox is the drug of choice for acute forms of the South American form of trypanosomiasis (Chagas disease). It is believed that the drug acts by forming a reactive radical (superoxide, hydroperoxide, hydroxyl) in the parasite, which leads to a loss of catalysis and glutathione peroxidase, and an increase in sensitivity to hydrogen peroxide, which alters its normal vital activities. Synonyms of this drug are lampit and others.

Suramin: Suramin, a hexasodium salt of [8,8' carbonyl-*bis*-[imino-3,1-phenylencarbonylimino(4-methyl-3,1-phenylen)carbonylimino]]-*bis*-1,3,5-naphthalintrisulfonic acid (37.4.13), can be made by reacting 1-aminonaphthalene-3,6,8-trisulfonic acid with 4-methyl-3-nitrobenzoyl chloride to make a nitrobenzoic derivative (37.4.8). The nitro group in this compound is reduced by activated iron to an amino derivative (37.4.9), which is acylated by *m*-nitrobenzoylchloride to make a new nitroderivative, *m*-nitrobenzoyl-(4-methyl-3-aminobenzoyl)-1-aminonaphthalene-3,6,8-trisulfonic acid (37.4.10). This is once again reduced to the amine (37.4.11) in the same manner. Reacting the resulting product with phosgene makes [8,8′-carbonyl-*bis*-[imino-3,1-phenylencarbonylimino(4-methyl-3,1-phenylen]-carbonylimino]-*bis*-1,3,5-naphthalenetrisulfonic acid (37.4.12), which upon being treated with sodium hydroxide gives suramin [60–63].





Suramin is a very old drug that was made in the 1920s, while researching toxins and dyes (Trypan Red and Blue, Afridol Purple) as drugs with trypanosocidal activity. The exact mechanism of action of this drug is not known. However, it is believed that suramin is absorbed in trypanosomes, where it is possible that it reversibly binds with proteins. Currently, it is rarely used for treating early forms of sleeping sickness. Synonyms of this drug are antripol, natrimin, germanin, and others.

37.5 DRUGS FOR TREATING OTHER PROTOZOAN INFECTIONS

Lambliosis, which is treated with quinicrine, is also considered a protozoan infection. In some cases, metronidazole and furazolidone are used for lambliosis. Metronidazole and tinidazole are used for treating trypchomonadiasis, another communicable protozoan infection. Sulfanilamides and chloridin are used for treating toxoplasmosis.

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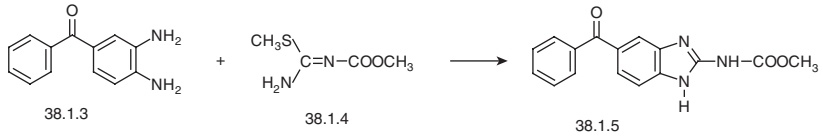
– 38 –

Antihelmintic Drugs

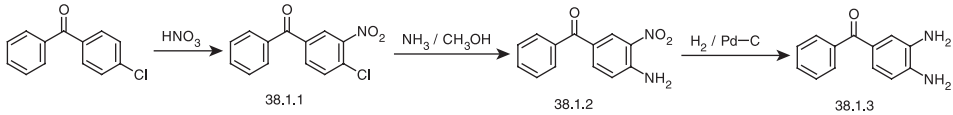
Helminth infections are a major problem in the lives of many millions of people on the earth, especially in the subtropics. Depending on the type and localization of the causative agent of helminthosis, it can run asymptomatic, or it can be the cause of anemia, or damaged blood vessels, liver, or eyes. There is intestinal and nonintestinal helminthosis. The causative agents are classified as roundworms (nematodes) and flatworms. These groups include tapeworms (cestoda) and fluke worms (trematoda). Most nematode infections are localized in the intestinal tract, although a few of them can pass into other organs, including the heart, liver, lungs, muscles, and so on, from which removal is significantly harder. Cestode infections are usually localized in the gastrointestinal tract, but there have been cases of them passing into the circulatory system. Trematodes cause chronic infection, called schistosomiasis, in which the blood vessels are attacked and various organ structures (liver, intestines, urinary tract) are damaged.

Antihelmintic drugs are intended for exterminating helminthes and removing them from the host organism. Examples include albendazole, diethylcarbamazine, mebendazole, nicolsamide (against tapeworms), suramin, and thiabendazole. Many members of the piperazine family are successful antihelmintics. Natural antihelmintics include black walnut, wormwood (*Artemisia absynthium*), clove (*Syzygium aromaticum*), tansy tea (*Tanacetum vulgare*), and the male fern (*Dryopteris filix-mas*). They are subdivided into drugs that damage neuromuscular coordination of helminthes, drugs that have an effect on the energetic processes of helminthes (in particular on the metabolism of glucose), and drugs that affect the enzymatic system, laying of eggs by helminthes, and so on. Most antihelmintic drugs are intended to have an effect on certain helminthes. Historically, halogenated carbohydrates, naphthoquinones, phenothiazine, a number of natural compounds isolated from leaves of sagebrush and ferns, ether oils (derivatives of pinene), alkaloids (arecoline group), alkaloids of the emetine group, and many others were used to treat helminthosis. However, the currently essential drugs for treating helminthosis are those described below.

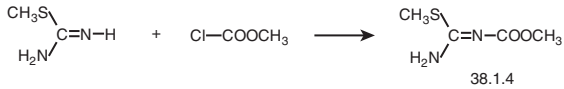
Mebendazole: Mebendazole, methyl-[5-(benzoyl)-1*H*-benzoimidazol-2-yl]carbamate (38.1.5), is a derivative of benzoimidazole, which is made by reacting 3,4-diaminobenzophenone (38.1.3) with *N*-methoxycarbonyl-*S*-methylthiourea (38.1.4) [1,2].



The necessary reagents are made in the following manner. Nitration of 4-chlorobenzophenone with nitric acid at a temperature lower than 5°C gives 4-chloro-3-nitrobenzophenone (38.1.1), in which the chlorine atom is replaced with an amino group by heating it to 125°C in a solution of ammonia in methanol to make 4-amino-3-nitrobenzophenone (38.1.2). Reducing the nitro groups in this compound with hydrogen using a palladium on carbon catalyst gives 3,4-diaminobenzophenone (38.1.3).

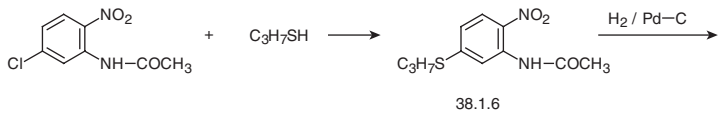


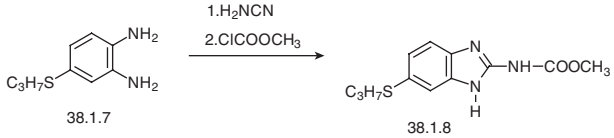
The second reagent, *N*-methoxycarbonyl-*S*-methylthiourea (38.1.4), is made by reacting methyl chloroformate with *S*-methylthiourea.



The exact mechanism of action of mebendazole is not conclusively known, but it seems likely that it causes irreversible inhibition of the uptake and utilization of glucose by the parasite and stops the formation of ATP, thus causing glycogen depletion and subsequent death of the parasite. Mebendazole is used for treatment of enterobiasis, ascariasis, ankylostomiasis, strongyloidiasis, trichocephaliasis, trichuriasis, and mixed helminthoses. It is used twice a day over the course of 3 days in doses of 100 mg, resulting in complete recovery in 90–100% of patients. Synonyms of this drug are vermox, mebutar, panfugan, and many others.

Albendazole: Albendazole, methyl-[5-(propylthio)-1*H*-benzoimidazol-2-yl]carbamate (38.1.18), is also made by the heterocyclization of a derivative of phenylenediamine to a derivative of benzimidazole. In order to do that, 3-chloro-6-nitroacetanylide is reacted with propylmercaptane to make 3-propylthio-6-nitroacetanylide (38.1.6). Reducing the nitro group in this compound with hydrogen using a palladium on carbon catalyst gives 4-(propylthio)-*o*-phenylenediamine (38.1.7). Reacting the resulting derivative of *o*-phenylenediamine with cyanamide and then with the methyl chloroformate gives the desired albendazole [3].

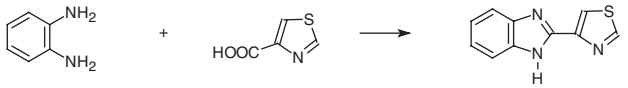




38.1.7 38.1.8

A derivative of benzimidazole, albendazole is a drug with a broad antihelmintic spectrum. It exhibits an antihelmintic effect against sensitive cestodes and nematodes by blocking the process of glucose uptake by the parasites, which is expressed in the depletion of glycogen reserves and subsequent reduction in the level of adenosintriphophate. As a result, the parasite stops moving and dies. It is used upon infection of *Acaris lumbricoides, Ancylostoma duodenale, Necator americanus, Enterobius vermicularis*, and *Trichuris trichiura*. Synonyms of this drug are SKF 62979 and others.

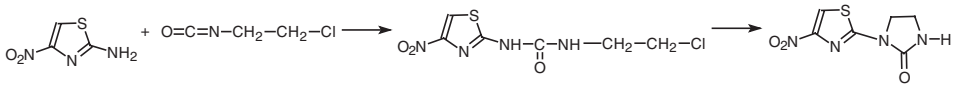
Thiabendazole: Thiabendazole, 2-(4′-thiazolyl)benzimidazole (38.1.9), is also made in the same manner—heterocyclization which occurs upon reacting *o*-phenylendiamine with 1,3-thiazol-4-carboxylic acid [4–6].



38.1.9

Thiabendazole is an antihelmintic drug with a broad spectrum of action. Although the details of its mechanism of action are not conclusively known, it seems likely that its action is mediated by the inhibition of a specific enzyme of helminthes—fumarate reductase. Thiabendazole is active with respect to most nematode infections, including *Angyostrongylus cantonesis, Strongyloides stercoralis, Trichinella spiralis, Toxocara canis, Toxocara cati, Ancylostoma caninum, A. braziliense6, A. duodenale, Dracunculus medinesis, Capillaria philippinesis,* as well as for treating *Acaris cantonesis* and *Shistosoma stercoralis*. Synonyms of this drug are mintezol, minzolum, and others.

Niridazole: Niridazole, 1-(5-nitro-2-thiazolyl)-2-imidazolidinone (38.1.11), is made by reacting 2-amino-5-nitrothiazol with 2-chloroethylisocyanate to make the disubstituted urea (38.1.10). Heating this compound results in an intramolecular N-alkylation reaction to form the desired imidazolidine derivative, niridazole [7–11].

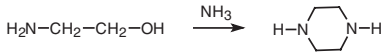


38.1.10 38.1.11

Niridazole exhibits schistosomicide and amebicidal action. The mechanism of action is not known. It seems likely that it is concentrated in the parasite organism, which causes inhibition of phosphorylase activation, which is expressed in the depletion of glycogen reserves.

It also may inhibit spermatogenesis of parasites by affecting the production of eggs. It is used for diseases caused by *Dracunculus meddinesis*, as well as *Shistosoma haematobium* and *Shistosoma mansoni*. It belongs to a group of tertiary drugs and is used only in the absence of the drug of choice. Synonyms of this drug are ambilhar and others.

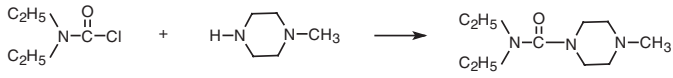
Piperazine: Piperazine (38.1.12) is a bulk product in organic synthesis. It is made from ethanolamine by heating it in ammonia at a temperature of 150–220°C and a pressure of 100–250atm. It is used as a drug in the form of a salt, and as a rule, in the form of adipinate [12,13].



38.1.12

Piperazine is an alternative drug and is used for treatment of various forms of nematodes, in particular for enterobiasis and ascariasis. It causes paralysis in the nematode by blocking acetylcholine transmission. This causes the parasite to detach from the mucous membrane, where it is removed from the body. Ascariasis requires treatment for 2 days, and enterobiasis, for 7 days. Synonyms of this drug are tasnon, uvilon, antepar, bexin, and many others.

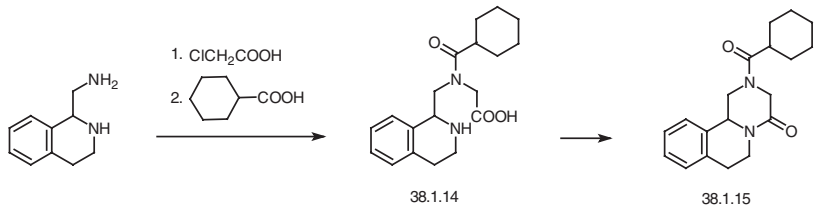
Diethylcarbamazine: Diethylcarbamazine, *N*, *N*-diethyl-4-methyl-1-piperazincarboxamide (38.1.13), is made by acylating 1-methylpiperazine with diethylcarbamoylchloride [14–16].



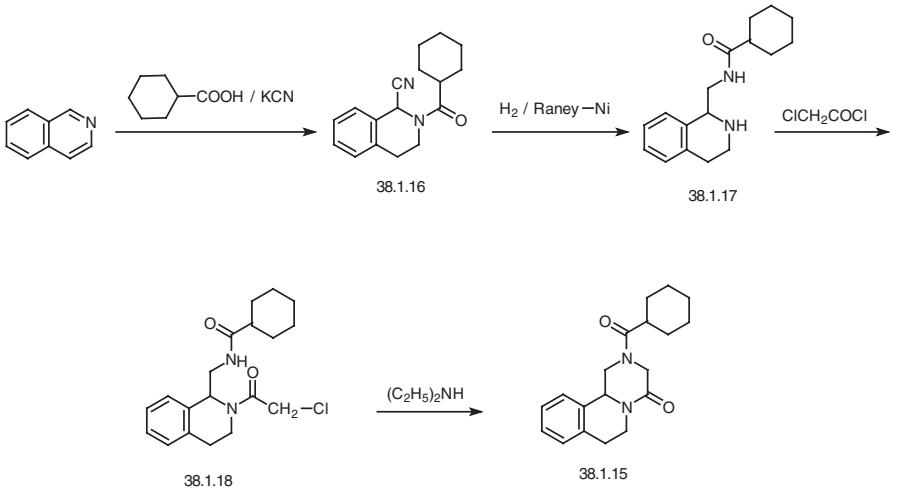
38.1.13

Diethylcarbamazine is a derivative of piperazine. The mechanism of its action is not completely understood. However, it is highly likely that it causes a reduction in muscular activity, and even paralysis in helminthes. It quickly gets rid of the parasites *Brugia malayi, Loa loa,* and *Wuchereria bancrofti*, and it is also used for diseases caused by *Onchocerca volvulus* and *Mansonella strptocerca.* Synonyms of this drug are hetrazan, notezine, banoside, and others.

Praziquantel: Praziquantel, 2-(cyclcohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino [2,1a]isoquinolin-4-one (38.1.15), is a derivative of pyrazinoquinoline that is made in two ways [17–19]. According to one of them, 1-aminomethyl-1,2,3,4-tetrahydroisoquinoline is alkylated with chloroacetic acid, and then the resulting amine is acylated with cyclohexanecarbonyl chloride to make 1-(*N*-carboxymethyl-*N*-cyclohexylcarbonyl-aminomethyl)-1,2,3,4-tetra-hydroisoquinoline (38.1.14), which is heated at 150°C to give the desired praziquantel.

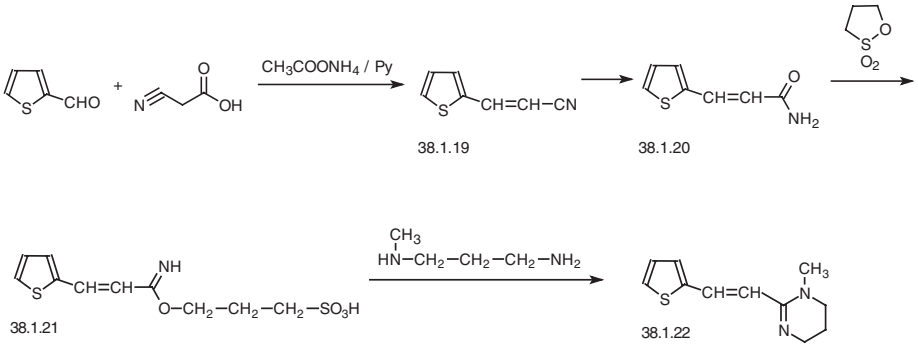


Another way of synthesizing this drug begins with isoquinoline, which is reacted with a mixture of cyclohexanecarbonyl chloride / potassium cyanide to make a dihydro derivative of isoquinoline (38.1.16). This is reduced by hydrogen over Raney nickel to give the reduction–reamidation product—the amide 1-(*N*-cyclohexylcarbonylaminomethyl)-1,2,3,4-tetrahydroisoquinoline (38.1.17). Acylating this with chloracetic acid chloride gives a chlroacetyl derivative (38.1.18), which when heated in the presence of diethylamine results in an intramolecular alkylation, giving the desired product—praziquantel.



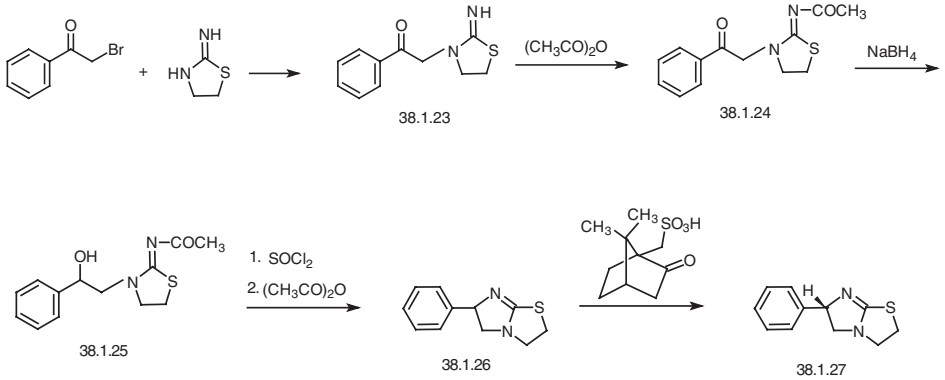
Praziquantel is an antihelmintic drug with a broad spectrum of action. It seems likely that it has an effect on the cellular membrane of schistosomes by increasing the permeability and consequently the flow of calcium ions into the cell, which results in paralysis of the parasite's muscles. As a result, the suckers of the parasite cease to work, and it is excreted from the organism. It is used for treatment of all forms of schizotomoniasis in humans. It is the drug of choice for treating *Shistosoma mansoni, Shistosoma haematobium, Shistosoma japonicum* as well as *Shistosoma intercalatum* and *Shistosoma mekongi*. Synonyms of this drug are droncit, biltricide, and cezol.

Pyrantel: Pyrantel, 1,4,5,6-tetrahydro-1-methyl-2-[trans-2-(2-thienyl)vinyl]-pyrimidine (38.1.22), a derivative of tetrahydropyrimidine, is made from 3-(2-thienyl)-acrylonitrile (38.1.19), which is made in a Knoevangel condensation of furfural with cyanoacetic acid. Acidic hydrolysis of this makes 3-2(-thienyl)acrylamide (38.1.20). Reacting this with propansulfone gives an iminoester (38.1.21), which when reacted with *N*-methyltrimethylenediamine gives the desired pyrantel [20–23].

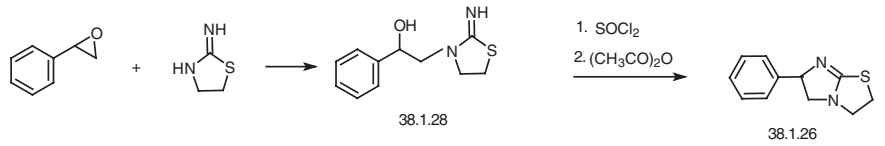


Pyrantel is a highly effective antihelmintic drug for enterobiasis, ascardiasis, ankylostomiasis, and necatoriasis. The antihelmintic effect is exhibited in the form of a powerful cholinomimetic effect on muscle cells of nematodes by binding with their cholinergic receptors, which leads to inhibition of neuromuscular transmission in the parasite, contraction of their musculature, and as a result, in the removal of the helminthes from the gastrointestinal tract of the host. It heals 85–100% of cases of ascariasis, and 90–100% of cases of enterobiasis. It is the drug of choice for *Enterobius vermicularis, Acaris lumbricoides,* as well as *Ancylostoma duodenale,* and *Necator americanus.* Synonyms of this drug are helmex, combantrin, antiminth, and others.

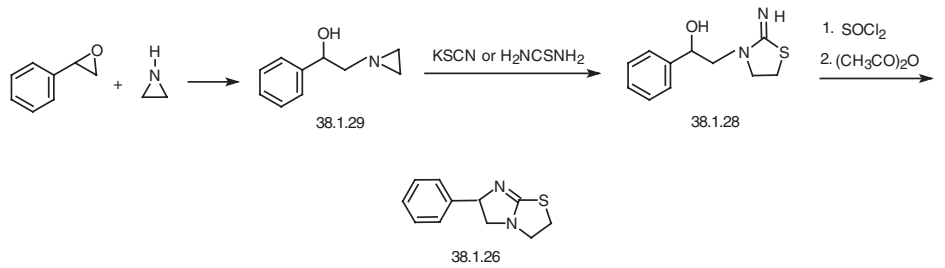
Levamisole: Levamisole, (−)-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]thiazol (38.1.27), is a derivative of imidazothiazol and is the L-isomer of D,L-tetramizole (±)-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]thiazol (38.1.26), which is made in various ways. One of them is from α-bromoacetophenone, which is reacted with 2-imino-1,3-thiazolidine to make the N-alkylated product 1-phenacyl-2-imino-1,3-thiazolidine (38.1.23). Acylating the product with acetic anhydride makes the 2-acetylimino derivative (38.1.24). Reduction of the ketone carbonyl group in this compound with sodium borohydride leads to the formation of the key product of the synthesis—1-(2-phenyl-2-hydroxyethyl)-2-acetylimino-1,3-thiazolidine (38.1.25). Replacing the hydroxyl group in this compound with chlorine using thionyl chloride and subsequent treatment of the product with acetic anhydride results in a heterocyclization reaction to a racemic mixture of (±)-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-b]thiazoles (38.1.26), which is also called tetramizole. Treating this with D-10-camphorsulfonic acid isolates the desired L-isomer—levamisole [24,25].



Two other ways of making levamisole differ only in the method of making 1-(2-phenyl-2-hydroxyethyl)-2-imino-1,3-thiazolidine (38.1.28). One of them begins with a reaction of styrene oxide and 2-imino-1,3-thiazolidine and subsequent treatment of the resulting product (38.1.28) with thionyl chloride and then with acetic anhydride, which leads to the formation of tetramizole [25].

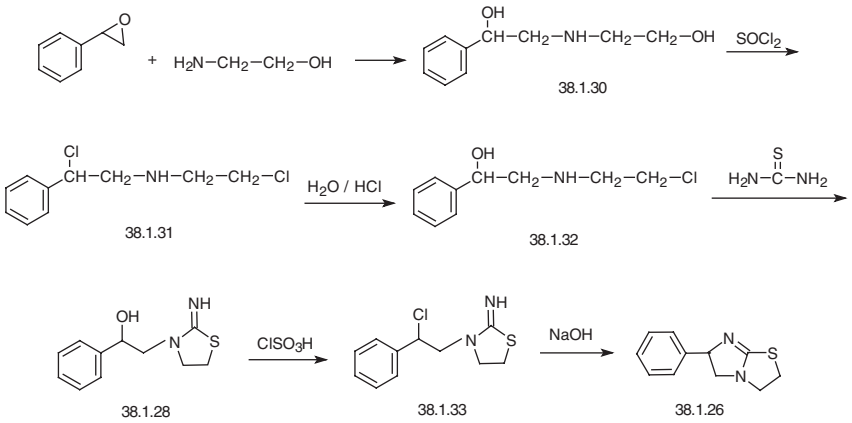


Another of the suggested methods consists of the initial reaction of styrene oxide with ethylenimine to make *N*-(2-phenyl-2-hydroxyethyl)ethylenimine (38.1.29), which is reacted with potassium thiocyanate or with thiourea to give 1-(2-phenyl-2-hydroxyethyl)-2-imino-1,3-thiazolidine (38.1.28). In the aforementioned manner, the product is treated first with thionyl chloride and then with acetic anhydride to make tetramizole [26–31].

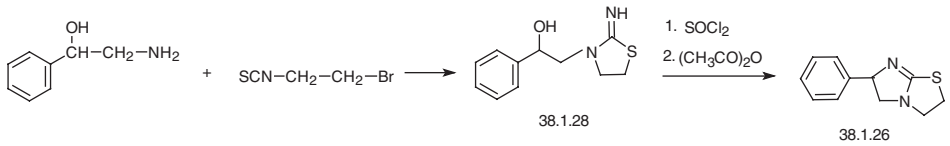


The main difference of one other way of making tetramizole of the above described, consists of carrying out the heterocyclization reaction in the presence of sodium hydroxide instead of acetic anhydride, which makes the possible mechanism of the heterocyclization more understandable. In the suggested method, 1-(2-phenyl-2-hydroxyethyl)-2-imino-1, 3-thiazolidine (38.1.28) is made by reacting styrene oxide with ethanolamine, and subsequent

replacement of the hydroxyl groups in obtained resulting product (38.1.30) with chlorine using thionyl chloride. Then a partial acidic hydrolysis of the resulting dichloride (38.1.31) leads to the primary chloride (38.1.32), and finally, by reacting this with thiourea to make 1-(2-phenyl-2-hydroxyethyl)-2-imino-1,3-thiazolidine (38.1.28). Reacting this with chlorosulfonic acid gives 1-(2-phenyl-2-chloroethyl)-2-imino-1,3-thiazoline (38.1.33), which cyclizes to the desired tetramizole when treated with an alkali [32–36].

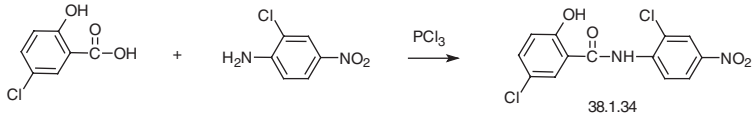


Finally, there is one more suggested way of making 1-(2-phenyl-2-hydroxyethyl)-2-imino-1,3-thiazolidine (38.1.28), which consists of reacting 2-amino-1-phenylethanol with 2-bromoethylisothiocyanate. This leads to the direct formation of the key 1-(2-phenyl-2-hydroxyethyl)-2-imino-1,3-thiazolidine (38.1.28), which is transformed to tetramizole by a subsequent reaction with thionyl chloride, and then with acetic anhydride [37].



Levimasole is also a drug of choice for ascardiasis. Numerous investigations show that a single dose of levamisole heals from 90 to 100% of patients with ascardiasis, in particular those infected with *A. duodenale*. It is less effective against ancylostomiasis and strongyloidiasis. However, it is not effective against *N. americanus.* It seems likely that it has a gangliostimulating effect on parasite tissues in both the parasympathetic and sympathetic regions. Moreover, it is presumed that this drug has an immunomodulatory effect on the host organism. Synonyms of this drug are decaris, solacil, ergamisol, tramisol, immunol, and others.

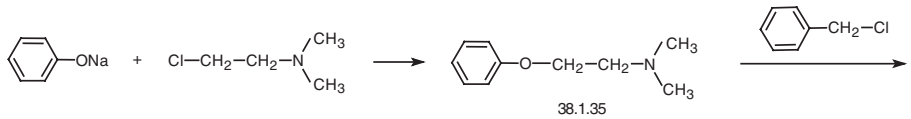
Niclosamide: Niclosamide, 2′,5-dichloro-4′nitrosaicylanilide (38.1.34), is made by reacting 5-chlorosalicylic acid with 2-chloro-4-nitroaniline in the presence of phosphorus trichloride [38–40].



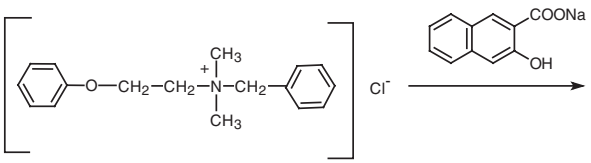
38.1.34

Niclosamide is a derivative of salicylamide and is an effective antihelmintic drug. Its action consists of inhibition of mitochondrial oxidative phosphorylation in both mammals as well as in parasites. It simultaneously inhibits glucose and oxygen uptake by the parasite. In therapeutic doses, it has practically no pharmacological effect on the host organism. Niclosamide is effective against intestinal cestodes, such as *Diphyllobothrium la-tum, Taenia saginata, Taenia solium, Dipilidium caninum, Hymenolepis diminuta* and *Hymenolepis diminuta*, but it is ineffective against nematodes. It is effective in a single dose of 2 g. Synonyms of this drug are iomesan, iclocid, trédémine, and others.

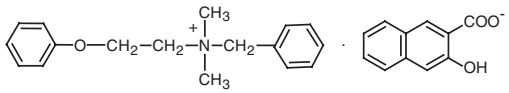
Bephenium: Bephenium, 3-hydroxy-2-naphthoat benzyldimethyl(2-phenoxyethyl) ammonia (38.1.37), is made by reacting the sodium salt of 3-hydroxy-2-naphthoic acid with benzyldimethyl(2-phenoxyethyl)ammonia chloride (38.1.36). This is in turn made from benzyl chloride and *N*-(2-phenoxyethyl)dimethylamine (38.1.35), which is synthesized by reacting sodium phenolate with 2-dimethylaminoethylchloride [41,42].



38.1.35



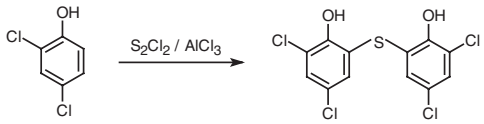
38.1.36



38.1.37

This drug exhibits antihelmintic action by acting as a cholinergic agonist, causing paralysis of the parasite musculature. This facilitates its removal from the intestines. It is used for treating ascariasis, ankylostomiasis, enterobiasis, trichostrongyliasis, and tricocefalosis. A single dose of bephenium heals from 80 to 100% of patients infected with *A. duodenale*. It is less effective with respect to *N. americanus.* Synonyms of this drug are aclopar and others.

Bithionol: Bithionol, 2,2′-thiobis(4,6-dichlorophenol) (38.1.38), is made by reacting a solution of 2,4-dichlorophenol in carbon tetrachloride with sulfur chloride in the presence of aluminum chloride [43,44].



38.1.38

Biothionol is *bis*-dichlorophenol, and it is structurally similar to hexachlorophene. It is the antihelmintic drug of choice for treating humans infected with *Fasciola hepatica.* It is an alternative drug to praziquantel that is used for treating pulmonary and cerebral paragonimiasis. The exact mechanism of action is not known, although it seems likely that it inhibits oxidative phosphorylation in *Paeagonumus westermani*. Synonyms of this drug are actamer, bitin, prevenol, and others.

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