MINISTRY OF HEALTH OF UKRAINE
ZAPORIZHZHIA STATE MEDICAL UNIVERSITY
DEPARTMENT OF PHARMACEUTICAL, ORGANIC AND BIOORGANIC CHEMISTRY

L. I. Kucherenko, O.O. Portna, O.V. Khromylova,
H.R. Nimenko, S.O. Borsuk

PHARMACEUTICAL CHEMISTRY

Section 2.1

(analysis of non-steroidal anti-inflammatory, hypnotic, antitussive, nootropic drugs)

Study Guide

for 3rd year English-speaking students of the specialty "Pharmacy, Industrial Pharmacy"

Zaporizhzhia
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Authors:

L. I. Kucherenko - PhD, Dr.hab., Professor, Head of the Department of Pharmaceutical, organic and bioorganic Chemistry, ZSMU;

O. O. Portna, PhD, Associate Professor;

O. V. Khromylova - PhD, Dr.hab., Associate Professor;

H. R. Nimenko - PhD, Senior Lecturer;

S. O. Borsuk - PhD, Senior Lecturer;

Reviewers:

S. O. Vasiuk – Doctor of Pharmaceutical Sciences, professor, Head of the Department of Analytical Chemistry of Zaporizhzhia State Medical University;

S. D. Trzhetsynskyi – Doctor of biological sciences, Associate Professor, Head of the Department of Pharmacognosy, Pharmacology and Botany of Zaporizhzhia State Medical University.

P78 **Pharmaceutical Chemistry. Section 2.1** (analysis of non-steroidal anti-inflammatory, hypnotic, antitussive, nootropic drugs): Study guide for 3rd year English-speaking students of the specialty "Pharmacy, Industrial Pharmacy" / L. I. Kucherenko, O. O. Portna, O. V. Khromylova [et al.]. – Zaporizhzhia: ZSMU, 2023. – 88 p.

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INTRODUCTION

Pharmaceutical chemistry is studied in accordance with the "Model curriculum for the training of specialists of the second (master's) level of higher education in the field of knowledge 22 "Health Protection" in higher educational institutions of the Ministry of Health of Ukraine in specialty 226 "Pharmacy"б educational qualification "Master of Pharmacy" as of 26.07.2016.

Most of the drawings were developed by the authors of this study guide.

According to the curriculum, pharmaceutical chemistry is taught in the III, IV and V courses. In the III course (V-VI semesters), the discipline program is structured into 2 meaningful blocks:

Block 1 - "Pharmaceutical analysis"

Block 2 - "Special pharmaceutical chemistry"

Block 2 consists of three sections.

SPECIFIC GOALS:

To learn the characteristics, classification, connection between structure and pharmacological action, mechanism of action, methods of production, methods of analysis of the use of antitussive, nootropic, non-steroidal anti-inflammatory, hypnotic drugs in medicine.

To explain the peculiarities of the identification of drugs according to the requirements of the State Pharmacopoeia of Ukraine (SPhU).

To interpret the results of studies on the maximum content of impurities in accordance with the requirements of the SPhU.

To propose and carry out a selection of physical, physico-chemical and chemical methods for determining the good quality of drugs in accordance with the requirements of the SPhU and other regulatory documentation, as well as Quality Control Methods (QCM).

PLAN OF PRACTICAL CLASSES

No.	**Lecture topic**	Number of hours
1.	Antitussives. Characteristics, classification, connection between structure and pharmacological action, mechanism of action, methods of production, methods of analysis. Use in medicine.	3
2.	Nootropic drugs. Characteristics, classification, connection between structure and pharmacological action, mechanism of action, methods of production, methods of analysis. Use in medicine.	3
3.	Nonsteroidal anti-inflammatory drugs. Characteristics, classification, connection between structure and pharmacological action, mechanism of action, methods of production, methods of analysis. Use in medicine.	3
4.	Sleep aids. Characteristics, classification, connection between structure and pharmacological action, mechanism of action, methods of production, methods of analysis. Use in medicine.	3
5.	Control lesson on the section	3

1. NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) - is a group of drugs that are widely used in clinical practice. This is explained by the fact that NSAIDs have anti-inflammatory, analgesic and antipyretic effects and bring relief to patients with the corresponding symptoms (inflammation, pain, fever), which are noted in many diseases: inflammatory diseases of the joints (rheumatoid arthritis, rheumatism, ankylosing spondylitis, chronic gouty arthritis), degenerative diseases (deforming osteoarthritis, osteochondrosis), lumbago, sciatica, neuralgia, myalgia, diseases of extra-articular tissues, post-traumatic pain syndrome accompanied by inflammation, postoperative pain, acute attack of gout, migraine attacks, renal and hepatic colics, infections of ENT organs.

Classification of NSAIDs:

Depending on the severity of anti-inflammatory activity and chemical structure, NSAIDs are divided into 2 groups.

- the first group – drugs with a pronounced anti-inflammatory effect;

- the second group – drugs that have a weak anti-inflammatory effect, often denoted by the terms "non-narcotic analgesics" or "analgesics-antipyretics".

NSAIDs with a pronounced anti-inflammatory effect	
Acids	
Salicylates	Acetylsalicylic acid (aspirin) Diflunisal Lysine monoacetyl salicylate
Pyrazolidines	Phenylbutazone
Derivatives of indoleacetic acid	Indomethacin Sulindak Etodolac
Derivatives of phenylacetic acid	Diclofenac

Oxicams	Piroxicam Tenoxicam Lornoxicam Meloxicam
Derivatives of propionic acid	Ibuprufen Naproxen Flurbiprofen Ketoprofen Tiaprofenic acid
Non-acid derivatives	
Alkanones	Nabumeton
Sulfonamide derivatives	Nimesulide Celecoxib Rofecoxib
NSAIDs with weak anti-inflammatory activity	
Derivatives of anthranilic acid	Mefenamic acid Etofenamate
Pyrazolone	Metamizole Aminophenazone Propifenazone
Derivatives of paraaminophenol	Phenacetin Paracetamol
Heteroarylacetic acid derivatives	Ketorolac

Mechanism of action

The main and general element of the mechanism of action of NSAIDs is inhibition of the synthesis of prostaglandins (PG) from arachidonic acid by inhibiting the enzyme cyclooxygenase (PG synthetase).

In recent years, it has been established that there are at least two isozymes of cyclooxygenase, which have been shown to be reduced by NSAIDs. The first isoenzyme - COX-1 - controls the production of prostaglandins, which regulates the integrity of the mucous membrane of the gastrointestinal tract, the function of platelets and renal circulation, and the second isoenzyme - COX-2 - is involved in the synthesis of prostaglandins during inflammation. Moreover, under normal conditions, COX-2 is absent, but is formed under the action of some tissue factors that initiate an inflammatory reaction (cytokines and others). In this regard, it is assumed that the anti-inflammatory effect of NSAIDs is due to suppression of COX-2, and their undesirable reactions are due to inhibition of COX, the classification of NSAIDs by selectivity in relation to various forms of cyclooxygenase is presented in the table. The ratio of the activity of NSAIDs in terms of blocking COX-1 / COX-2 allows us to judge their potential toxicity. The smaller this value, the more selective the drug is for COX-2 and, therefore, less toxic. For example, it is 0.33 for meloxicam, 2.2 for diclofenac, 15 for tenoxicam, 33 for piroxicam, and 107 for indomethacin.

Classification of NSAIDs by selectivity in relation to various forms of cyclooxygenase

Expressed selectivity for COX-1	aspirin indomethacin ketoprofen piroxicam sulindac
Moderate selectivity for COX-1	diclofenac ibuprofen naproxen other

Approximately equal inhibition of COX-1 and COX-2	lornoxicam
Moderate selectivity for COX-2	etodolac meloxicam nimesulide nabumetone
Expressed selectivity for COX-2	celecoxib rofecoxib

Other mechanisms of action of NSAIDs

The anti-inflammatory effect can be associated with inhibition of lipid peroxidation, stabilization of lysosome membranes (both of these mechanisms prevent damage to cellular structures), reduction of ATP formation (reduces the energy supply of the inflammatory reaction), inhibition of neutrophil aggregation (disruption of the release of inflammatory mediators from them), inhibition of production of rheumatoid factor in patients with rheumatoid arthritis. The analgesic effect is to some extent associated with the disruption of pain impulses in the spinal cord (metamizole).

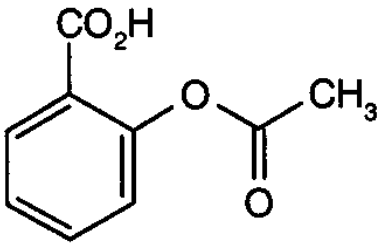
PHARMACOKINETICS

All NSAIDs are well absorbed in the gastrointestinal tract. They are almost completely bound to plasma albumins, displacing some other drugs, and in newborns – bilirubin, which can lead to the development of bilirubin encephalopathy. The most dangerous in this respect are salicylates and phenylbutazone. Most NSAIDs penetrate well into the synovial fluid of the joints. NSAIDs are metabolized in the liver and excreted through the kidneys.

They are available in tablets, capsules, solutions for injections, ointments, gels, suppositories (candles).

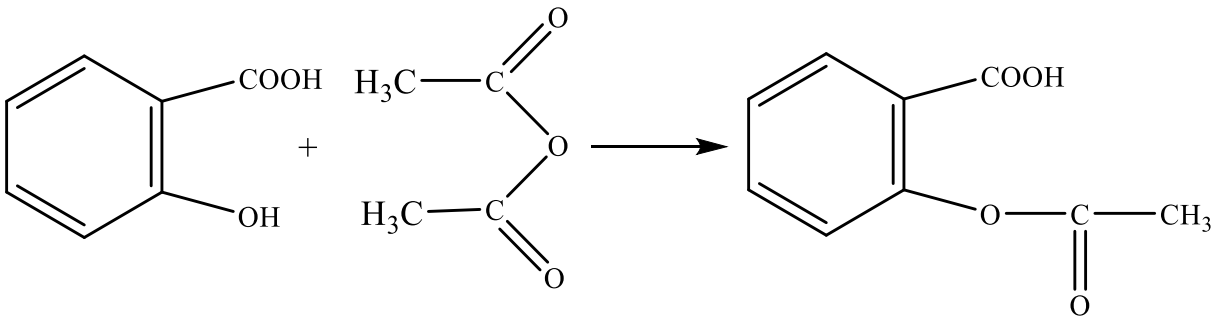
We will consider the analysis of drugs of this group using an example Acetylsalicylic acid**:**

Acetylsalicylic acid - Acidum acetylsalicylicum (SPhU)

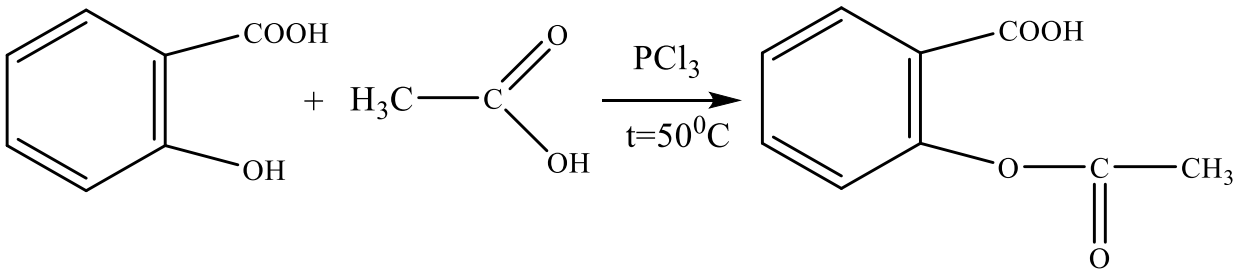


2-(Acetoxy)benzoic acid

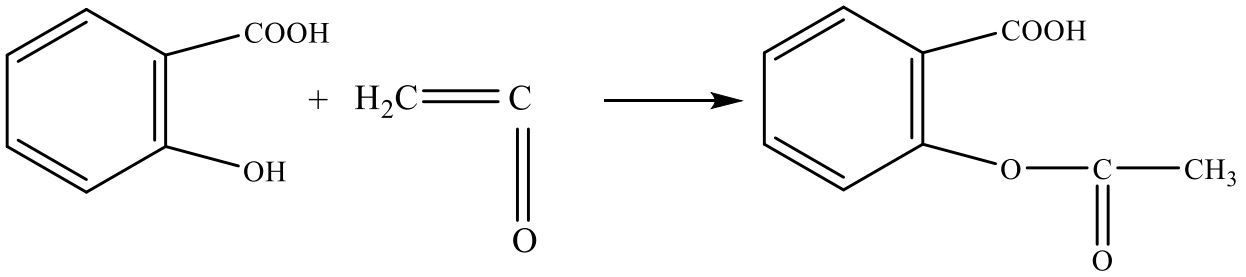
Extraction: Acetylation of salicylic acid with acetic anhydride :



Acetylation of salicylic acid with acetic acid in the presence of phosphorus trichloride:



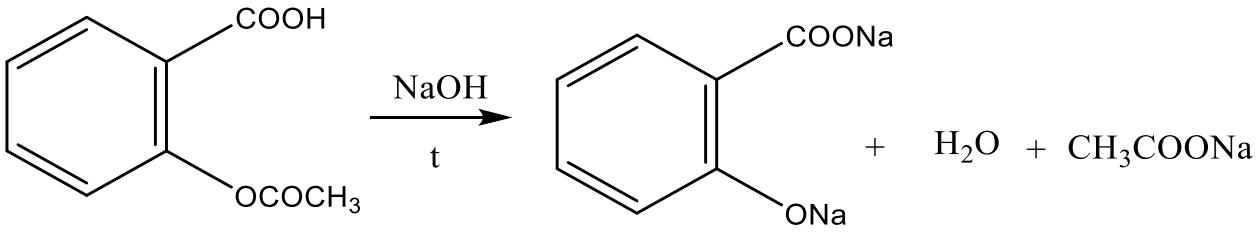
The interaction of salicylic acid with ketene:



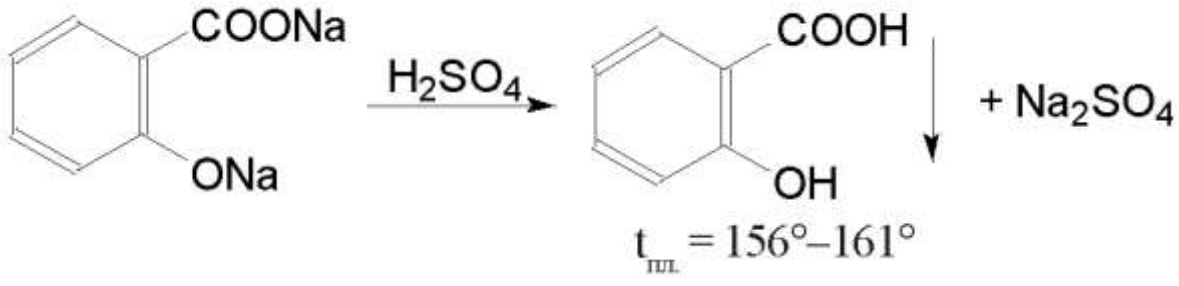
Properties. White crystalline powder or colorless crystals. The drug is stable in dry air, in wet air it is gradually hydrolyzed with the formation of acetic and salicylic acids. Sparingly soluble in water, easily soluble in 96% alcohol, soluble in ether, solutions of alkali metal hydroxides and carbonates.

Identification: IR spectroscopy.

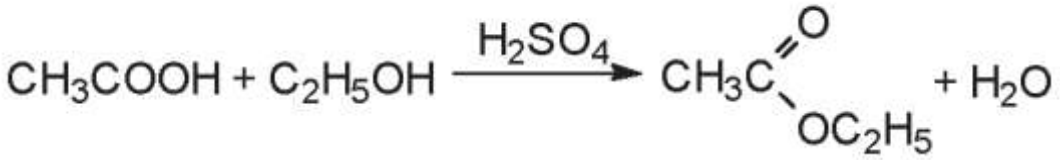
The medicinal product is subjected to alkaline hydrolysis:



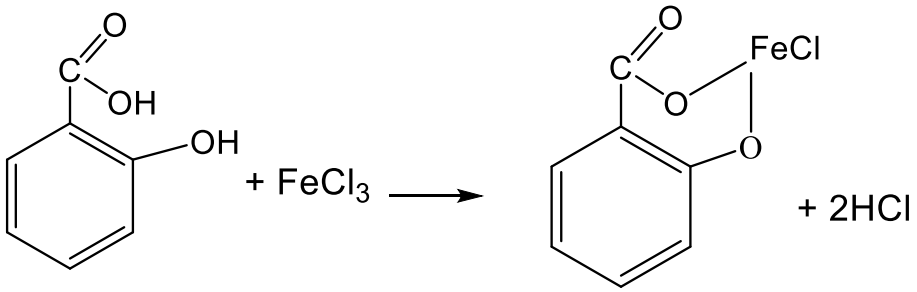
Then it is acidified with dilute sulfuric acid - the formation of a white crystalline precipitate of salicylic acid is observed, which is identified by its melting point [10, p. 242]:



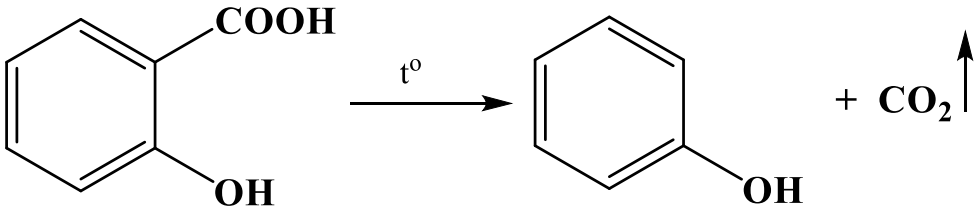
The reaction mixture is filtered, alcohol and concentrated sulfuric acid are added to the filtrate: acetic ethyl ester is formed, which has a characteristic odor (non-pharmacopoeial reaction) [10, p. 242]:



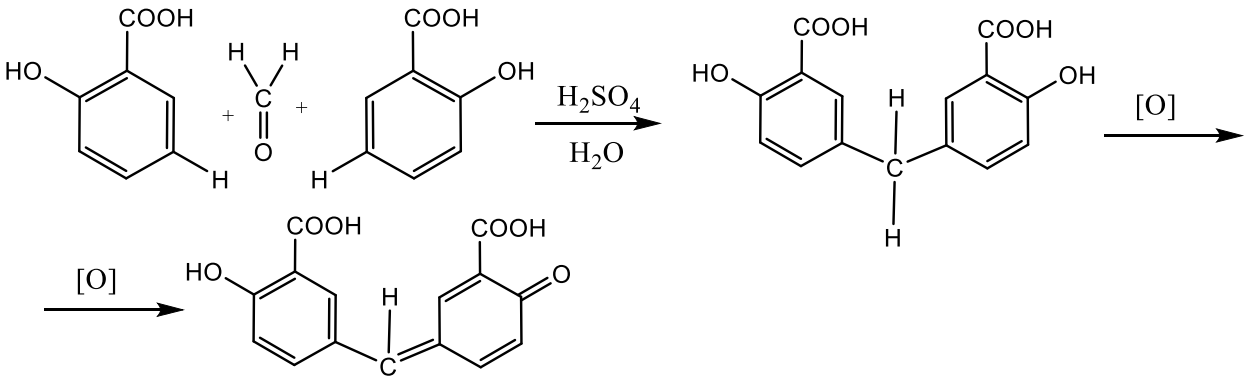
Salicylic acid contained in the precipitate is identified with a solution of ferrum (III) chloride by the appearance of a purple color (SPhU).



When salicylic acid is heated above 160 °C, its decarboxylation occurs with the formation of phenol (smell). To prevent sublimation, the reaction is carried out in the presence of salts of organic acids (sodium citrate):



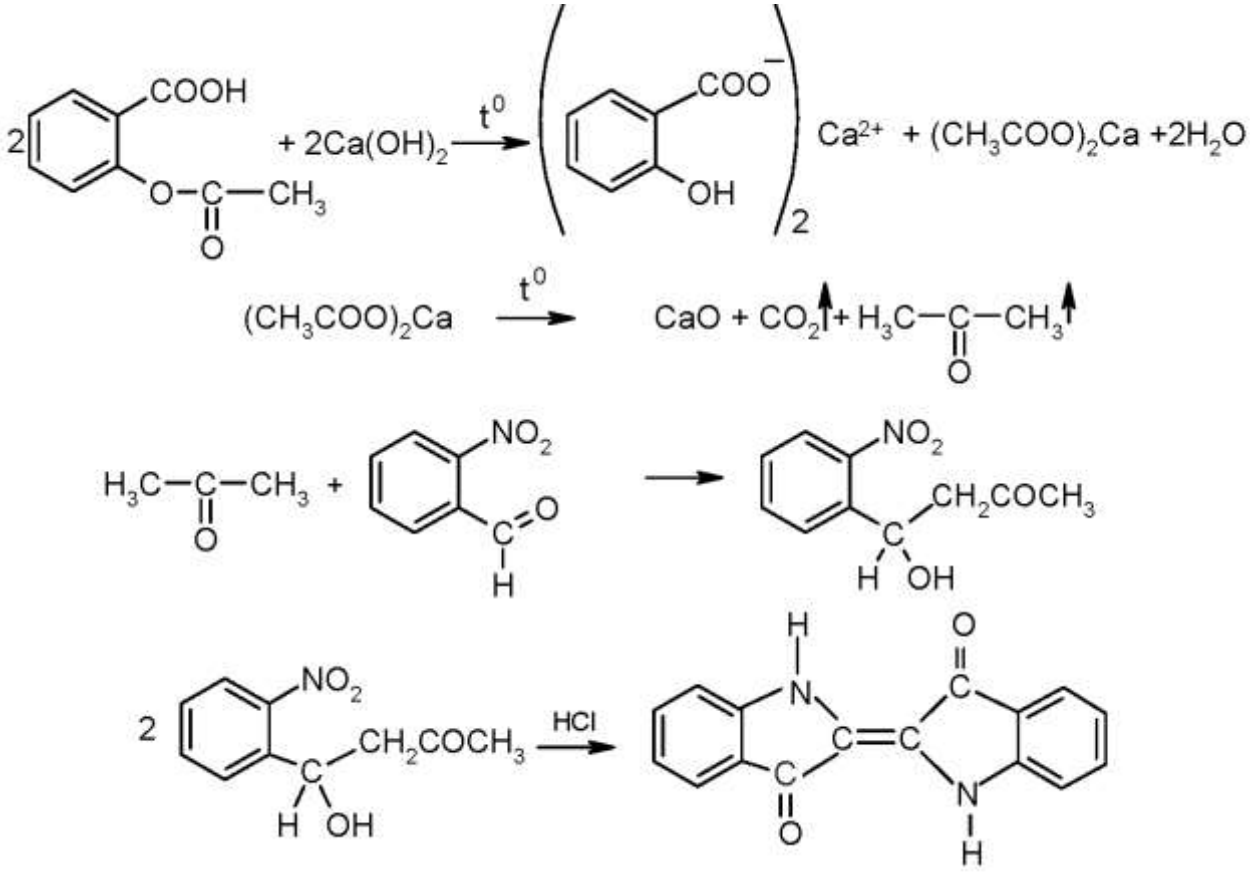
The reaction of the formation of an auric dye with a formaldehyde solution in the presence of concentrated sulfuric acid (Marquis reagent):



Purity test. During the synthesis of salicylic acid, small amounts of oxydiphenyl may be formed:

The drug substance is dissolved in sodium carbonate solution, in which hydroxydiphenyl does not dissolve, it is extracted with ether, the ether layer is separated, evaporated, and the residue is weighed.

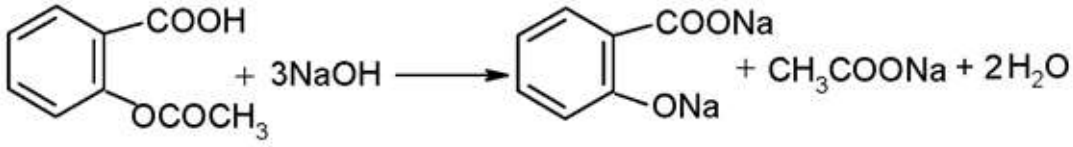
When calcined with calcium hydroxide, acetone is formed, the vapors of which color the filter paper moistened with *o*-nitrobenzaldehyde yellow-green, blue-green, and when moistened with a solution of hydrochloric acid - blue [10, p. 242]:



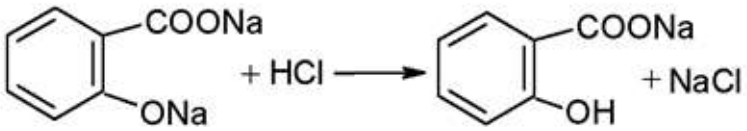
Non-pharmacopoeial reaction: acid hydrolysis. When concentrated sulfuric acid is added, the smell of acetic acid appears. If you then add a formaldehyde solution to the mixture, a pink color (salicylic acid) appears.

Quantitative definition:

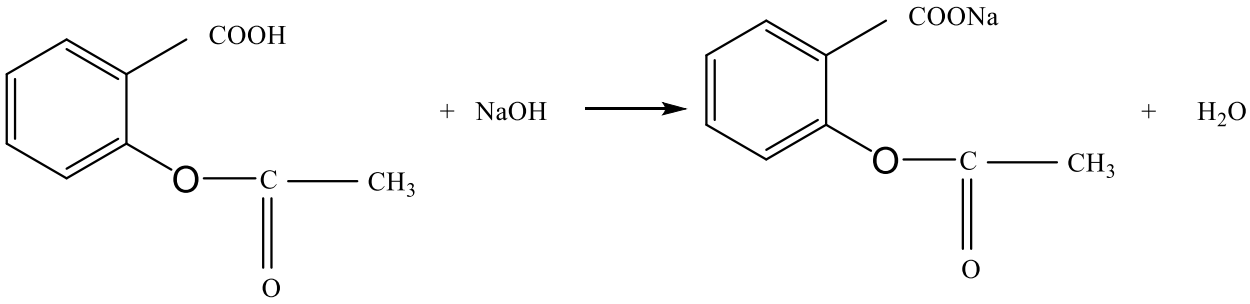
Alkalimetry, reverse titration (SPhU). The method is based on the saponification of the substance with a solution of sodium hydroxide, the excess of which is titrated with hydrochloric acid (the indicator is phenolphthalein). In parallel, a control experiment is conducted [10, p. 243]:



$$NaOH + HCl \rightarrow NaCl + H_2O$$



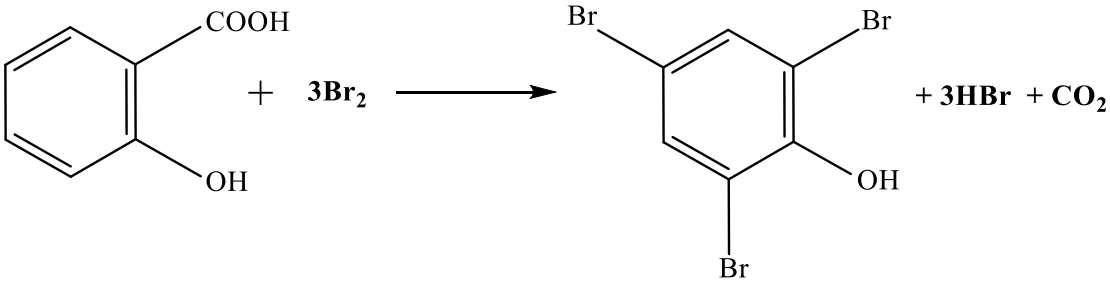
Alkalimetry, direct titration in phenolphthalein-neutralized alcohol:



At a temperature above 20 °C, the drug substance can be partially hydrolyzed.

Bromatometry after hydrolysis.

- $KBrO_3 + 5KBr + 3H_2S0_4 \longrightarrow 3Br_2 + 3H_20 + 3K_2S0_4$



$$Br_2 + 2KI \longrightarrow I_2 + 2KBr$$

$$I_2 + 2Na_2S_2O_3 \longrightarrow 2NaI + Na_2S_4O_6$$

Storage. In a sealed container.

Use. Antirheumatic, anti-inflammatory, antipyretic, pain reliever, as well as to prevent the formation of blood clots, in case of thrombosis of retinal vessels, violation of cerebral blood circulation, to prevent complications and reduce angina attacks in ischemic heart disease.

TEST TASKS ON THE TOPIC «NONSTEROIDAL ANTI-INFLAMMATORY DRUGS»

1. Specify a drug that exhibits pronounced selectivity in relation to COX-2:

A. Nimesulide
B. Acetylsalicylic acid
C. Celecoxib
D. Ibuprofen
E. Acetoaminophen

2. Choose an international non-proprietary name for aspirin:

A. Diclofenac
B. Phenylbutazone
C. Nimesulide
D. Acetylsalicylic acid
E. Ibuprofen

3. One of the NSAIDs belongs to the group of non-narcotic analgesics:

A. Analgin
B. Ibuprofen
C. Paracetamol
D. Indomethacin
E. Fentanyl

4. One of the NSAIDs belongs to the drugs of the pyrazolone group:

A. Indomethacin

B. Ibuprofen

C. Phenacetin

D. Acetylsalicylic acid

E. Analgin

5. Which NSAID has the weakest anti-inflammatory effect:

A. Diclofenac

B. Piroxicam

C. Paracetamol

D. Celecoxib

E. Indomethacin

6. A patient suffering from a headache, who was prescribed a cyclooxygenase inhibitor - an aminophenol derivative, came to the pharmacy for consultation. What drug was prescribed to the patient?

A. Diclofenac

B. Paracetamol

C. Ketorolac

D. Ibuprofen

E. Acetylsalicylic acid

7. The doctor prescribed an antipyretic drug to the patient. Specify this drug.

A. Ascorbic acid

B. Cyanocobalamin

C. Oxytocin

D. Famotidine

E. Paracetamol

8. The doctor prescribed paracetamol, a cyclooxygenase inhibitor, to a patient with arthritis. The formation of which biologically active compounds is inhibited by this drug?

A. Catecholamines

B. Prostaglandins

C. Cytokines

D. Iodothyronine

E. Interferons

9. What is the mechanism of action of diclofenac sodium?

A. Suppresses cholinesterase

B. Activates the synthesis of phosphodiesterase

C. Blocks cyclooxygenase

D. Activates adenylate cyclase

E. Inhibits phosphodiesterase

10. A patient with osteoarthritis was prescribed a drug that caused a side effect in the form of an ulcer.

A. Meloxicam

B. Diclofenac-Sodium

C. Nimesulid

D. Celecoxib

E. Rofeccoxib

11. To relieve inflammation and pain, the doctor prescribed a drug that belongs to the group of NSAIDs. Specify this drug:

A. Glibenclamide

B. Diclofenac-Sodium

C. Loratadine

D. Prednisolone

E. Calcium chloride

12. The doctor recommended a patient with an acute myocardial infarction to take an antiplatelet drug that blocks platelet cyclooxygenase. What is this drug?

A. Tiklopidine

B. Clopidogrel

C. Dipyridamol

D. Acetylsalicylic acid

E. Abciximab

13. Acetylsalicylic acid is used to treat rheumatism. What process does acetylsalicylic acid affect?

A. Breakdown of glucose

B. Synthesis of glycogen

C. Fat breakdown

D. Synthesis of amino acids

E. Synthesis of prostaglandins

14. What nonsteroidal anti-inflammatory drugs selectively block COX-2?

A. Ortofen, Voltaren

B. Meloxicam, nimesulide

C. Indomethacin, sodium diclofenac

D. Ibuprofen, ketoprofen

E. Mefenamic acid, naproxen

15. Help the doctor choose a drug from the group of nonsteroidal anti-inflammatory drugs, which is a COX-2 inhibitor and does not damage the stomach?

A. Acetylsalicylic acid

B. Paracetamol

C. Celecoxib

D. Indomethacin

E. Diclofenac sodium

16. Acetylsalicylic acid is identified by saponification products. Name the products that come out after its saponification:

A. Phenol and acetic acid

B. Salicylic acid and acetic acid

C. Benzoic acid and acetic acid

D. Ethyl acetate

E. Benzene and phenol

17. Bromatometric determination of drugs, phenol derivatives is based on the reaction:

A. Oxidation

B. Substitution

C. Accession

D. Elimination

E. Recovery

18. The indicator for the inverse bromatometric method of quantitative determination of drugs is:

A. Starch

B. Neutral red

C. Metallic red

D. Methyl orange

E. Thymolphthalein

19. Acetylsalicylic acid belongs to the class of esters. With improper and long-term storage, we felt a smell of:

A. Ammonia

B. Acetic acid

C. Hydrogen sulfide

D. Formaldehyde

E. Alcohol

20. The pharmacist of Control and Analytical Laboratory performs the identification of the drug substance "Acetylsalicylic acid" in accordance with the requirements of the SPhU. What is the result of the reaction with iron (III) chloride?

A. A purple color appears, which does not disappear after the addition of acetic acid

B. A pink solution is formed, which decolorizes after the addition of ammonia solution

C. A white precipitate insoluble in dilute hydrochloric acid is formed

D. Filter paper moistened with a solution of diphenylcarbazide turns purple-red

E. An orange-red precipitate is formed, which dissolves when a solution of diluted sodium hydroxide is added

21. Quantitative determination of acetylsalicylic acid according to normative and technical documentation is carried out by the method of alkalimetry. Titration at a temperature of 8-10 ºC is recommended in order to prevent:

A. A side reaction of esterification

B. Hydrolysis of the ester group

C. Oxidation of drug substance

D. Decarboxylation

E. Precipitation of the formed salt

22. Which of the following compounds is the starting point for the synthesis of the drug paracetamol?

A. *p* -Aminophenol

B. *p* -Nitrotoluene

C. *m*-Aminophenol

D. *o*-Aminophenol

E. *p*-Xylene

23. State which set of reagents is used in pharmaceutical analysis to confirm the presence of a primary aromatic amino group in the structure of sodium p-aminosalicylate:

A. Sodium nitrite, solution of hydrochloric acid, alkaline solution of β-naphthol

B. Sodium chloride, solution of hydrochloric acid, alkaline solution of β-naphthol

C. Copper (II) sulfate, hydrochloric acid solution, phenol solution

D. Sodium nitrate, sodium hydroxide solution, alkaline β-naphthol solution

E. Sodium thiosulfate solution, hydrochloric acid solution, resorcinol solution

24. Which compound is most often used in pharmaceutical analysis as an azo component in azo coupling reactions with aryldiazonium salts?

A. Naphthalene

B. Naphthysin

C. β-Naphthol

D. Ninhydrin

E. Nitrobenzene

25. Paracetamol substance was received for analysis. When it interacts with a solution of iron (III) chloride, a blue-violet color is formed, which indicates the presence in its structure of:

A. Ester group

B. Keto groups

C. Phenolic hydroxyl

D. Aldehyde group

E. Alcoholic hydroxyl

26. Choose the reagent that is most often used in pharmaceutical analysis to confirm the presence of phenolic hydroxyl in the structure of drugs:

A. Potassium iodide solution

B. 2,4-dinitrochlorobenzene solution

C. Hydroxylamine solution

D. Iron (III) chloride solution

E. Sodium bicarbonate solution

27. Checking the good quality of butadione according to normative and technical documentation, the chemist of the Quality Control Department of the pharmaceutical enterprise determines the presence of a specific impurity. Specify which impurity he defines:

A. Hydrazobenzene

B. 4-Aminoantipyrine

C. p-phenetidine

D. p-Aminophenol

E. Vanillin

28. In order to identify acetylsalicylic acid, its hydrolysis is carried out. Which of the reagents is used to identify hydrolysis products?

A. Iron (III) chloride

B. Potassium phosphate

C. Magnesium sulfate

D. Ammonium molybdate

E. Sodium nitrate

29. The pharmacist of Control and Analytical Laboratory conducts the analysis of the drug substance "Acetylsalicylic acid" in accordance with the requirements of the SPhU. The test with iron (III) chloride gives a purple color, since this reaction to:

A. Benzoic acid, which was formed after acid hydrolysis

B. p-Acetaminophenol formed after reduction

C. Salicylic acid, which was formed after alkaline hydrolysis

D. A specific admixture of acetic anhydride

E. A specific admixture of phosphorus trichloride

30. A chemist-analyst of the laboratory of the tablet workshop of a pharmaceutical enterprise analyzes the manufactured tablets of acetylsalicylic acid of 0.5 g. Which of the listed methods does he use to determine the quantitative content of the active substance in these tablets?

A. Alkalimetric

B. Permanganatometric

C. Complexometric

D. Nitritometric

E. Argentometric

31. Name the industrial method of obtaining paracetamol:

A. Interaction of m-cresol and vanillin

B. Interaction of ethylene and cyclohexane

C. Interaction of adamantane and 2-methylbutadiene

D. Acetylation of p-aminophenol

E. Extraction from oil

32. Paracetamol is studied in the control and analytical laboratory. With which reagent does the substance under study form a purple color that does not change to red?

A. Sodium hydroxide

B. Magnesium sulfate

C. Potassium dichromate

D. Sodium chloride

E. Zinc sulfate

33. Specify the product of the interaction of paracetamol with potassium dichromate in an acidic environment:

A. Indophenol dye

B. Aurine dye

C. Schiff base

D. Azo dye

E. Thiochrome

34. Quantitative content of paracetamol in accordance with the requirements of the SPhU is determined by the cerimetry method. As a titrant we use a solution of:

A. Potassium permanganate

B. Iodine monochloride

C. Cerium sulfate

D. Silver nitrate

E. Hydrochloric acids

35. Quantitative determination of the substance "Paracetamolum" according to the SphU is carried out after preliminary acid hydrolysis by the method of:

A. Nitritometric, titrant - sodium nitrite, indicator - tropeolin 00

B. Cerimetric, titrant - cerium sulfate, indicator - ferroin

C. Nitritometric, titrant - sodium nitrate, indicator - methylene blue

D. Nitritometric, titrant - sodium nitrite, indicator - neutral red

E. Nitritometric, titrant - sodium nitrite, external indicator - iodine-starch paper

36. Paracetamol is quantitatively determined by the cerimetric method after preliminary acid hydrolysis, while para-aminophenol is oxidized by cerium (IV) sulfate to:

A. Quinone

B. Hinonymina

C. Hydroquinone

D. Indophenol

E. Resorcinol

37. The pharmacist performs quantitative determination of paracetamol by the cerimetry method. Specify which indicator the SPhU recommends to use for the indicated method:

A. Tropeolin 00

B. Phenolphthalein

C. Methyl orange

D. Ferroin

E. Potassium chromate

38. The quantitative content of which drug substance can be determined by the nitritometry method only after preliminary hydrolysis?

A. Paracetamol

B. Anesthesin

C. Procaine hydrochloride

D. Sodium para-aminosalicylate

E. Dicainum

39. A heterocycle is present in the structure of the drug analgin:

A. Pyridine

B. Pyrazole

C. Pyrimidine

D. Piperidine

E. Pyrrol

40. Analgin substance was received for analysis. Select the method by which you can determine the quantitative content of analgin:

A. Iodometry

B. Alkalimetry

C. Permanganatometry

D. Complexonometry

E. Acidimetry

41. The solubility of butadione (phenylbutazone) in hydroxides of alkali metals is explained by its ability to undergo tautomeric transformations. What type of tautomerism is characteristic of butadione?

A. Amino-imine tautomerism

B. Keto-enol tautomerism

C. Lacto-lactim tautomerism

D. Azole tautomerism

E. aci-Nitrotautomerism

42. Indomethacin belongs to non-steroidal anti-inflammatory drugs. The basis of its structure is a condensed heterocyclic system. What cycles does it consist of?

A. Pyrrole and benzene

B. Benzene and thiazole

C. Benzene and pyridine

D. Two residues of 4-oxycoumarin

E. Pyrimidine, imidazole

43. In the laboratory for quality control of drug products, the benign quality of indomethacin is checked. Its chemical name is as follows:

A. [1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid

B. Ethyl ester of di-(4-oxycoumarin-3)-acetic acid

C. 5-Nitro-8-hydroxyquinoline

D. 4-chloro-2-(furfurylamino)-5-sulfamoylbenzoic acid

E. 1,2-Diphenyl-4-butylpyrazolide-indione-3,5

44. Indomethacin forms complex compounds with salts of heavy metals (Fe^{3+}, Cu^{2+}) due to the presence in its structure:

A. Methyl group

B. Benzene ring

C. Carboxyl group

D. Covalently bonded chlorine

E. Methoxy groups

45. To identify the sodium salt of mefenamic acid, the pharmacist of the control and analytical laboratory should use the reagent:

A. Sodium nitrite solution

B. Sodium hydroxide solution

C. Lithium carbonate solution

D. Magnesium sulfate solution

E. Ammonium sulfide solution

46. Which of the physicochemical methods is used to establish the equivalence point in nitritometry?

A. Polarimetry

B. Potentiometry

C. Spectrophotometry

D. Refractometry

E. Photoelectrocolorimetry

47. For what purpose is potassium bromide added during nitritometric titration:

A. To raise the temperature of the reaction environment

B. To change the pH of the environment

C. As a buffer solution

D. As a catalyst

E. As a reaction inhibitor

48. Anthranilic acid (ortho-aminobenzoic) preparations include mefenamic acid (N-(2,3-dimethyl) anthranilic acid). Quantitative determination of the indicated drug can be carried out by any method, except:

A. Acid-base titration

B. Bromatometry

C. Complexonometry

D. Nitritometry

E. Iodometry

49. Analgin (sodium 2,5-dimethyl-2-phenyl-3-oxo-2,3-dehydro-1H-pyrazole-4-N-methyl-methanesulfonate) belongs to pyrazole derivatives, when it is heated with mineral acids, it is released:

A. Sulfur gas and ammonia

B. Sulfur gas and carbon dioxide

C. Sulfur gas and formaldehyde

D. Sulfur gas and nitrogen oxide

E. Sulfur gas and nitrous oxide

50. The pharmacist of a pharmaceutical company received the substance metamizole sodium (analgin) for analysis. Quantitative determination of this substance should be carried out by the iodometric method. According to normative and technical documentation, titration is carried out without an indicator until the appearance of:

A. Red color of the solution

B. Green color of the solution

C. Brown color of the solution

D. Black color of the solution

E. Yellow color of the solution

51. When certifying the analgin substance, the analytical chemist must identify the cation:

A. Sodium

B. Iron (III)

C. Iron (II)

D. Calcium

E. Magnesium

52. One of the directions of biotransformation of paracetamol in the liver is oxidation by microsomal enzymes. As a result, a toxic metabolite is formed:

A. phenol

B. o-xylene

C. phthalic anhydride

D. m-dioxybenzene

E. quinonymine

53. Paracetamol belongs to non-steroidal anti-inflammatory drugs and is biotransformed in the body by deacetylation. What metabolite is formed?

A. *p*-aminophenol

B. Aminobenzene

C. *o*-xylene

D. Nitrobenzene

E. *m*-dioxybenzene

54. An acidic environment is optimal for the absorption of the main metabolite of acetylsalicylic acid. Name this metabolite:

A. Barbituric acid

B. Phenylacetic acid

C. Salicylic acid

D. Uric acid

E. Valproic acid

2. HYPNOTICS (SLEEP AIDS)

HYPNOTICS – a group of psychoactive drugs that are used to facilitate the onset of sleep and ensure its sufficient duration, as well as during anesthesia. Drugs of various pharmacological groups are used as sleeping aids.

Drugs are classified based on the principle of their action and chemical structure:

Sleep aids with non-narcotic type of action.

Agonists of benzodiazepine receptors.

1. Benzodiazepine derivatives

- nitrazepam (Radedorm, Eunoctin)
- flunitrazepam (Rohypnol)
- triazolam (Halcyon)
- midazolam (Dormicum)

2. Drugs of a different chemical structure (non-benzodiazepines).

- zopiclone (Imovan, Piclodorm)
- zolpidem (Ivadal, Sanval)

3. Blockers of H1 - histamine receptors.

- doxylamine (Donormil)

Sleep aids with a narcotic type of action.

1. Derivatives of barbituric acid (barbiturates).

- phenobarbital (Luminal)

2. Aliphatic compounds.

- chloral hydrate

Individual drugs of other groups:

- Blockers of H1 histamine receptors, M-cholinoblockers: diphenhydramine, doxylamine
- Means for anesthesia: sodium oxybutyrate
- Preparations of the hormone epiphysamelatonin.

Benzodiazepine derivatives are most widely used as sleeping pills. Unlike barbiturates, they disrupt the normal structure of sleep to a lesser extent, are much less dangerous in terms of the formation of addiction, and do not cause pronounced side effects.

Mechanism of action.

The mechanism of sedative, hypnotic and other effects of benzodiazepines is associated with their interaction with special benzodiazepine receptors, the latter are part of the macromolecular GABA-receptor complex, which includes receptors sensitive to GABA, benzodiazepine and barbiturates, as well as chlorine ionophores. Due to allosteric interaction with specific receptors, benzodiazepines increase the affinity of GABA to GABA receptors and enhance the inhibitory effect of GABA. There is a more frequent opening of chlorine ionophores. At the same time, the influx of chlorine ions into neurons increases, which leads to an increase in the inhibitory postsynaptic potential.

Benzodiazepines, which are used in medicine, differ mainly in terms of pharmacokinetics. Some of them undergo biotransformation with the formation of active long-term metabolites (flurazepam, diazepam, etc.). In such drugs, the total duration of action consists of the duration of the effects of both the original substance and its metabolites. A number of benzodiazepines do not form active metabolites or they are quickly inactivated (lorazepam, temazepam, etc.). Drugs of this type are better as hypnotics, as their after-effect is less pronounced.

According to the duration of the psychosedative effect, benzodiazepine derivatives can be represented by the following groups.

1. Medium-acting drugs.

A ($t_{1/2}$ = 12-18 h): lorazepam (Ativan), nosepam (oxazepam, tazepam), temazepam (restroil).

B ($t_{1/2} \approx$ 24 h): nitrazepam (Radedorm, Eunoctin).

2. Long-acting drugs ($t_{1/2}$ = 30-40 hours or more): phenazepam, flurazepam (Dalman), diazepam (sibazon, seduxen).

Nitrazepam (and other benzodiazepine derivatives) differ from barbiturates for the better in the following ways:

a) changes the structure of sleep to a lesser extent;

b) has a greater breadth of therapeutic action, therefore there is less danger of acute poisoning;

c) less pronounced induction of liver enzymes;

d) there is less risk of drug addiction (however, it is necessary to take this into account).

A significant number of such sleeping pills belong to derivatives of barbituric acid. The main effect of barbituric acid derivatives is related to their effect on the barbiturate - benzodiazepine - GABA - receptor complex, as a result of which the affinity of GABA to the corresponding receptor increases; their hypnotic and sedative effects are mainly due to GABA mimetic activity.

According to the duration of action, barbiturates are divided into 3 groups:

1. *Ultrashort-acting drugs* - thiopental, hexenal. They act within 30-40 minutes. They are used as anesthetics.

2. *Medium-acting drugs* - barbamil, etaminal-sodium (not used) and cyclobarbitap. The duration of action is 4-6 hours.

3. *Long-acting drugs* - barbital, sodium barbital (not used) and phenobarbital. Act within 6-10 hours.

Depending on the dose, the depressant effect of barbiturates on the central nervous system is of a diverse nature: in doses equal to 1/3-1/15 of a sleeping pill, they have a sedative effect, in doses from 0.1 to 0.6 g they have an anticonvulsant effect.

Today, barbituric acid derivatives are not widely used due to the large number of side effects:

1. Disruption of the sleep structure (barbiturates shorten the REM sleep phase) and the occurrence of the "return" syndrome in the form of painful insomnia and nightmares.

2. With long-term use of drugs, addiction develops.

3. Development of mental and physical dependence.

4. Cumulations are manifested by apathy, drowsiness, dizziness, weakness. Hallucinations, psychomotor excitement, convulsions are possible.

5. Cause the development of allergic reactions, mainly skin.

6. Long-term use of drugs in connection with the accelerated metabolism in the liver of folic acid, vitamins D and K can lead to the appearance of megaloblastic anemia, neutropenia, rickets-like osteopathy and hemorrhage.

7. They have a small range of therapeutic action.

8. Toxic doses of barbiturates (5-10 g) lead to deep depression of the central nervous system - narcosis, even death, due to paralysis of the respiratory and vascular centers.

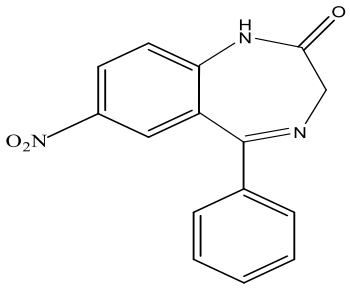
9. The hypnotic effect of barbiturates is caused by their influence on the conduction of excitation in the hypothalamus, limbic system, and thalamus.

10. Most sleeping pills cannot restore normal sleep. Only two drugs can guarantee physiological sleep - sodium oxybutyrate and chloral hydrate.

Chemical structures of some hypnotics

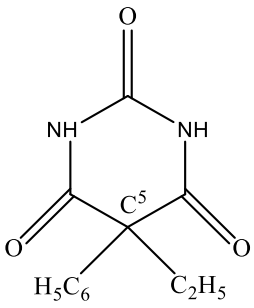
Benzadiazepine derivatives

Nitrazepam



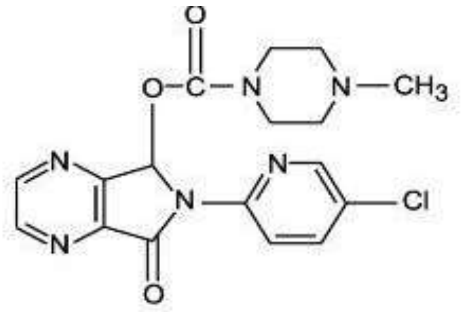
Derivatives of barbituric acid

Phenobarbital

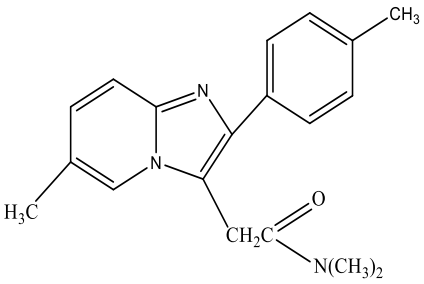


Different chemical structure

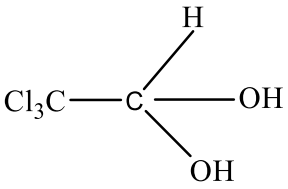
Zopiclone



Zolpidem



Aliphatic compounds

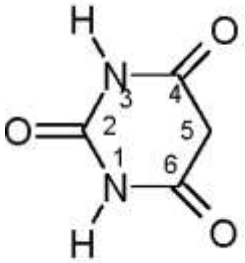


Chloral hydrate

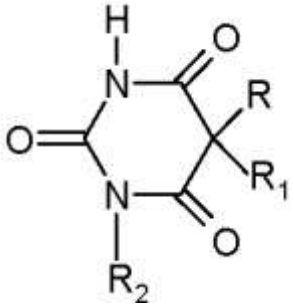
We will consider the analysis of drugs of this group using an example drug substances of the barbiturate group:

Drig substances - derivatives of barbituric acid

The structure of barbituric acid, which can be considered as a cyclic ureide, is based on the pyrimidine cycle. Derivatives of barbituric acid - barbiturates - are used in medicine as hypnotics, sedatives and anticonvulsants.

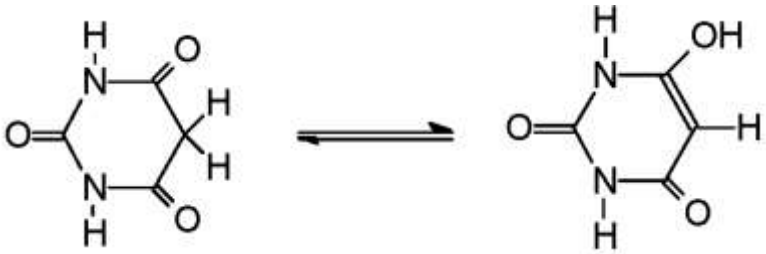


Barbituric acid



Barbiturates (general formula)

The acidic properties of barbituric acid are due to the mobility of hydrogen atoms of methylene and imide groups. In this regard, barbituric acid is characterized by two types of tautomerism: keto-enol, due to the mobility of the hydrogen of the methylene group:



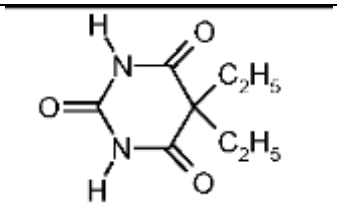
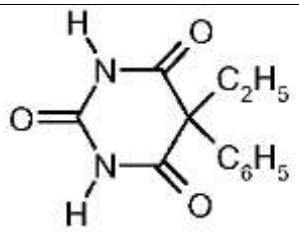
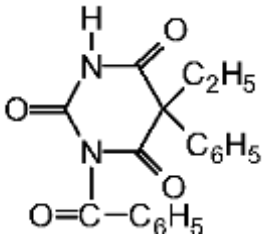
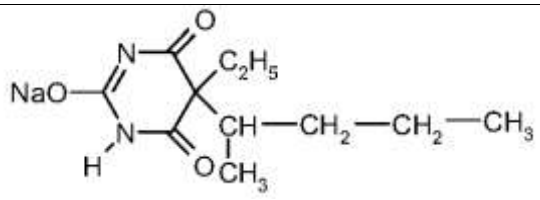
ketone form enol form

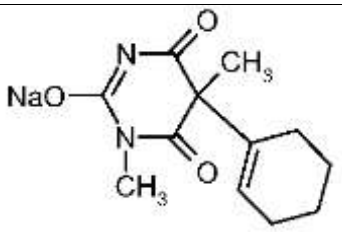
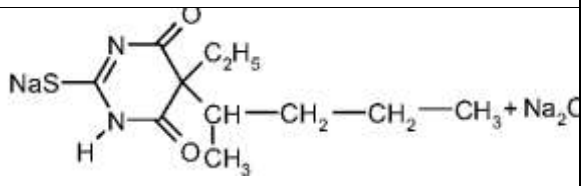
lactam-lactim, due to the mobility of the hydrogen of the imide group:

lactam form lactim form

Barbituric acid is 5-6 times stronger than acetic acid. 5-Monosubstituted barbituric acids are also quite strong acids (for example, 5-ethylbarbituric acid), and 5,5-disubstituted (for example, 5,5-diethylbarbituric acid) are very weak acids, weaker than carbonate. The acidic properties of barbiturates make it possible to obtain salt forms that, unlike acid forms, are soluble in water:

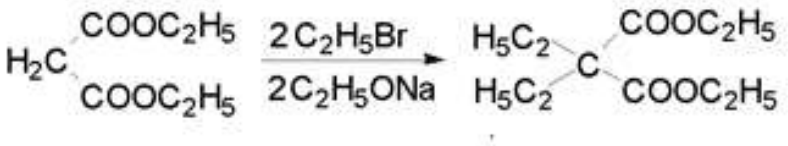
Drug substances of the barbiturate group

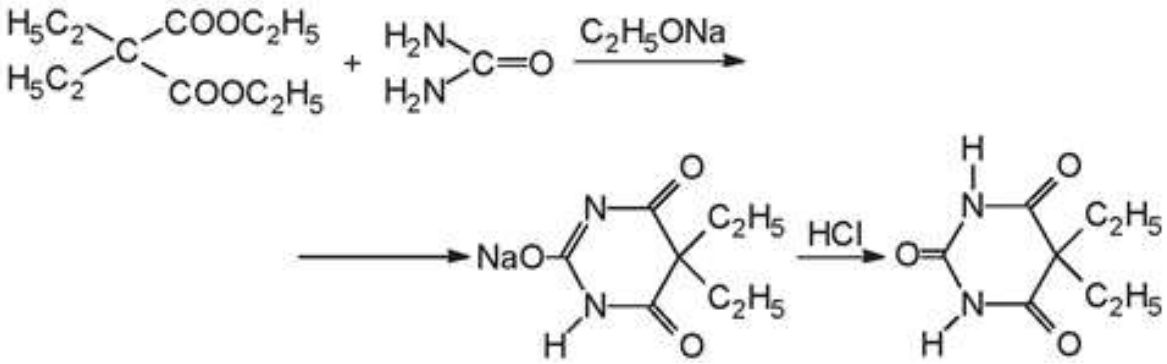
Drug substance **Latin, Ukrainian, international name**	**Chemical structure, chemical name**
Barbitalum Barbital*	 5,5-diethylbarbituric acid
Phenobarbitalum Luminal*	 5-ethyl-5-phenylbarbituric acid
Benzonalum Benzobarbitalum* Benzobarbital*	 1-benzoyl-5-ethyl-5-phenylbarbituric acid
Aethaminalum-natrium Nembutal* Pentobarbitalum Natricum*	 5-ethyl-5-(2'-amyl)-sodium barbiturate

Hexenalum Hexobarbital Sodium* Hexobarbitalum Natricum*	 Sodium 1,5-dimethyl-5-(cyclohexen-1'-yl)-barbiturate
Thiopentalum-natrium Thiopentalum Natricum cum Natrii Carbonate* Thiopental Sodium with Sodium Carbonate*	 mixture of sodium 5-ethyl-5-(2'-amyl)-2-thiobarbiturate with anhydrous sodium carbonate

Extraction. The synthesis of barbituric acid derivatives consists of two stages: obtaining the corresponding malonic acid ester; condensation of the obtained ester with urea in the presence of sodium alkoxide in a solution of absolute alcohol.

As an example, we can cite the barbital synthesis scheme:





Properties. White crystalline substances, white foamy mass (hexenal) or dry porous mass of yellowish color with a peculiar smell (thiopental-sodium), bitter to the taste. Acid barbiturates are practically insoluble or very slightly soluble in water, soluble or hardly soluble in alcohol and other organic solvents, easily soluble in alkali solutions. Barbiturates are hygroscopic salts, soluble or easily soluble in water and alcohol, practically insoluble in ether.

Identification:

Physico-chemical methods: determination of the melting point, IR spectroscopy, thin-layer chromatography.

Formation of complex salts with cations of heavy metals:

• argentum nitrate - white precipitate;

• cobalt (II) nitrate in the presence of calcium chloride - blue-violet color and precipitate (group reaction to barbiturates, with the exception of N-substituted ones) (SPhU);

• copper (II) sulfate in the presence of potassium bicarbonate and potassium carbonate (specific reaction):

• barbital - blue color and red-lilac precipitate;

• phenobarbital - a light lilac-colored precipitate that does not change upon standing;

• benzonal - gray-blue color, changing to bright blue, after which a white precipitate falls out;

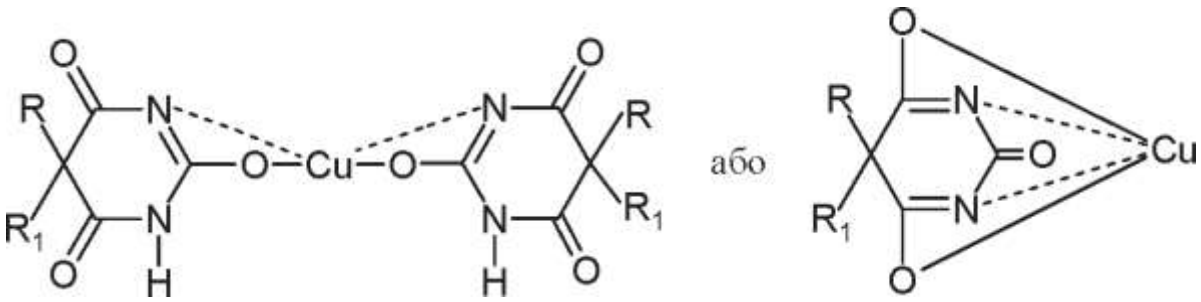
• sodium ethaminal - a blue precipitate;

• hexenal - blue color, changing to bright blue, after which a white precipitate falls out;

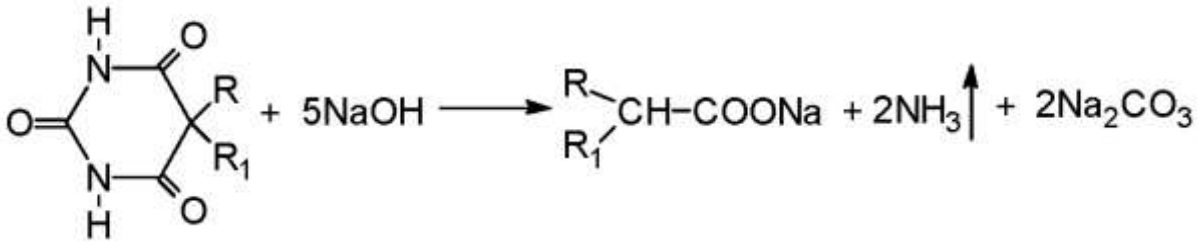
• sodium thiopental - yellow-green color with suspension.

The reactions must be carried out in a neutral environment (to prevent the formation of precipitates of metal hydroxides). Acidic forms are initially neutralized with sodium hydroxide solution.

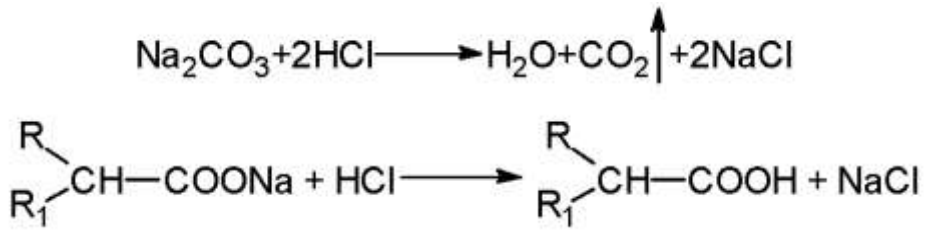
It is assumed that the composition of complexes can be as follows:



Fusion reaction with sodium hydroxide with the formation of salts of disubstituted derivatives of acetic acid, ammonia and sodium carbonate:



During further acidification, gas bubbles (CO_2) are released and the characteristic smell of acetic acid derivatives is felt:

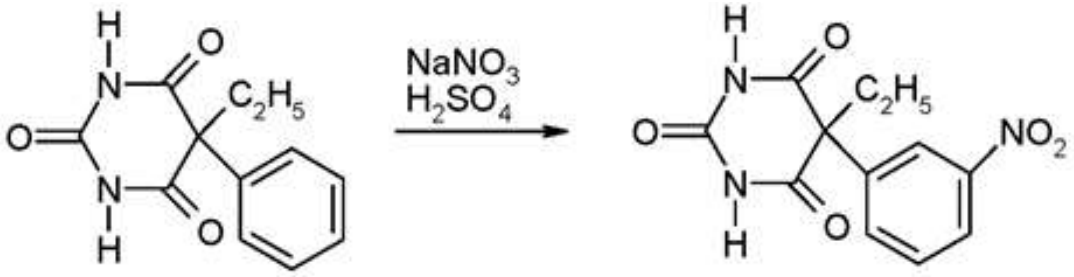


Formation reactions of colored products during condensation: with formaldehyde and concentrated sulfuric acid: phenobarbital, benzonal - pink color; hexenal - dark red with green fluorescence;

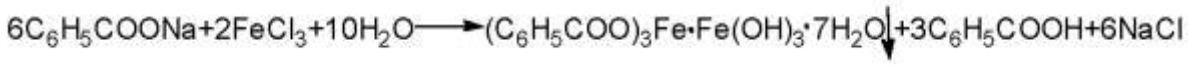
with p-dimethylaminobezaldehyde and concentrated sulfuric acid: ethaminal sodium - cherry-red color; barbital - yellow.

Specific reactions are due to the presence of substituents in positions 1 and 5.

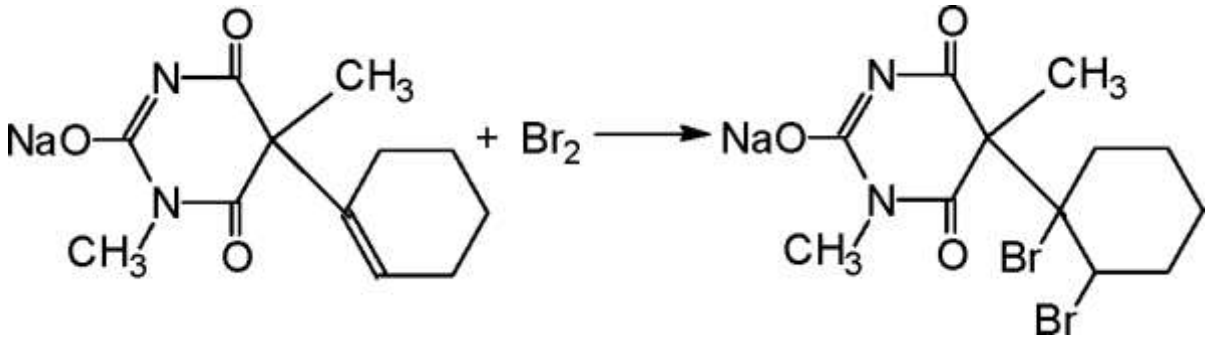
When phenobarbital interacts with sodium nitrate and concentrated sulfuric acid, a yellow color appears (reaction to the phenyl radical):



Benzonal after alkaline hydrolysis gives a reaction to the benzoate ion (from ferrum (III) chloride - a pinkish-yellow precipitate).

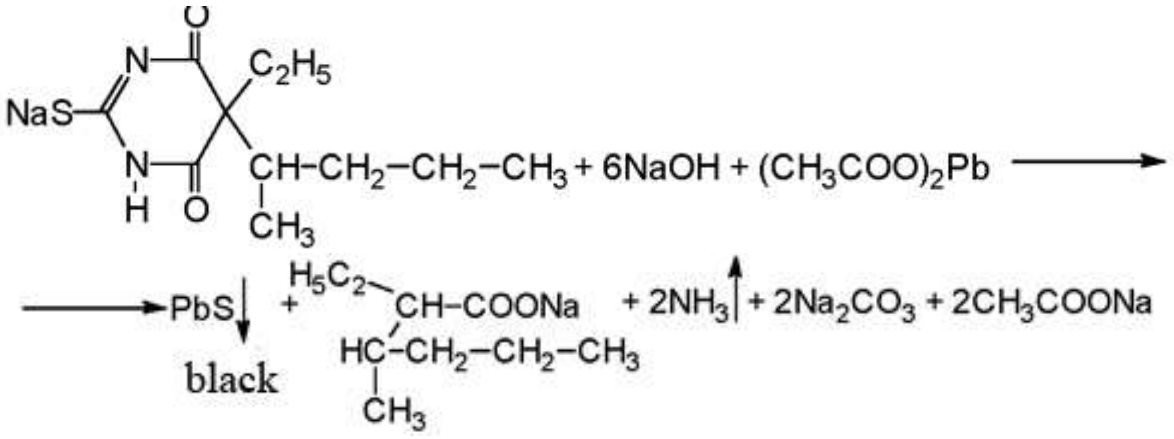


Hexenal decolorizes a solution of potassium permanganate and bromine water (due to the presence of a double bond):



Sulfur in sodium thiopental is detected:

a) when heated with solutions of lead (II) acetate and sodium hydroxide:



After acidification, hydrogen sulfide is released:

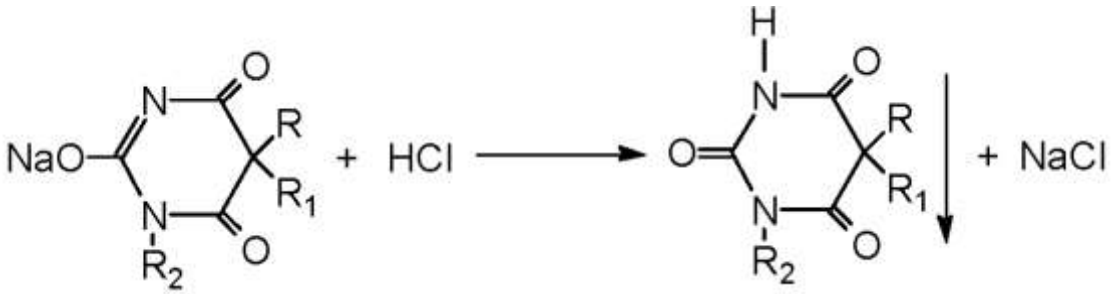
reaction to sulfate ions with barium chloride after dry mineralization with a mixture of sodium carbonate and potassium nitrate, releases a white precipitate of barium sulfate, insoluble in water, mineral acids or alkalis (even when heated).

$$\mathbf{SO_4^{2-} + BaCl_2 \rightarrow BaSO_4\downarrow + 2Cl^-.}$$

Sodium salts of barbiturates are also identified by:

a) corresponding reactions to sodium;

b) melting point of the acidic form after adding hydrochloric acid:



Purity test. In barbital and phenobarbital, in addition to general impurities, an admixture of 5-ethyl- or 5-phenylbarbituric acid, respectively, is determined by acidic properties. Since these acids are stronger than the corresponding barbiturates, when methyl red is added, the solution should be red-orange (but not red).

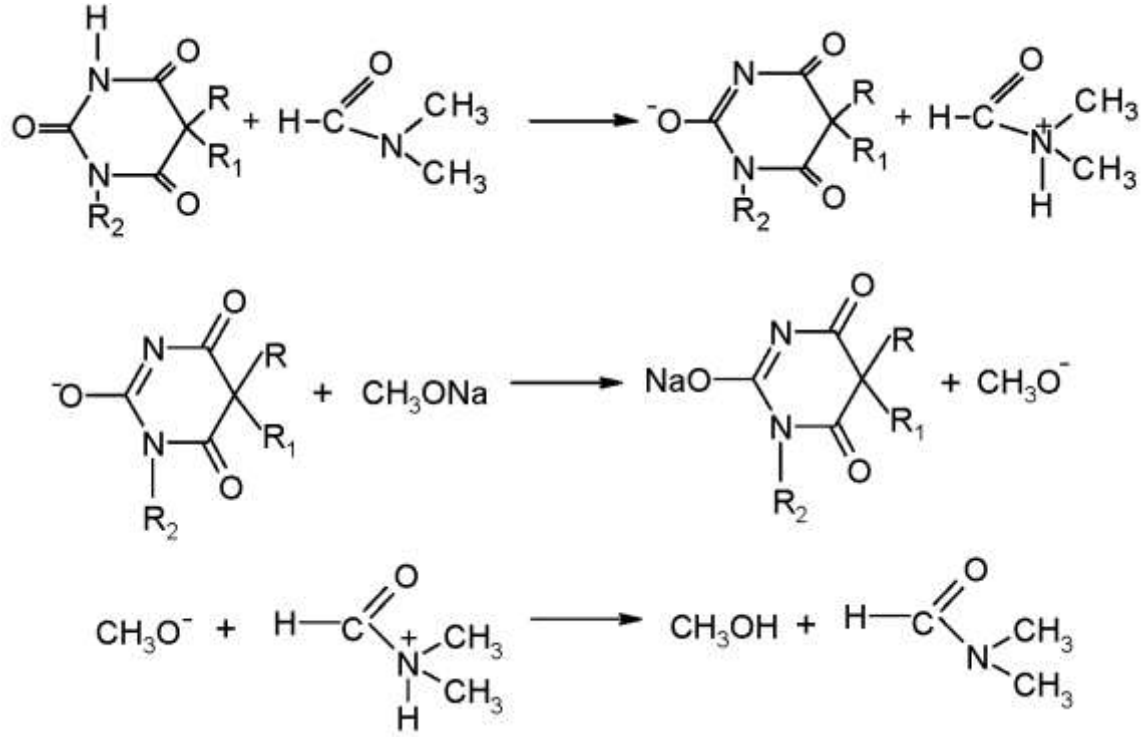
In salt forms of barbiturates, allowable impurities are determined:

free alkali (by titration with hydrochloric acid, indicator - thymolphthalein);

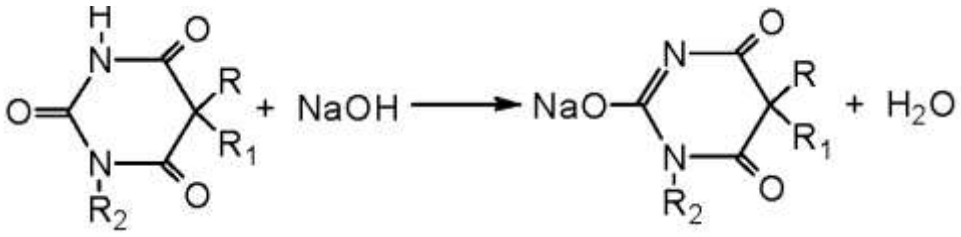
methyl alcohol by reaction with chromotropic acid (see metamizole sodium salt).

Quantitative definition: Acid-base titration:

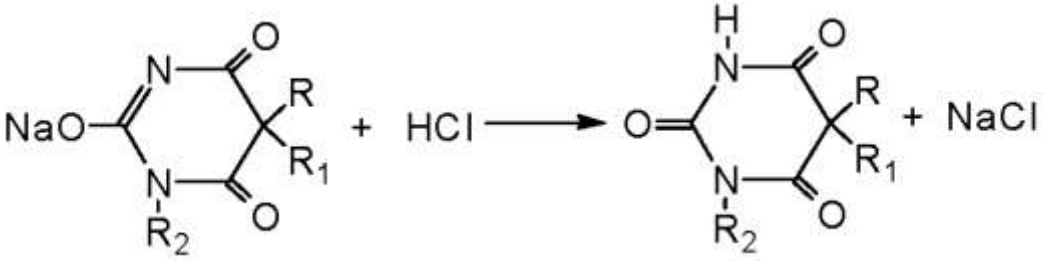
a) alkalimetry in a non-aqueous environment for acid forms of barbiturates. The weight of the substance is dissolved in dimethylformamide (DMF) or a mixture of dimethylformamide and benzene, neutralized by thymol blue (strengthens the acidic properties of barbiturate) and titrated with a solution of sodium methylate or a solution of sodium hydroxide in a mixture of methanol and benzene, the indicator is thymol blue:



b) alkalimetry in a water-alcohol environment for acid forms of barbiturates. The sample is dissolved in thymolphthalein-neutralized alcohol to improve the solubility of barbiturates and reduce the hydrolysis of their salts:



acidimetry in an aqueous environment for sodium salts of barbiturates, indicator - methyl orange:



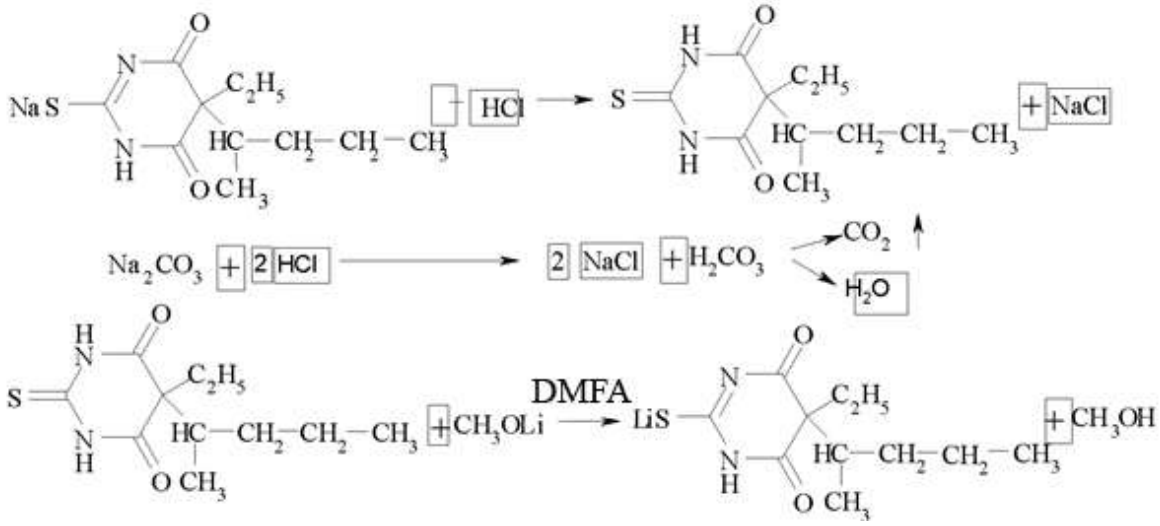
At the same time, the admixture of free alkali is also titrated. The content of barbiturate sodium salt (%) in terms of dry matter is calculated according to the formula:

$$\% = \frac{V_{HCl} \cdot K\Pi \cdot T \cdot 100 \cdot 100}{m \cdot (100 - \%_{\text{moisture}})} - \%_{\text{alkali}} \cdot K,$$

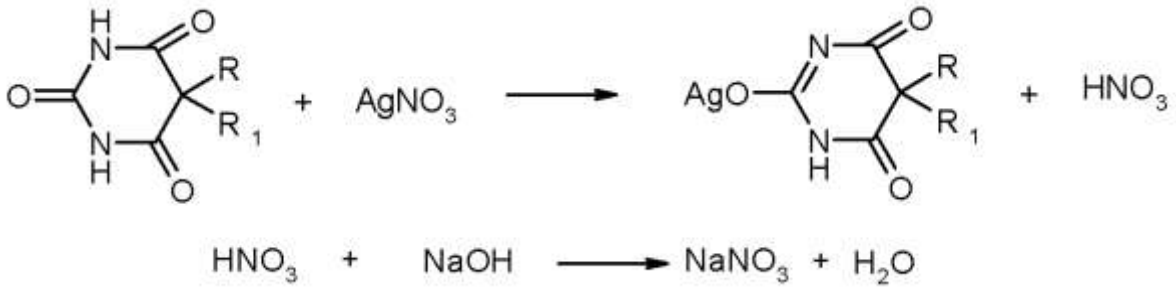
where: % alkali - percentage content of free alkali in the substance;

K - coefficient, which is calculated as a ratio of M.m. salt to M.m. sodium hydroxide.

Sodium thiopental is converted into an acid form and titrated with a solution of lithium methylate:

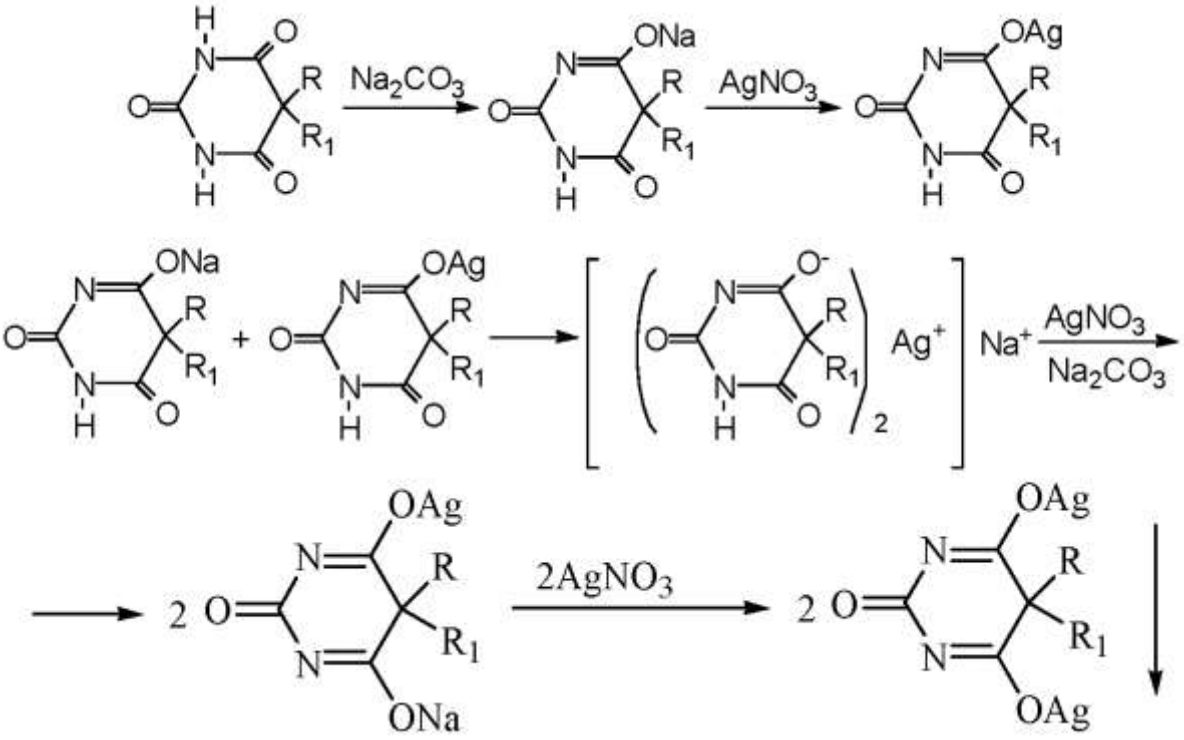


Alkalimetry by substitute. The method is based on the formation of a silver salt during the interaction of a barbiturate with a solution of argentum nitrate in pyridine, as a result of which an equivalent amount of nitric acid is released, which is titrated with an alcoholic solution of sodium hydroxide, the indicator is thymolphthalein. In parallel, a control experiment is carried out:



Gravimetry. Acidic forms of barbiturates are extracted with ether from an acidic solution. The ether is distilled off, the residue is dried and weighed. The method is used for the analysis of sodium thiopental.

Argentometry. A weight of acid or salt form is dissolved in a 5% solution of anhydrous sodium carbonate and titrated with a solution of argentum nitrate without an indicator until the appearance of permanent turbidity (disubstituted argentum barbiturate salt):



Storage. In well-stoppered glasses. Phenobarbital and benzonal – in glasses made of dark glass in a place protected from light. Hexenal and sodium thiopental – in glass vials of 0.5-1.0 g, hermetically closed with rubber stoppers, crimped with aluminum caps, in a dry, cool, protected from light place.

As a stabilizer, 0.05-0.25% sodium hydroxide is added to hexenal; sodium thiopental – 5-6% of sodium carbonate.

Aqueous solutions of sodium salts of barbiturates are easily hydrolyzed, so their solutions are prepared ex tempore.

Use. Sedatives and hypnotics. Phenobarbital and benzonal are used as antiepileptic drugs. Hexenal and sodium thiopental solutions are used for intravenous anesthesia.

TEST TASKS ON THE TOPIC «HYPNOTICS (SLEEP AIDS)»

1. A woman turned to a neurologist with complaints of poor sleep, feelings of fear, anxiety. What drug should be prescribed to the patient?
   A. Levodopa

B. Diazepam

C. Oxytocin

D. Nitroglycerin

E. Lisinopril

2. A 50-year-old patient was prescribed a benzodiazepine derivative to treat insomnia. Name this drug.

A. Bromizoval

B. Phenobarbital

C. Zolpidem

D. Nitrazepam

E. Donormil

3. Which drug from the group of barbiturates will discolor bromine water?

A. Hexenal

B. Barbital

C. Phenobarbital

D. Benzonal

E. Sodium barbital

4. The introduction of which position of radicals determines the pharmacological effect of barbituric acid derivatives:

A. 5

B. 4

C. 1

D. 2

E. 3

5. Replacing the ethyl radical with a phenyl radical in the 5th position leads to an increase in the pharmacological effect and the appearance of:

A. Soporific effect

B. Local irritant action

C. Aseptic action

D. Exciting action

E. Anticonvulsant action

6. To determine the covalently bound bromine in the bromisoval, we carry out:

A. Reaction with silver nitrate solution without prior mineralization

B. Mineralization of the substance with sodium hydroxide solution followed by reaction with bromides

C. Reaction with silver nitrate solution after destruction of the drug with concentrated nitric acid

D. Reaction with mercury dichloride solution

E. Reaction with a solution of iron (III) chloride

7. Barbiturates according to their chemical structure are:

A. Cyclic ureides

B. Complex esters

C. Lactones

D. Ureids

E. Acyclic ureides

8. The interaction of barbiturates with salts of heavy metals is due to the following properties:

A. Main

B. Acidic

C. Oxidative

D. Restorative

E. Amphoteric

9. The general group reaction for barbiturates is:

A. Salt and complex formation with salts of heavy metals

B. With solutions of aldehydes in concentrated sulfuric acid

C. Formation of azo dye

D. Hydrolytic decomposition

E. Reduction reactions

10. The formation of a precipitate is observed when the following solution is acting on aqueous solutions of salt forms of barbiturates:

A. Sodium hydroxide solution

B. Hydrochloric acid solution

C. Ammonium hydroxide solution

D. Sodium bicarbonate solution

E. Potassium carbonate solution

11. Which of the listed drugs is determined by the argentometric method after preliminary boiling with sodium hydroxide solution:

A. Sodium barbital

B. Bromisoval

C. Sodium thiopental

D. Benzonal

E. Phenobarbital

12. In the control and analytical laboratory, an analysis of barbital is carried out for the presence of chloride impurities. For this, the pharmacist should use as a reagent a solution of:

A. Silver nitrate

B. Acetic acids

C. Barium chloride

D. Sodium sulfide

E. Ammonium oxalate

13. What druf substance is synthesized by the reaction between diethylmalonic ether and urea in the presence of sodium ethylate followed by treatment with hydrochloric acid?

A. Barbital

B. Benzoic acid

C. Benzonal

D. Nicotinic acid

E. Ascorbic acid

14. Which drug substance from the group of barbiturates corresponds to the chemical name 1-benzoyl-5-ethyl-5-phenylbarbituric acid?

A. Barbital

B. Benzonal

C. Phenobarbital

D. Hexenal

E. Benzobamil

15. The hypnotic drug bromisoval contains in its structure:

A. Carbamide group

B. Oxygenated heterocycle

C. Phenolic hydroxyl

D. Complex ether group

E. Nitro- and carboxyl groups

16. Quantitative determination of which of the specified drug substances can be carried out by the Folgard method only after alkaline hydrolysis?

A. Bromisoval

B. Procaine hydrochloride

C. Sulfacyl sodium

D. Phthalazole

E. Drotaverin hydrochloride

17. The reaction of diazotization followed by azo compound is common to substances that contain a primary aromatic amino group. Which of the following drugs does not cause this reaction:

A. Barbital

B. Benzocaine

C. Procaine hydrochloride

D. Procainamide hydrochloride

E. Streptocide

18. The drug phenobarbital has a sedative, hypnotic and antiepileptic effect. Specify its international non-proprietary name:

A. Chloramphenicol

B. Nitrofural

C. Luminal

D. Diazepam

E. Salol

19. The pharmacist performs the identification reaction of barbiturates according to the SPhU. With which reagents do they form a violet-blue color with the formation of a precipitate?

A. Cobalt nitrate, calcium chloride, sodium hydroxide

B. Copper sulfate, potassium bicarbonate, potassium carbonate

C. Iron (III) chloride, potassium bicarbonate, potassium carbonate

D. Lead nitrate, calcium chloride, sodium hydroxide

E. Nickel nitrate, potassium bicarbonate, potassium carbonate

20. Specify the color of the complex salt, which is formed during the identification of phenobarbital by reaction with a solution of cobalt (II) nitrate:

A. Pink-lilac

B. Yellow

C. Blue-violet

D. Orange-red

E. Yellow-green

21. The pharmacist identifies the drug, a derivative of barbituric acid, by reaction with copper (II) sulfate in the presence of potassium bicarbonate and potassium carbonate. At the same time, the appearance of a blue color and the formation of a red-lilac precipitate make it possible to detect:

A. Barbital

B. Phenobarbital

C. Benzonal

D. Ethaminal sodium

E. Hexenal

22. In which drug from the group of barbiturates can a fragment of benzoic acid be identified with a hydroxam test?

A. Sodium barbital

B. Barbital

C. Phenobarbital

D. Hexanal

E. Benzonal

23. The specialist of the Department of Technical Control of the chemical-pharmaceutical enterprise fuses the drug substance with sodium hydroxide. Further acidification of the reaction product leads to the release of gas bubbles (carbon dioxide) and the appearance of the characteristic smell of phenylethylacetic acid. Name the drug substance that can be identified by these tests:

A. Phenobarbital

B. Resorcinol

C. Codeine

D. Streptocide

E. Phenoxymethylpenicillin

24. Drug products from the barbiturate-acid group are quantitatively determined by the method of alkalimetry in a non-aqueous environment. The following should be used as a solvent:

A. Dimethylformamide

B. glacial acetic acid

C. Acetic anhydride

D. Ethyl alcohol

E. Glycerin

3. ANTITUSSIVES

Cough is a complex protective reflex that occurs in response to mechanical or chemical irritation of the receptors of the larynx and lower respiratory tract.

By nature, the cough can be dry (unproductive), which is not accompanied by sputum discharge, and wet (productive) — with sputum discharge. According to the duration of the symptom, cough is classified as acute (lasting up to 3 weeks), subacute (3–6 weeks) and chronic (lasting more than 6–8 weeks). Among the main factors for the occurrence of acute cough are stimuli that activate receptors located outside the respiratory organs, in particular in the ear canal, esophagus, stomach, intestines, on the skin - infectious agents, chemical irritants, foreign bodies and allergens, as well as excitation of the central nervous system.

The most frequent (in 80–90% of cases) causes of chronic cough include: smoking, chronic obstructive pulmonary disease, transient bronchial hyperreactivity, bronchial asthma, postnasal drainage syndrome, gastroesophageal reflux. Infrequent (in 10–20% of cases) causes of chronic cough include: tuberculosis, lung cancer, interstitial lung diseases, lung abscess, cystic fibrosis, recurrent aspiration, bronchial foreign bodies, heart failure, use of a number of medications, psychogenic cough.

Medicines of the following pharmacological groups are most often prescribed for the treatment of cough:

1. Antitussives.
2. Expectorants.
3. Broncholytic drugs.
4. Antiallergic and anti-inflammatory drugs.

Antitussives are drugs that suppress the cough reflex.

This group of medicines is used for dry, supersedative, debilitating, unproductive cough. Such a cough can increase arterial, intrathoracic and intraocular pressure, which is unacceptable in case of concomitant arterial

hypertension, glaucoma, impaired cerebral circulation and threatens hypertensive crisis, stroke, development of pulmonary heart failure, emphysema.

Antitussive drugs affect the central and peripheral links of the cough reflex, they are classified depending on the localization of action.

Classification of antitussives by mechanism of action

1. Antitussives of the central type of action (drugs that suppress the central links of the cough reflex — the cough center):

1.1. Narcotic drugs:

- Methylmorphine (codeine phosphate) and combined drugs based on it (codeterpin, codesan, cafetin, etc.).

- Dextromethorphan and combined drugs based on it (Akodin, Atusin, Robusin, Coldrex Night, Gripex, etc.).

1.2. Non-narcotic drugs:

- Glaucine hydrochloride (glauvent) and combined preparations based on it (broncholitin).

- Oxeladin (tusuprex, paxeladine).

- Butamirate citrate (sinecode) and combined preparations based on it (stoptusin).

2. Antitussives of the peripheral type of action (drugs that suppress the peripheral links of the cough reflex - block receptors of the respiratory tract):

- Prenoxdiazine (Libexin, Glibexin).

Antitussives of the central type of action

The basis of the action of antitussive drugs of the central type of action is their ability to suppress the activity of the cough center of the medulla oblongata, which, depending on the development of possible complications (development of euphoria and drug addiction), are divided into narcotic and non-narcotic drugs. Today, preparations containing opium alkaloids, in particular methylmorphine (codeine), have not lost their relevance. In addition, a synthetic analogue of methyl morphine - dextromethorphan - is used.

The pharmacological effect of drugs of this group develops as a result of their interaction with opiate receptors of the cough center of the medulla oblongata. Drugs can cause depression of the respiratory center (which is especially dangerous in children), drowsiness, constipation. Long-term use leads to the development of tolerance and drug addiction. That is why the release of these drugs in the form of monopreparations is allowed only by prescription.

Antitussives of the peripheral type of action

This group of antitussives is represented by prenoxdiazine (Libexin, Glibexin) - a synthetic drug with a combined effect. The drug slightly suppresses the cough center, blocks peripheral receptors of the upper respiratory tract (local anesthetic effect) and exhibits an antispasmodic effect, which prevents bronchospasm. When using this drug, dryness in the mouth and throat, development of arterial hypotension are possible. When prenoxdiazine is chewed, numbness and loss of sensitivity of the mucous membrane of the mouth and throat are possible.

One of the pathogenetic mechanisms of cough in patients with bronchial and lung pathology is the formation of viscous sputum, which is poorly excreted and leads to violation of bronchial patency. At the same time, antitussive drugs are contraindicated, because suppression of wet cough can lead to sputum retention and progression of the infectious process. With a productive cough, it is necessary to improve the discharge of sputum from the upper respiratory tract, and therefore it is advisable to use expectorants - drugs that thin sputum and facilitate its removal.

Classification of expectorants by mechanism of action

1. Secretomotor expectorants.

1.1. Preparations of the reflex type of action (galenic preparations from the grass of anise, licorice roots, altea, plantain, ivy; terpin hydrate, guaifenesin; essential oils of medicinal plants, etc.).

1.2. Preparations of the resorptive type of action (sodium iodide, potassium iodide, sodium bicarbonate, etc.).

1.3. Drugs of mixed type of action (mukaltin).

2. Mucolytic agents.

2.1. Enzyme preparations (crystalline trypsin, ribonuclease, etc.).

2.2. Synthetic mucolytics (acetylcysteine; carbocysteine).

2.3. Surfactant synthesis stimulants (bromhexine, ambroxol hydrochloride).

2.4. Surfactant substitutes (exosurf).

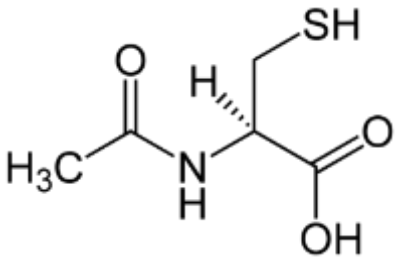
3. Combined drugs

Today, all expectorants are conventionally divided into 2 groups based on the mechanism of action. The drugs of the first group thin the bronchial secretion by increasing the secretion of the bronchial glands (mainly the aqueous component of mucus) and are therefore called secretomotor expectorants.

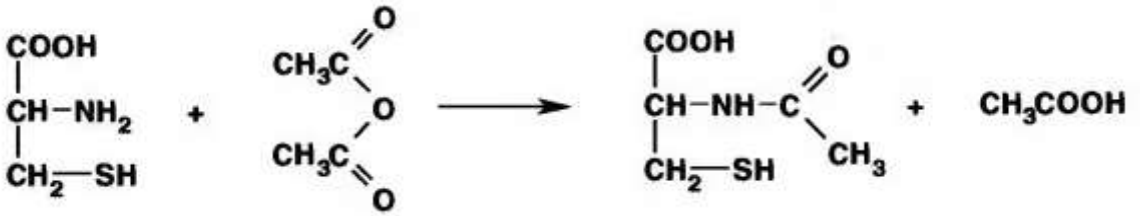
Mucolytics, drugs of the second group, reduce the viscosity of sputum by disrupting the structure of mucopolysaccharides, which determine the specific consistency of bronchial secretions.

We will consider the analysis of drugs of this group using an example Acetylcysteine:

Acetylcysteine



The production of acetylcysteine is based on the ability of amino acids to be acetylated by the amino group:



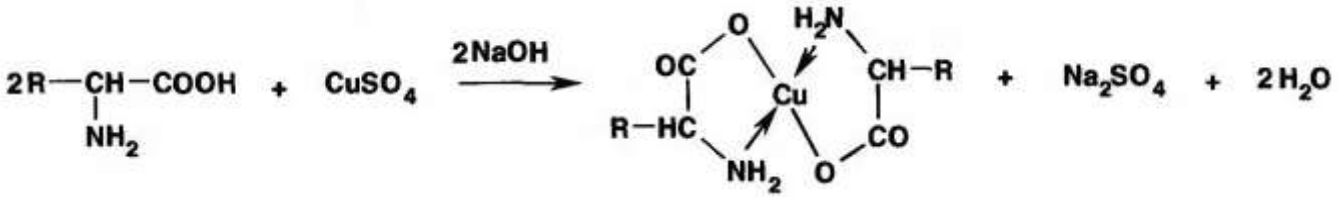
N-acetyl-L-cysteine

Description: White or white with a slightly yellowish tinge crystalline powder with a weak specific smell. Melting point: 106-110°C. Specific rotation from +21 to +26 ° (in sodium hydroxide solution). Acetylcysteine is easily soluble in water.

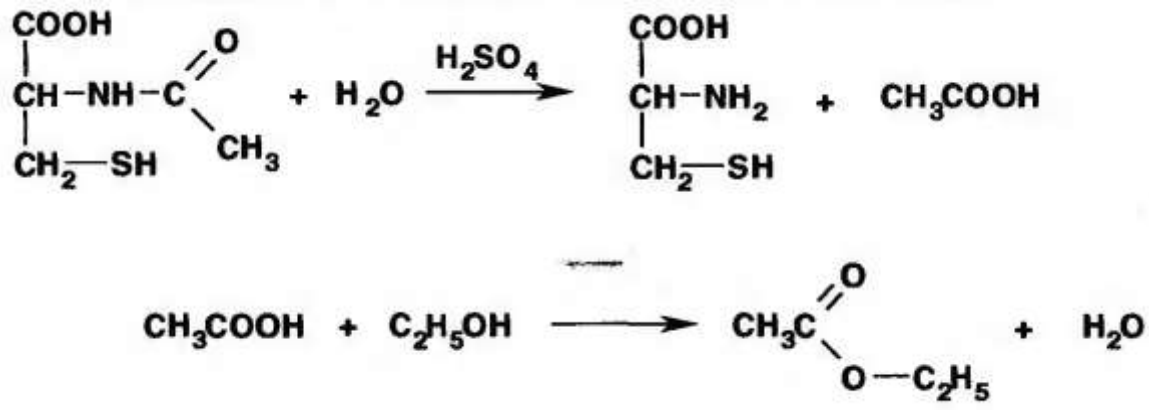
Such physical constants as melting point and specific rotation are used for identification.

The UV absorption spectrum of acetylcysteine has an absorption maximum at 233 nm (solvent 0.1 M sodium hydroxide solution). The specific absorption index is 353.

A general color reaction with ninhydrin is used to test the authenticity of amino acids. As a result of the reaction, an ammonium salt of the enol form of diketohydrindenketohydrinamine is formed, which has a blue-violet color.



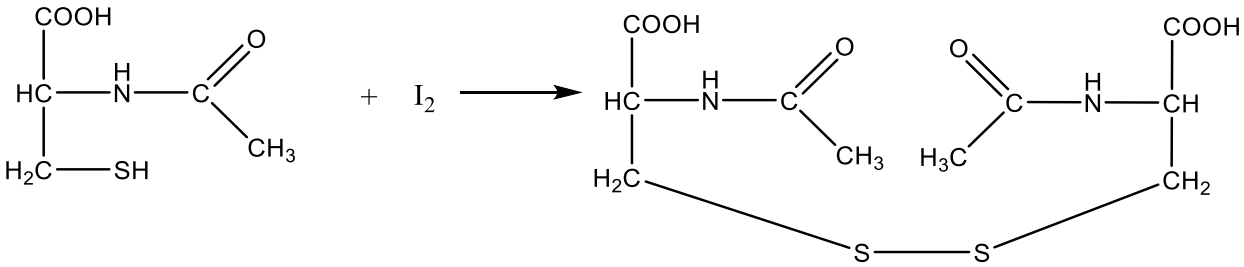
The reaction of the formation of ethyl acetate is used to detect the acetyl group in acetylcysteine. It is pre-boiled with a solution of potassium dichromate in sulfuric acid, and then ethanol is added.



The presence of a thio group in a cysteine molecule can be established by a color reaction in an alkaline environment with sodium nitroprusside (red-violet color).

The thio group in the molecule of cysteine and acetylcysteine is confirmed by a color reaction with iron (III) chloride by the appearance of a rapidly disappearing blue color, or sodium nitrite is used as a reagent in the presence of acetic acid (red color). When cysteine and acetylcysteine solutions are treated with selenium acid, a red precipitate is formed.

Sulfur-containing amino acids are determined by the iodometric method. Cysteine and acetylcysteine are titrated in an acidic environment with a 0.1 M iodine solution. The definition is based on the oxidation of sulfhydryl groups according to the general scheme:



Amino acids are stored in a well-sealed container protected from light in a dry, cool, light-protected place to prevent decomposition.

Acetylcysteine belongs to list B.

Acetylcysteine has a mucolytic effect (thins sputum and facilitates its separation). They are used in the form of 20% solutions for inhalation.

M-derivative of the natural amino acid cysteine. The action of the drug is associated with the presence of a free sulfhydryl group in the structure of the molecule, which cleaves the disulfide bonds of macromolecules, mucus glycoprotein by the sulfhydryl-disulfide substitution reaction; as a result, disulfides of M-acetylcysteine are formed, which have a much lower molecular weight, and the viscosity of sputum decreases.

Acetylcysteine

• has a stimulating effect on mucous cells, the secret of which has the ability to lyse fibrin and blood clots;

• able to increase the synthesis of glutathione, which is important for detoxification, in particular, in case of poisoning with paracetamol and pale toadstool;

• protective properties directed against such factors as free radicals, reactive oxygen metabolites responsible for the development of acute and chronic inflammation in the lung tissue were found.

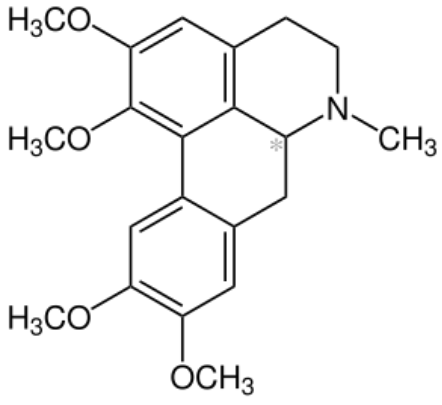
Pharmacokinetics and pharmacodynamics

When taken orally, the drug is quickly and well absorbed, in the liver it is metabolized (hydrolyzed) into an active metabolite - cysteine. Due to the "first pass" effect, the bioavailability of the drug is low (about 10%). The maximum concentration in blood plasma is reached after 1-3 hours.

Indications and contraindications

Acetylcysteine is indicated as an auxiliary agent for various bronchopulmonary diseases with the presence of thick, viscous sputum of a mucous or muco-purulent nature: chronic obstructive bronchitis, bronchiolitis, bronchopneumonia, bronchiectasis, bronchial asthma, cystic fibrosis.

Glaucine hydrochloride

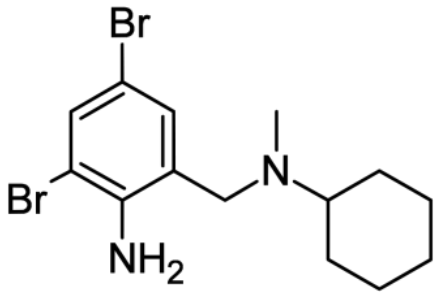


Pharmacological action. Centrally acting antitussive. Alkaloid of the plant Glaucium flavum. Long-term use does not cause drug dependence and addiction. Has adrenolytic properties, can cause a decrease in blood pressure. Glaucine also relieves the spasm of bronchial smooth muscles in bronchitis. It is prescribed for tracheitis, pharyngitis, acute bronchitis, whooping cough. When used, depression

of breathing, delay in the suppression of secretions from the bronchi and expectoration of sputum are noted. A moderate decrease in blood pressure is possible, so Glaucine is not prescribed to people suffering from hypotension and people with myocardial infarction.

Glaucin is a part of combined drugs (Bronholitin, Bronchitussen Vramed, Bronchoton, Broncholin sage) - the dose of the drug is selected according to age. General contraindications are: myocardial infarction, arterial hypotension, cough with sputum.

Bromhexine

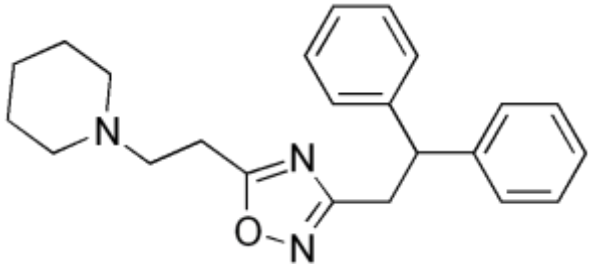


Pharmacological action - expectorant, mucolytic, antitussive.

Causes depolymerization of mucoprotein and mucopolysaccharide polymer molecules (mucolytic effect). Stimulates the production of endogenous surfactant, which ensures the stability of alveolar cells during breathing, their protection from adverse factors, improvement of the rheological properties of bronchopulmonary secretion, its sliding along the epithelium and the release of sputum from the respiratory tract.

When taken orally, it is almost completely (99%) absorbed in the gastrointestinal tract within 30 minutes. Bioavailability is 80% due to the effect of "first passage" through the liver. It binds to proteins in plasma. Penetrates through the blood-brain barrier and the placental barrier. It undergoes demethylation and oxidation in the liver. Part of the formed metabolites retains activity. T1/2 - hour, but the terminal T1/2 reaches 15 hours due to slow back diffusion from tissues. It is excreted by the kidneys. With repeated use, it can accumulate.

Libexin (Prenoxdiazine)



Prenoxdiazine is a peripherally acting antitussive. The drug blocks the peripheral links of the cough reflex due to the following effects: local anesthetic effect, which reduces the irritability of peripheral sensitive (cough) receptors of the respiratory tract; bronchodilatory action, thanks to which the stretch receptors involved in the cough reflex are suppressed; a slight decrease in the activity of the respiratory center (without respiratory depression).

TEST TASKS ON THE TOPIC «ANTITUSSIVES»

1. A chemist of a pharmaceutical enterprise can confirm the sodium cation in the tested substance, according to the SPhU, with a solution of:
   A. Potassium pyroantimonate
   B. Potassium ferrocyanide
   C. Potassium chloride
   D. Potassium hydroxide
   E. Potassium nitrate

2. The pharmacist determines the quantitative content of sodium benzoate by the method of acidimetry in a non-aqueous environment in accordance with the requirements of the SPhU. What reagent does he use as a solvent?
   A. Concentrated sulfuric acid
   B. Pyridine
   C. Anhydrous acetic acid
   D. Dimethylformamide
   E. Sulfanilic acid

3. The reaction of the formation of ethyl acetate is used to detect the acetyl group in Acetylcysteine when adding which reagent:

A. Iron chloride

B. Sodium hydroxide solution

C. 2,4 - dinitrochlorobenzene

D. 96% alcohol

E. Boiling with a solution of potassium dichromate in sulfuric acid and subsequent addition of ethanol.

4. Which reagent should be used to detect the thiogroup in the acetylcysteine molecule:

A. With iron oxide chloride

B. With alkali

C. With alcohol

D. With chloroform

E. With chloramine

5. What reagent must be added to determine the carboxyl group in Acetylcysteine:

A. Concentrated acid

B. Heavy metal salt

C. Dimethylformamide

D. Perhydrol

E. Alkali

6. What method can quantitatively determine acetylcysteine:

A. Iodometric

B. Bromatometric

C. S. Iodochlormetric

D. Argentometric

E. Complexonometric

7. What is the iodometric titration of acetylcysteine based on:

A. physical and chemical properties

B. presence of a primary amino group in the drug

C. S. specific rotation index

D. oxidation of sulfhydryl groups

E. pharmacological properties

8. Suggest a reagent for detecting the primary aromatic amino group in the bromhexine molecule:

A. Sodium nitrite, sulfuric acid and β-naphthol

B. Sodium nitrate, hydrochloric acid and β-naphthol

C. Sodium nitrite, hydrochloric acid and β-naphthol

D. Sodium nitrite, hydrochloric acid

E. Hydrochloric acid and β-naphthol

9. The presence of bromine in bromhexine hydrochloride is established after the destruction of the organic part of the molecule to sodium bromide by boiling in a 30% solution of sodium hydroxide and the subsequent addition of:

A. Dilute hydrochloric acid, 5% chloramine and tetrachloromethane

B. Dilute sulfuric acid, 5% chloramine

C. Dilute sulfuric acid, tetrachloromethane

D. Dilute sulfuric acid

E. Tetrachloromethane

10. To confirm the reliability of bromhexine hydrochloride and establish the absence of extraneous impurities, we use the following method:

A. thin-layer chromatography

B. HPLC

C. Photoelectric Colorimetry

D. Refractometry

E. Polarimetry

11. When identifying glaucin hydrochloride, a reagent was added to the preparation, a white curdled precipitate is formed, dissolved in an ammonia solution. What reagent was added:

A. Sodium hydroxide

B. Concentrated sulfuric acid

C. Alkali solution

D. Potassium dichromate

E. Silver nitrate

12. Identification of bromhexine and ambroxol can be carried out with the help of general alkaloid reagents. Which reaction has the most sensitivity with the reagent:

A. Dragendorf

B. Marquis

C. Froehde

D. Bouchard

E. Wagner

13. One of the possible methods of quantitative determination of bromhexine hydrochloride is the method of:

A. Complexonometry

B. Nitritometry

C. Cerimetry

D. Permanganatometry

E. Iodometry

14. Bromhexine hydrochloride can be determined quantitatively using non-aqueous titration as a titrant with:

A. Iodine solution

B. Hydrochloric acid solution

C. Potassium permanganate solution

D. Perchloric acid solution

E. Sodium thiosulfate solution

15. Bromhexine hydrochloride can be determined quantitatively using non-aqueous titration as an indicator with:

A. Crystal violet

B. Phenolphthalein

C. Etching black

D. Methyl orange

E. Tropeolin 00

16. Ambroxol hydrochloride belongs to the following group of antitussives according to the mechanism of action:

A. Non-narcotic drugs

B. Narcotic drugs

C. Peripheral-type antitussives

D. Mucolytics

E. Expectorants

17. Bromhexine hydrochloride belongs to the following group of antitussives according to the mechanism of action:

A. Non-narcotic drugs

B. Narcotic drugs

C. Peripheral-type antitussives

D. Expectorants

E. Mucolytics

18. Acetylcysteine belongs to the following group of expectorants according to the mechanism of action:

A. Synthetic mucolytics

B. Surfactant synthesis stimulants

C. S. Enzyme drugs

D. Drugs of mixed type

E. Drugs of the resorptive type of action

19. When determining the chloride ion from silver with nitrate in Glaucine hydrochloride, a precipitate of what color falls out:

A. White, curdled

B. The solution is white

C. chloroform layer is purple in color

D. Yellow

E. Yellow solution

20. The second phase of drug metabolism (conjugation phase) includes interactions of xenobiotics or their metabolites, which have active functional groups, with hydrophilic endogenous molecules. This phase includes the process of:

A. S-Oxidation

B. Glucuronidation

C. Hydroxylation

D. Recovery

E. Hydrolysis

21. Drugs are metabolized in several stages. Functional groups in the drug substance molecule undergo biochemical transformation during the following phase:

A. Conjugations

B. Secretions

C. Hydration

D. Functionalization

E. Depolarization

22. Drugs are metabolized in several stages. Biochemical conjugation of functional groups of the molecule with acid residues, such as glucuronic and sulfate, or glycine, occurs in the phase of:

A. Functionalization

B. Secretions

C. Hydration

D. Depolarization

E. Conjugations

23. Metabolism of drugs is one of the stages of pharmacokinetics. Agents that are metabolically transformed into biologically active substances are called:

A. Vitamins

B. Prodrugs

C. Hormones

D. Enzymes

E. Conjugates

24. Drugs are able to undergo biotransformation in the body. The metabolic phase of functionalization is aimed at:

A. Binding to endogenous molecules

B. Increase in hydrophilicity

C. Mineralization of matter

D. Formation of polymers

4. NOOTROPIC DRUGS

Nootropics (Greek: Noos - thinking, mind; tropos - direction) are drugs that have a specific positive effect on the higher integrative functions of the brain. They improve mental activity, stimulate cognitive functions, learning and memory, increase the resistance of the brain to various negative factors, including extreme loads and hypoxia. In addition, nootropics have the ability to reduce neurological deficits and improve corticosubcortical communication.

There is a group of "true" nootropic drugs, for which the ability to improve memory functions is the main, and sometimes the only effect, and a group of nootropic drugs of mixed action ("neuroprotectors"), in which this effect is supplemented, and often overlapped by other, not less significant manifestations of action. A number of substances belonging to the group of nootropic agents have a fairly wide spectrum of pharmacological activity, including antihypoxic, anxiolytic, sedative, anticonvulsant, muscle relaxant and other effects.

The nootropic effect of the drug can be both primary (direct effect on the nerve cell) and secondary, due to the improvement of cerebral blood flow and microcirculation, antiplatelet and antihypoxic effects.

There are a number of synonyms for substances of this group: neurodynamic, neuroregulatory, neuroanabolic or eutrophic agents, neurometabolic cerebroprotectors, neurometabolic stimulants. These terms reflect the general property of drugs - the ability to stimulate metabolic processes in nervous tissue, especially in various disorders (anoxia, ischemia, intoxication, trauma, etc.), returning them to a normal level.

After the successful introduction of piracetam into medical practice, more than 10 original nootropic drugs of the pyrrolidine series were synthesized, which are currently in phase III of clinical trials or have already been registered in a number of countries: oxiracetam, aniracetam, etiracetam, pramiracetam, dupracetam, rolziracetam, cebracetam, nefiracetam, isacetam, detiracetam, etc. Based on their chemical structure, these nootropic drugs were called "racetams".

Following them, other groups of nootropic drugs began to form, including cholinergic, GABAergic, glutamatergic, peptidergic; in addition, nootropic activity has been identified in some previously known substances.

Existing nootropic drugs can be classified as follows:

1. Pyrrolidine derivatives (racetams): piracetam, etiracetam, aniracetam, oxiracetam, pramiracetam, dupracetam, rolziracetam, etc.

2. Derivatives of dimethylaminoethanol (precursors of acetylcholine): deanol aceglumate, meclofenoxat.

3. Pyridoxine derivatives: pyritinol, biotredin.

4. Derivatives and analogs of GABA: gamma-aminobutyric acid (Aminalon), nicotinoyl-GABA (Picamilon), gamma-amino-beta-phenylbutyric acid hydrochloride (Phenibut), hopanthenic acid, pantogam, calcium gamma-hydroxybutyrate (Neurobutal).

5. Cerebrovascular means: ginkgo biloba.

6. Neuropeptides and their analogs: Semax.

7. Amino acids and substances affecting the system of excitatory amino acids: glycine, biotredin.

8. Derivatives of 2-mercaptobenzimidazole: ethylthiobenzimidazole hydrobromide (Bemityl).

9. Vitamin-like means: idebenone.

10. Polypeptides and organic composites: Cortexin, Cerebrolysin, Cerebramine.

11. Substances of other pharmacological groups with a nootropic component:

- Correctors of cerebral blood circulation disorders: nicergoline, vinpocetine, xanthine nicotinate, vincamine, naphthydrofuryl, cinnarizine;
- General tonics and adaptogens: acetylaminosuccinic acid, ginseng extract, melatonin, lecithin.
- Psychostimulants: salbutiamine;

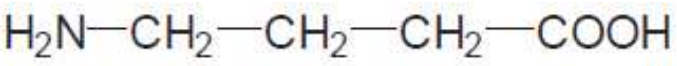
- Antihypoxants and antioxidants: oxymethylethylpyridine succinate (Mexidol).

Nootropics are used in dementia of various genesis (vascular, senile, Alzheimer's disease), chronic cerebrovascular insufficiency, psychoorganic syndrome, consequences of impaired cerebral circulation, craniocerebral trauma, intoxication, neuroinfection, intellectual and memory disorders (memory impairment, attention concentration, thinking), asthenic, astheno-depressive and depressive syndrome, neurotic and neurotic disorder, vegetative-vascular dystonia, chronic alcoholism (encephalopathy, psycho-organic syndrome, abstinence), to improve mental performance. In children's practice, the indications for the appointment of these drugs are delayed mental and language development, mental retardation, consequences of perinatal damage to the central nervous system, cerebral palsy, and attention deficit syndrome. Piracetam, choline alfoscerate, glycine, cerebrolysin have been shown to be effective in acute conditions in a neurological clinic (acute ischemic stroke, traumatic brain injury). Some nootropics are used to correct neuroleptic syndrome (deanol aceglumate, pyrithinol, pantogam, pantogam), stuttering (phenibut, pantogam), hyperkinesis (phenibut, hopanthenic acid, memantine), urination disorders (nicotinoyl-GABA, pantogam), sleep disorders (glycine , phenibut, calcium gamma-hydroxybutyrate), migraines (nicotinoyl-GABA, pyritinol, semax), dizziness (piracetam, phenibut, ginkgo biloba), for the prevention of staggering (phenibut, GABA). In ophthalmology (as part of complex therapy) nicotinoyl-GABA is used (open-angle glaucoma, vascular diseases of the retina and macula), ginkgo biloba (senile macular degeneration, diabetic retinopathy).

We will consider the analysis of drugs of this group using an example Aminalonum:

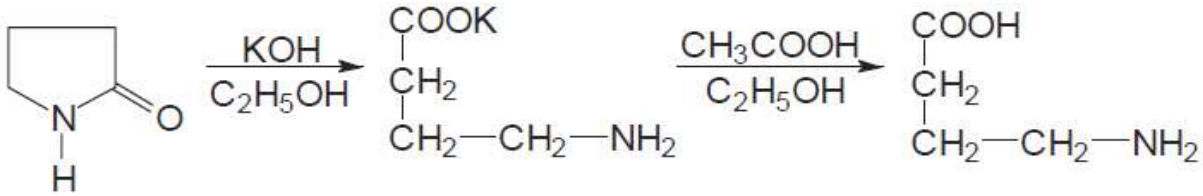
Aminalonum

Acidum gamma-aminobutyricum



γ-aminobutyric acid or 4-aminobutanoic acid

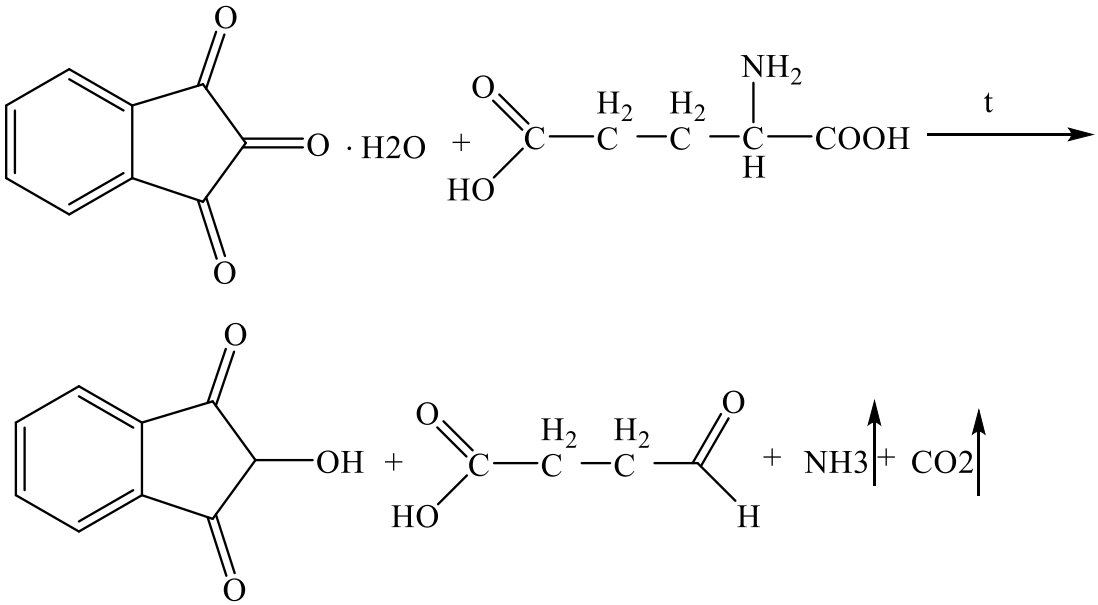
Extraction. Alkaline hydrolysis of pyrrolidone-2:

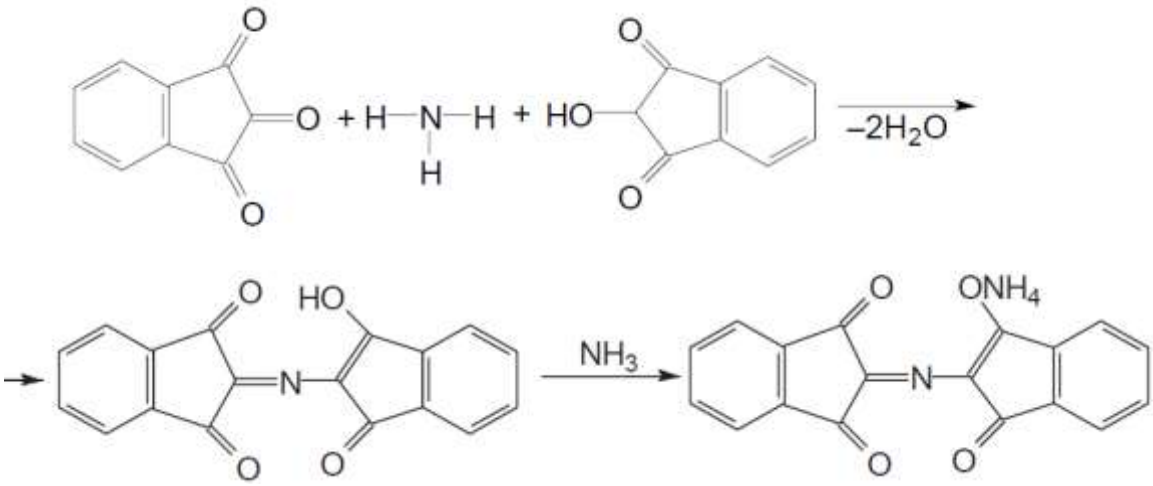


Properties. White crystalline powder with a weak specific smell, bitter taste. Hygroscopic. Easily soluble in water, very slightly soluble in alcohol, practically insoluble in chloroform, acetone.

Identification: Reaction with ninhydrin.

1. A blue-violet color is formed:





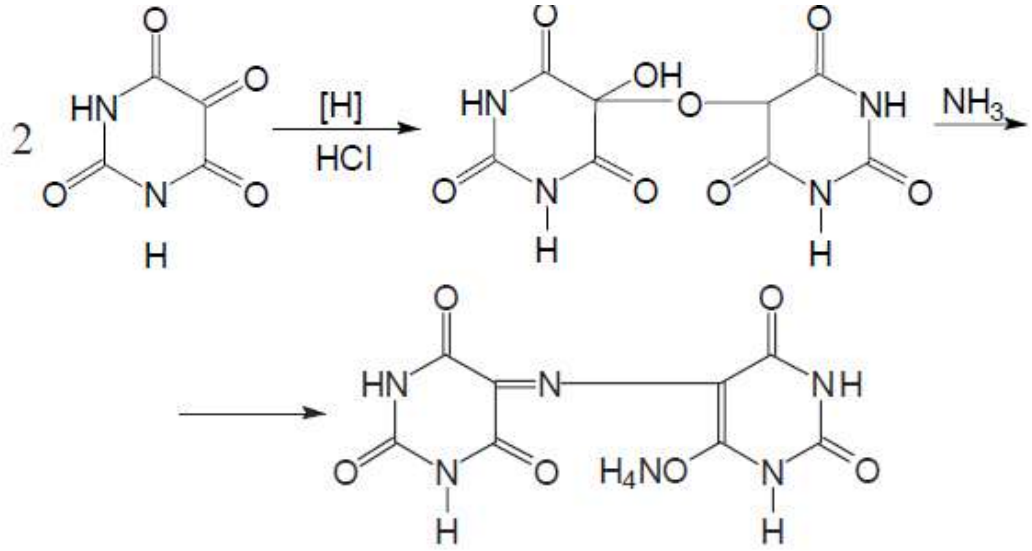
Ammonium salt

Diketohydrindenketohydrinamine

2. When fusing with potassium thiocyanate, hydrogen sulfide is released, which is detected using paper moistened with lead (II) acetate.

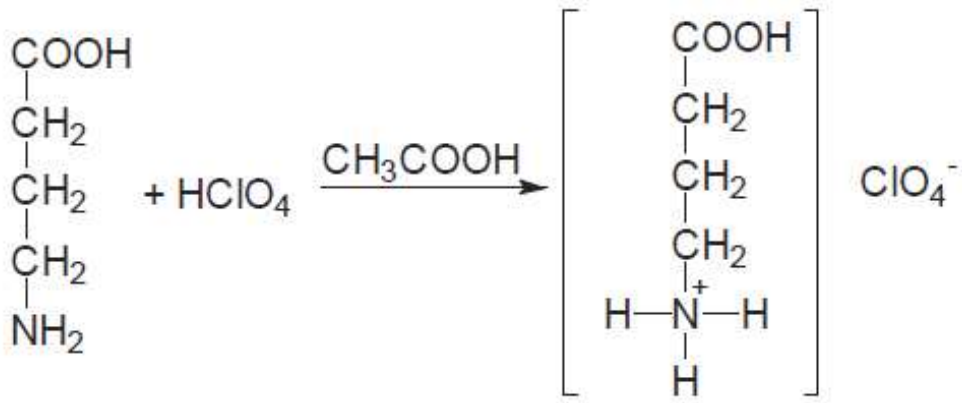
$$\mathbf{H_2S + (CH_3COO)_2Pb \rightarrow PbS\downarrow + 2CH_3COOH}$$

3. When a mixture of aminalon and alloxan is heated in an environment of dimethylformamide, a bright crimson color is formed:



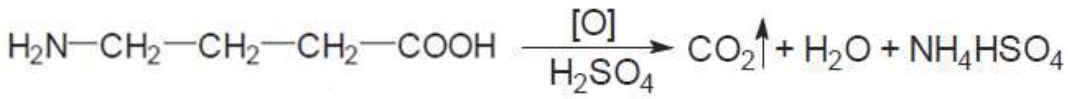
Quantitative determination:

1. Acidimetry in a non-aqueous environment, direct titration, indicator – crystal violet, s = 1:



2. Determination of nitrogen after mineralization with sulfuric acid.

The method includes two stages: mineralization of organic matter (boiled in a special device in the presence of K_2SO_4, $CuSO_4$, concentrated H_2SO_4 and selenium) and acidimetry:



Then add a concentrated NaOH solution:

$$\xrightarrow{t^\circ}$$

$$\mathbf{NH_4HSO_4 + 2NaOH \rightarrow NH_3 \uparrow + 2H_2O + Na_2SO_4}$$

The released ammonia is distilled into a receiving flask containing a 0.01 M solution of hydrochloric acid:

$$\mathbf{NH_3 + HCl \rightarrow NH_4Cl}$$

The excess of hydrochloric acid is titrated with a 0.01 M solution of sodium hydroxide, using a mixed solution of methyl red as an indicator:

$$\mathbf{HCl + NaOH \rightarrow NaCl + H_2O}$$

The test is repeated using glucose instead of the tested substance (control experiment).

The nitrogen content is calculated according to the formula:

$$nitrogen\ content, \% = \frac{0{,}01401 * (n_1 - n_2)}{m_н}$$

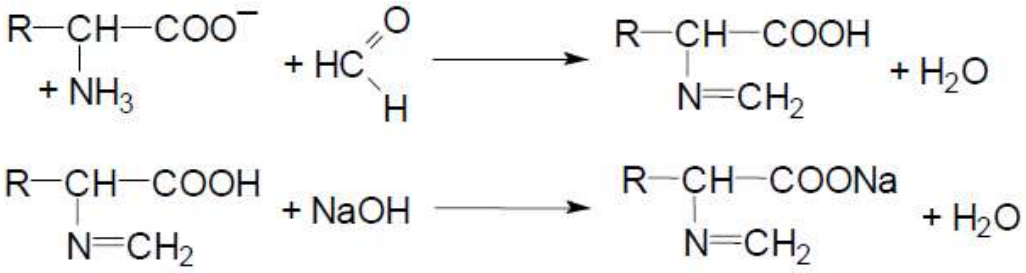
where: n_1 - volume of 0.01 M NaOH in the main experiment, ml;

n_2 - volume of 0.01 M NaOH in the control experiment, ml;

$m_н$ - weight of the tested substance.

3. Alkalimetry according to the Sorensen's method (formal titration).

Titration of amino acids with alkali is difficult because they exist in the form of internal salts, so formalin neutralized by phenolphthalein is added to the solution of amino acids. In this case, an N-methylene derivative is formed, and the liberated carboxyl group can be titrated with sodium hydroxide:



Pharmaceutical form. Coated tablets.

Indication. As part of complex treatment of diseases of the central nervous system:

• vascular diseases of the brain (atherosclerosis, damage to cerebral vessels in arterial hypertension);

• chronic insufficiency of cerebral blood circulation with impaired memory, concentration of attention, speech, dizziness, headache;

• encephalopathy (alcoholic, post-stroke, post-traumatic);

• children's cerebral palsy;

• retardation of mental development in children (aged 5 and over);

• dementia in old age (initial stages of dementia);

• sea and air sickness (for the prevention and treatment of the wavering symptom complex).

Storage conditions. Store in the original packaging at a temperature not higher than 25 ºC. Keep out of the reach of children.

Pharmacotherapeutic group. Psychoanaleptics. Other psychostimulants and nootropics.

Pharmacological properties.

Pharmacodynamics. Gamma-aminobutyric acid (GABA) is the main mediator of the central nervous system, which is involved in the processes of central inhibition. Under its influence, the energy processes of the brain are activated, the utilization of the last glucose improves, the respiratory activity of tissues increases, and the blood supply improves. The drug improves the dynamics of nervous processes in the brain, thinking, memory, and attention, promotes the recovery of movements and speech after a violation of cerebral blood circulation, has a mild psychostimulant effect. Contributes to the reduction and stabilization of elevated blood pressure (BP) and reduction of subjective symptoms of arterial hypertension (dizziness, sleep disturbances). It has a moderate antihypotoxic and anticonvulsant effect. In patients with diabetes, it reduces the glucose content, with a normal blood glucose content, it has the opposite effect (due to glycogenolysis). By nature of action, the drug is similar to nootropics.

Pharmacokinetics. It is quickly absorbed from the digestive tract. The maximum concentration is manifested in the blood plasma. The final product of GABA metabolism in tissues is succinic acid, which is included in the Krebs cycle. Part of the drug undergoes transamination with the formation of g-guanidinebutyric acid, which in the liver and kidneys is partially broken down into GABA and urea. G-aminobutyrylcholine, GABA-pantoyl, homocarnosine, less oxybutyric acid are also synthesized. GABA transformation products and the unchanged drug are excreted with urine, partly with carbon dioxide from exhaled air.

Indications. As part of complex treatment of diseases of the central nervous system:

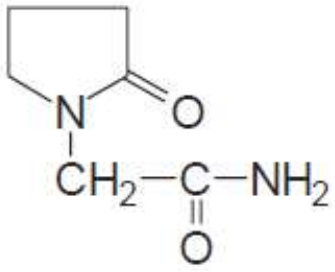
- vascular diseases of the brain (atherosclerosis, damage to cerebral vessels in arterial hypertension);

- chronic insufficiency of cerebral blood circulation with impaired memory, concentration of attention, speech, dizziness, headache;
- encephalopathy (alcoholic, post-stroke, post-traumatic);
- infantile cerebral palsy;
- retardation of mental development in children (aged 5 years and older);
- senile dementia (initial stages of dementia);
- sea and air sickness (for the prevention and treatment of the wavering symptom complex).

Contraindications. Hypersensitivity to any components of the drug. Acute renal failure.

Piracetam (Pyracetamum)

Nootropil



2-(2-Oxopyrrolidin-1-yl)acetamide

Pharmacotherapeutic group. Psychostimulants and nootropics.

Pharmacological properties. *Pharmacodynamics*. The active component of the drug is piracetam, a cyclic derivative of gamma-aminobutyric acid.

Piracetam is a nootropic agent that acts on the brain, improving cognitive functions such as learning ability, memory, attention, and mental performance. There are probably several mechanisms of the drug's effect on the central nervous system: a change in the speed of propagation of excitation in the brain; strengthening of metabolic processes in nerve cells; improving microcirculation by affecting the rheological characteristics of blood, without causing a vasodilating effect. It improves connections between brain hemispheres and synaptic conduction in neocortical structures. Piracetam suppresses the aggregation of platelets and restores the elasticity of the erythrocyte membrane, reduces the

adhesion of erythrocytes. Piracetam has a protective and restorative effect in the case of impaired brain function due to hypoxia and intoxication, electroconvulsive therapy. Piracetam reduces the severity and duration of vestibular nystagmus, as monotherapy it is effective in the treatment of cortical myoclonus.

Pharmacokinetics. It is quickly absorbed from the digestive tract and after 30-40 minutes it reaches the maximum concentration in the blood. Penetrates well through the blood-brain and placental barriers. It accumulates in brain tissue after 1-4 hours. The half-life is approximately 4 hours. It is removed from the cerebrospinal fluid much more slowly, which indicates a high tropism for the brain tissue. It is practically not metabolized. 90% is excreted unchanged by the kidneys.

Glycine

2-Aminoacetic acid

Pharmacotherapeutic group: agents acting on the nervous system.

Pharmacological properties. *Pharmacodynamics*. Glycine belongs to replaceable amino acids. Glycine easily penetrates into most biological fluids and tissues of the body, including the brain, and is metabolized; its accumulation in tissues does not occur. It is rapidly destroyed in the liver by glycine oxidase to water and carbon dioxide.

Pharmacokinetics. Glycine is a central neurotransmitter that regulates metabolism; normalizes and activates protective inhibition processes in the central nervous system. Improves metabolic processes in brain tissues, has an antidepressant and sedative effect. It also has GABA-ergic, alpha$_1$-adrenoblocking, antioxidant, antitoxic effects; regulates the activity of glutamate (NMDA) receptors, thereby reducing psycho-emotional stress, aggressiveness and conflict; increases social adaptation, improves mood; facilitates falling asleep and normalizes sleep, increases mental capacity, reduces the severity of vegetative-vascular disorders.

L-glycine (glycocol) is involved in the synthesis of the most important substances for the body: nucleic acids, glutathione, bile acids, etc. Glycine is used in the synthesis of porphyrin - the precursor of heme in the hemoglobin molecule, as well as purine bases - the most important elements of nucleic acids. Glycine is included in the structure of glutathione-containing substances, which plays a special role in the antiradiation protection system.

Glycine participates in detoxification reactions, being included in the composition of hippuric acid, as well as in the synthesis of bile acids (glycocholic acid). In addition, glycine is important for the biosynthesis of oxalic acid.

5. METABOLISM OF DRUGS

All medicinal products (drugs) in relation to the body can be conditionally divided into two groups: biogenic and foreign. The composition of biogenic drugs includes substances peculiar to the human body. These are drugs based on amino acids, peptides, proteins, carbohydrates, hormones, etc. The second group consists of substances that are not normally present in the body. They are called xenobiotics (from the Greek xenos - foreign, bios - life). All drug substances of biogenic origin, as well as most xenobiotics, undergo biotransformation in the body. Biogenic compounds are included in the metabolism, and the transformation of xenobiotics depends on their reactivity and the presence of enzymes capable of catalyzing these processes.

The processes of chemical transformation of substances in the body are called metabolism, and the products of these transformations are called metabolites. The vast majority of drug transformations in the body are carried out under the influence of enzyme systems, but some metabolic reactions occur due to interaction with endogenous molecules of a non-enzymatic nature. The metabolism of xenobiotics is a protective function of the body, thanks to which it tries to get rid of foreign compounds that enter it from the outside, transforming them into new, more water-soluble compounds that are easily excreted.

Drugs are excreted through the kidneys with urine, as well as with the secretion of digestive glands (for example, bile) in the gastrointestinal tract, through the skin with sweat, and volatile substances are excreted through the lungs. Excretion of xenobiotics, including water-soluble drug substances and metabolically inert drugs, can partially occur without changing their structure.

Modification of the structure of drug substances in the body in most cases leads to a decrease in toxicity and loss of activity. But in some cases, as a result of metabolism, new compounds with a high therapeutic effect and toxicity can be formed.

Depending on the localization of metabolic processes, the following types of metabolism are distinguished:

1) cavity (enteral);

2) extracellular (humoral);

3) intracellular.

Enteral metabolism is localized in the gastrointestinal tract. It is carried out mainly by hydrolysis under the influence of hydrolytic enzymes that have group specificity and are able to hydrolyze compounds in the structure of which there are ester, amide, peptide, and glycosidic bonds.

Humoral metabolism takes place in body fluids — blood and lymph.

Intracellular metabolism. The main metabolic transformations of drugs take place in the cells of the liver, which has a powerful set of enzyme systems of relatively low specificity. Water-soluble compounds are metabolized mainly with the participation of enzymes localized in mitochondria and lysosomes, lipophilic compounds with the participation of monooxygenase systems of the endoplasmic reticulum. Enzyme systems such as *oxidoreductases* (catalyze redox reactions: oxidases — oxidation, reductases — reduction), *hydrolases* (catalyze hydrolysis reactions), *transferases* (catalyze conjugation reactions) play the most important role in metabolism.

Since the liver is the main organ in which metabolic transformations of drugs take place, its diseases can lead to disruption of these processes, which should be taken into account when choosing the dose of the drug and the terms of its use.

A number of factors affect the processes of biotransformation of drugs in the body:

Genetic factors. A person may have certain peculiarities of the body's reaction to the administration of drugs. This is often caused by different activity of enzyme systems, including genetically inherited ones. Today, these processes are being studied by pharmacogenetics, which is developing very actively.

Physiological factors. These include age, gender differences, pregnancy, quality of nutrition, etc. Enzyme systems are underdeveloped in childhood, and enzyme activity decreases in the elderly people. Physiological factors also include changes in intestinal microflora and the presence of certain diseases (primarily liver).

Pharmacodynamic factors are, first of all, the route of administration, dose, frequency of administration, the ability of compounds to bind to blood proteins, lymph, etc.

Environmental factors. These include environmental pollution, exposure to ionizing radiation, stress due to adverse natural conditions, etc. Toxic chemicals, such as herbicides, pesticides, carbon(II) oxide and others that can enter the body from the environment, "poison" enzymes, reduce their activity.

Conventionally, metabolic processes are divided into two phases.

In the first phase, the so-called functionalization phase, as a result of oxidation, reduction, or hydrolysis, new functional groups are formed in the molecule — hydroxyl, carboxyl, primary or secondary amino groups, etc.

In the second phase — the conjugation phase — with the participation of the formed functional groups, conjugation occurs with endogenous molecules — carriers of glucuronic, sulfate, acetic acid residues and some amino acids. As a result, the hydrophilicity of the drug substance increases, which facilitates its removal from the body.

TEST TASKS ON THE TOPIC «NOOTROPIC DRUGS»

1. The doctor prescribed piracetam to a patient after a traumatic brain injury. To which pharmacological group does this drug belong?
   A. Nootropic drugs
   B. Non-narcotic analgesics
   C. Tranquilizers
   D. Means for anesthesia
   E. Neuroleptics

2. When identifying the substance of nootropil (piracetam) by heating with sodium hydroxide solution, ammonia is released. The pharmacist confirms its formation with the help of:

A. Wetted lignin paper

B. Wetted litmus paper

C. Addition of $FeCl_3$ solution

D. Addition of $FeCl_2$ solution

E. Addition of $AgNO_3$ solution

3. The presence of an amide group in the piracetam structure is confirmed by the pharmacist by reaction with sodium hydroxide when heated. What characteristic product is formed as a result of alkaline hydrolysis of piracetam?

A. Ethanol

B. Urea

C. Hydroxylamine

D. Ammonia

E. Sodium acetate

4. To identify piracetam, a reaction is carried out, as a result of which ammonia is released when heated. What reagent is used in this reaction?

A. Sodium hydroxide solution

B. Hydrochloric acid solution

C. Copper (II) sulfate solution

D. Silver nitrate solution

E. Ammonium oxalate solution

5. Indicate which drug substance corresponds to the chemical name "4-aminobutanoic acid"?

A. Methionine

B. Cysteine

C. Alanine

D. Glutamic acid

E. Aminalon

6. Identification of nootropic drugs from the group of amino acids of the aliphatic series is carried out by the appearance of a blue-violet color with:

A. Ninhydrin

B. Aniline

C. Pyridine

D. Methylamine

E. Resorcinoma

7. Specify the reagent that can be used to confirm glycine belonging to amino acids during pharmaceutical analysis:

A. Saturated sodium bicarbonate solution

B. Sulfuric acid solution

C. Sulfosalicylic acid solution

D. Ninhydrin solution

E. Barium hydroxide solution

8. The control and analytical laboratory received the glycine substance. According to the SPhU, its identification involves the determination of substances detected by ninhydrin. This test is carried out by the method of:

A. Thin-layer chromatography

B. Gas chromatography

C. Liquid chromatography

D. Gas-liquid chromatography

E. Ion exchange chromatography

9. A control and analytical laboratory specialist uses formol titration (according to Sorensen) for the quantitative determination of nootropic drugs from the group of amino acids. At the same time, the role of formaldehyde is reduced to:

A. Carboxylation of the amino group

B. Blocking of the amino group

C. Neutralization of the carboxyl group

D. Alkylation of the carboxyl group

E. Formation of betaines

10. The pharmacist of the laboratory of the State Service of Ukraine on Medicines carries out quantitative determination of "Aminolone" in accordance with the requirements of the SPhU. Indicate by what method he should carry out quantitative determination:

A. Nitritometry

B. Acidimetry in a non-aqueous medium

C. Bromatometry

D. Argentometry

E. Complexonometry

11. Aminalon in the environment of dimethylformamide forms a bright crimson color when heated with the reagent of:

A. Formaldehyde solution

B. Sodium nitrite

C. Ninhydrin

D. Alloxon

E. Sulfuric acid

12. With what reagent when aminalon is fused, hydrogen sulfide is released, which is detected using paper impregnated with lead (II) acetate:

A. Sodium nitrite

B. Potassium thiocyanate

C. Ninhydrin

D. Formaldehyde solution

E. Alloxon

13. By what quantitative method is it possible to determine aminolone:

A. Kjeldahl method

B. Nitritometry

C. Acidimetry

D. Complexonometry

E. Iodometry

14. What heterocycle is included in the chemical structure of piracetam:

A. Morpholin

B. Piperazine

C. Pyrimidine

D. Thiazole

E. Pyrrolidine

15. When glycine is identified, oxidative decarboxylation of the drug is carried out under the action of NaOCl during heating. What is formed at the same time?

A. Phenol

B. Acetic acid

C. Formaldehyde

D. Sodium nitrite

E. Alloxon

16. When heating which drug with alloxone, a bright crimson color is formed:

A. Aminalon

B. Glycine

C. Piracetam

D. Acetylsalicylic acid

E. Streptocide

17. Aminalon is identified by reaction with ninhydrin. A positive result of the reaction should be considered:

A. Appearance of red color

B. Release of gas bubbles

C. Appearance of a characteristic smell

D. Appearance of a blue-violet color

E. Precipitation of a white precipitate

18. Drugs containing pyrrolidine in their structure include:

A. Piracetam

B. Phenobarbital

C. Furacilin

D. Isoniazid

E. Analgin

19. For quantitative determination of azote [Nitrogen] in drug substances of organic nature, use:

A. Kjeldahl method

B. Kolthoff method

C. Kolbe-Schmidt method

D. Mohr's method

E. Fajans method

Recommended literature

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