MINISTRY OF HEALTH OF UKRAINE

ODESSA NATIONAL MEDICAL UNIVERSITY

Faculty of Pharmacy

Department of Pharmaceutical Chemistry and Drug Technology

APPROVED by

Vice-rector for scientific and pedagogical work

_____Eduard BURYACHKIVSKY

_____, 202_

METHODOLOGICAL DEVELOPMENT
TO THE LECTURES ON THE EDUCATIONAL DISCIPLINE

Faculty, course Pharmaceutical, V course

Educational discipline Pharmaceutical chemistry

(the name of the educational discipline)

Approved:

The meeting of the department Pharmaceutical chemistry

Odesa National Medical University

Minutes № _ dated _____

Head of Department (_____) Volodymyr GELMBOLDT
(signature) *(Name, last name)*

Developers:

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Lecture No. 1

Topic: Medicines for thyroid hormones, antithyroid drugs. Antidiabetic drugs. Pancreatic hormone drugs.

Actuality of theme: Pharmaceutical chemistry is a science that studies methods of preparation, structure, physical and chemical properties of medicinal products; relationship between their chemical structure and action on organism; methods of quality control of medicines and changes that occur during their storage, as well as their use in medicine. Therefore, it is urgent to solve the problems facing pharmaceutical chemistry with the help of physical, chemical and physico-chemical methods, which are used both for synthesis, as well as for the analysis of medicinal products.

Goal: the formation of students' knowledge about the peculiarities of the storage of medicinal products, which affect the afferent nervous system, as well as the characteristics, classification, relationship between structure and pharmacological action, mechanism of action, methods of obtaining, methods of analysis, application in medicine. As a result of the lecture, students should learn the properties and methods of medical analysis means thyroid hormones, antithyroid drugs, antidiabetic drugs, pancreatic hormone drugs.

Basic concepts:pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

Plan and organizational structure of the lecture:

1.Preparatory stage

1.1.Determination of educational goals.

1.2.Providing positive motivation.

2. The main stage

Presentation of lecture material

Plan:

- thyroid hormones

-antithyroid drugs

-antidiabetic drugs

- medicines for pancreatic hormones

3. The final stage

3.1. Summary of the lecture, general conclusions.

3.2. The lecturer's answers to possible questions

3.3. Tasks for self-training of students.

Content of lecture material (lecture text):

Hormones- biologically active substances that are produced by endocrine glands in small quantities and regulate all vital processes occurring in the body.

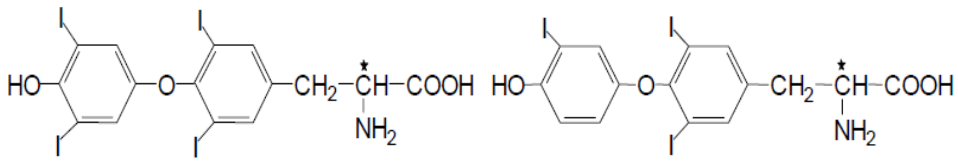
Currently, about 50 hormones are known in endocrinology. For the needs of medicine, hormones are isolated from endocrine glands (these can be both individual substances and total biological preparations). Synthetic and semi-synthetic analogues of hormones are also used.

Classification. In pharmaceutical chemistry, a chemical classification of hormones is adopted, according to which they can be divided into two groups, which, in turn, are divided into subgroups according to the producer gland:

- hormones - amino alcohols, amino acids, polypeptides, proteins and compounds close to them in chemical structure (hormones of the medulla of the adrenal glands, pituitary gland, thyroid and parathyroid glands, pancreas);
- hormones of a steroid structure (hormones of the adrenal cortex, female and male sex hormones).

Thyroid hormones

Thyroid- one of the most important glands of internal secretion. Violation of its functions causes serious disorders of the body: slowing of metabolism, retardation of growth, mental development (cretinism). The thyroid gland produces biologically active iodinated derivatives of thyronine:



3,5,3`,5`-тетрайодтиронін (тироксин) 3,5,3`-трийодтиронін

In medical practice, synthetic L-thyroxine is used, as well as thyroidin, which is obtained by grinding defatted and dried thyroid glands of slaughter cattle.

Thyroidin (Thyreoidinum)

Mechanism of action. It has a wide range of action, in which 2 main directions are distinguished: regulation of energy metabolism and influence on the growth and development of the body, differentiation of tissues.

Properties. Yellowish-gray powder with a weak odor, characteristic of dried animal tissues. Insoluble in water and other solvents. Contains the hormones L-thyroxine and L-3, 5, 3'-triiodothyronine.

Identification:

- the protein is detected by the formation of a yellow color after boiling thyroidin in sodium hydroxide solution. With further addition of dilute sulfuric acid, the solution becomes discolored and a colloidal precipitate falls out;
- to detect organically bound iodine, the substance is mineralized by roasting with a mixture of KNO3 and Na2CO3. The formed iodides are extracted with water and identified by the reaction of oxidation with chloramine in the medium of HCl acid. The released iodine colors the chloroform layer red-violet;
- more modern is the method of burning thyroidin in a flask with oxygen. A starch solution containing 0.2% sulfamic acid is used as an absorbent mixture. The iodine formed during combustion colors the absorption layer blue.

Quantitative definition. The content of organically bound iodine is determined in thyroidin. Mineralization is carried out with H2O2 in the presence of concentrated H2SO4. The formation of iodides and their partial oxidation to iodates occurs. After cooling, iodides are oxidized to iodates with a KMnO4 solution:

$$5HI + 6KMnO_4 + 9H_2SO_4 \longrightarrow 5HIO_3 + 6MnSO_4 + 3K_2SO_4 + 9H_2O$$

$$HI + 2KMnO_4 + H_2SO_4 \rightarrow 2MnO_2\downarrow + HIO_3 + K_2SO_4 + H_2O$$

Excess potassium permanganate and manganese (IV) oxide are removed using sodium nitrite:

$$2KMnO_4 + 5NaNO_2 + 3H_2SO_4 \longrightarrow 2MnSO_4 + 5NaNO_3 + K_2SO_4 + 3H_2O$$

$$MnO_2 + NaNO_2 + H_2SO_4 \longrightarrow MnSO_4 + NaNO_3 + H_2O$$

A possible excess of nitrites is destroyed with the help of urea:

$$2HNO_2 + H_2N{-}\overset{\overset{O}{\|}}{C}{-}NH_2 \longrightarrow CO_2\uparrow + 2N_2\uparrow + 3H_2O$$

In the solution, iodate (iod) acid remains in an amount equivalent to the iodine content in a measure of thyroidin. A solution of potassium iodide is added, and the released iodine is titrated with sodium thiosulfate:

$$HIO_3 + 5HI \rightarrow 3I_2 + 3H_2O$$

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

Thyroidin should contain 0.17–0.23% iodine.

The content of organically bound iodine in thyroidin can also be determined using the combustion method in a flask with oxygen.

Storage. In well-stoppered glasses of dark glass.

Application. With hypofunction of the thyroid gland, which leads to hypothyroidism, myxedema, cretinism, obesity or endemic goiter.

Antithyroid drugs

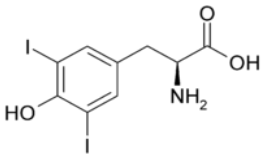
Antithyroid drugs- compounds of various chemical nature that inhibit the function of the thyroid gland.

Mechanism of action and classification.

According to the direction of action, the following Antithyroid drugs can be distinguished:

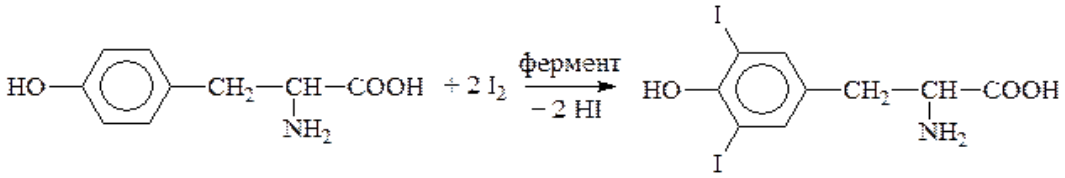
1. Medicines that suppress the production of thyroid-stimulating hormone of the anterior part of the pituitary gland (iodine, diiodotyrosine).
2. Medicines that suppress the synthesis of thyroid hormones in the thyroid gland (mercazolil, carbamisole, propylthiouracil).
3. Drugs that disrupt the absorption of iodine by the thyroid gland (potassium perchlorate).
4. Medicines that destroy thyroid follicle cells (radioactive iodine).

Diiodotyrosine



Mechanism of action. Suppresses the synthesis of thyroid-stimulating hormone of the anterior part of the pituitary gland.

Synthesis.



Properties. White or white with a grayish tint crystalline powder, odorless, slightly bitter taste; hardly soluble in water and alcohol, easily soluble in alkali solutions. Contains about 55% of organically bound iodine.

Identification:

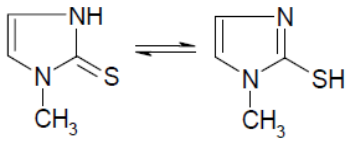
- the presence of organically bound iodine is confirmed by heating the crystals of the drug - violet vapors of free iodine are released;
- reaction with ninhydrin solution - a purple color appears.

Quantitative definition. It is based on dehaloidation of the drug when heated with zinc dust in an alkaline environment. The equivalent amount of iodides formed is determined by the direct argentometric method.

Storage. In well-stoppered glasses of dark glass.

Application. It is used in hyperthyroidism as a means that suppresses the synthesis of thyroid-stimulating hormone of the pituitary gland.

Mercazolil



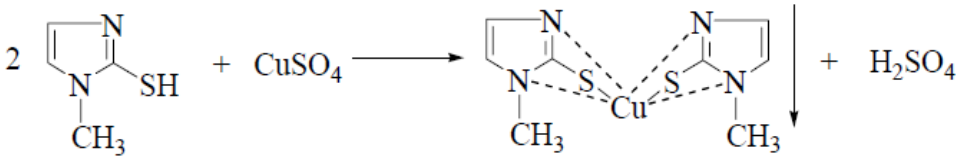
1-Метил-1,3-дигідро-2*H*-імідазол-2-тіон

Mechanism of action. The mechanism of thyrostatic action is due to the inhibition of the activity of the peroxidase enzyme, which is involved in the iodination of thyroid hormones of the thyroid gland, which leads to a violation of the synthesis of thyroxine and triiodothyronine.

Properties. White or yellowish crystalline powder with a weak specific smell, bitter taste. Easily soluble in water, ethanol, chloroform, slightly soluble in ether.

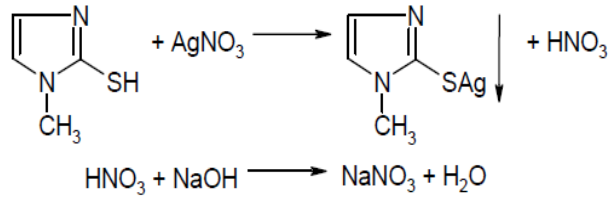
Identification.

- definition of T. pl., IR- and UV-spectroscopy, TLC;
- formation of mercaptides with salts of heavy metals: with AgNO3 – white precipitate, with CuSO4 – gray-blue, with Pb(CH3COO)2 – yellow:



- when an alkaline mercazolyl solution reacts with sodium nitroprusside, a yellow color appears, which changes to green, and after the addition of acetic acid - to blue;
- with ammonium vanadate - blue-green color.

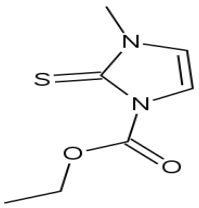
Quantitative definition. Alkalimetry by substitution, direct titration, indicator – bromothymol blue, s = 1:



Storage. In a tightly closed container, protected from light, in a dry place.

Application. Antithyroid drug.

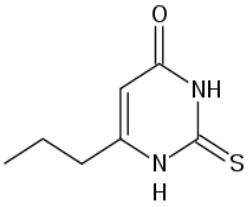
Carbamisole



Mechanism of action. Depending on its dosage, it inhibits the incorporation of iodine into tyrosine, and therefore, the additional synthesis of thyroid hormones.

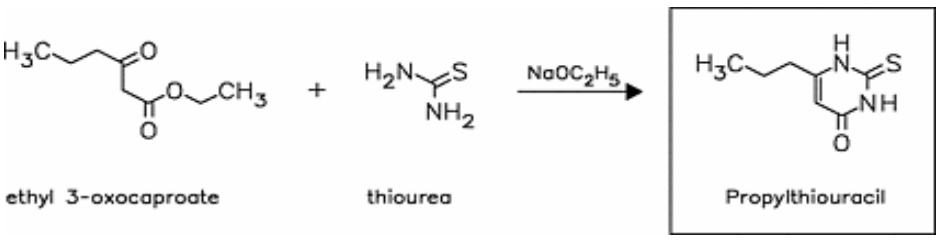
Carbimazole is a prodrug: after absorption, it turns into the active form - meracazolil (thiamazole).

Propylthiouracil



Mechanism of action. Propylthiouracil has a thyrostatic effect, thanks to which the thyroperoxidase is blocked, which leads to a violation of the iodization of thyroglobulin and the impossibility of the synthesis of thyroxine and triiodothyronine.

Synthesis.



Properties. White crystalline or amorphous powder, sparingly soluble in water, alcohol, insoluble in ether, well soluble in alkali solutions.

Identification:

- identify by the IR absorption spectrum of the substance; determine T. pl.; by the TLC method on silica gel plates in the system glacial acetic acid – 2-propanol – chloroform (0.1 : 96 : 50), the chromatogram is treated with iodine vapor and viewed in UV light at a wavelength of 254 nm;
- the substance is oxidized by bromine water with the formation of a sulfate ion, which is determined using barium chloride.

Quantitative definition. Quantitatively determined by potentiometric titration. A solution of the substance in a weakly alkaline environment is treated by heating with a 0.1 M AgNO3 solution. Then titrate with 0.1 M NaOH solution.

Storage. In a dry place protected from light, at a temperature not higher than 25 °C.

Application. Hyperthyroidism of various etiologies: diffuse toxic goiter, multinodular toxic goiter, toxic adenoma. Propylthiouracil is used in pregnant patients with hyperthyroidism, since taking this drug has a lower teratogenic effect compared to methimazole.

Potassium perchlorate

KClO4

Mechanism of action. Inhibits the accumulation of iodine in the thyroid gland, suppresses the formation of thyroxine, has a thyrostatic effect.

Synthesis

$NaClO4 + KCl \rightarrow KClO4\downarrow + NaCl.$

Properties. White crystalline substance, poorly soluble in water - 2.03 g per 100 g of water at 25 °C, insoluble in alcohol. Non-hygroscopic, unlike almost all perchlorates.

Storage. In a place protected from light, at a temperature not higher than 25 °C.

Application. Toxic goiter (mild and moderate form); prevention of radiation damage to the thyroid gland (in complex therapy with potassium iodide).

Radioactive iodine - sodium iodide NaI-131

Mechanism of action. ^{131}I emits β- and γ-radiation. β-radiation irreversibly damages thyroid cells, has a small range of action (≈ 2 mm) and its effect is limited to the thyroid gland. Part of the injected 131I, which was not absorbed by the thyroid gland, is quickly excreted in the urine; exposure of organs sensitive to radiation (bone marrow, gonads) is small.

ExtractionThe radioactive isotope of iodine [13II] is obtained from tellurium oxide when irradiated with neutrons in a nuclear reactor or from the decay products of uranium. The half-life of iodine-131 is 8.02 days.

Application. Treatment of benign diseases of the thyroid gland: inert nodular goiter, hyperthyroidism of the thyroid gland, Graves' and Basedov's disease, nodular and multinodular goiter. It is also used to treat differentiated thyroid cancer: after surgery to ablate remaining thyroid tissue to sterilize other cancer sites, and to treat metastatic thyroid cancer.

Antidiabetic drugs

Classification. Synthetic antidiabetic drugs are used to treat patients with diabetes mellitus (DM) type 2. Pathogenesis of DM type 2 includes two main links: deficiency of insulin secretion and insulin resistance. Based on this, oral hypoglycemic drugs, depending on their action, are divided as follows:

1. Insulin sensitivity stimulators (insulin sensitizers).

1.1. Biguanides.

1.2. Thiazolidinediones.

2. Insulin secretion stimulators (secretagogues).

2.1. Derivatives of sulfonylureas:

2.1.1. Short duration of action;

2.1.2. Long acting.

2.2. Derivatives of benzoic acid.

3. Stimulators of the activity of incretin hormones (incretinomimetics).

3.1. Dipeptidyl peptidase-4 (DPP-4) inhibitors.

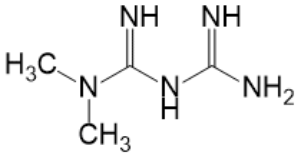
3.2. Glucagon-like peptide-1 (GLP-1) agonists.

4. Means that slow down the absorption of glucose into the blood:

4.1. Inhibitors of α-glucosidase

Biguanides

Metformin



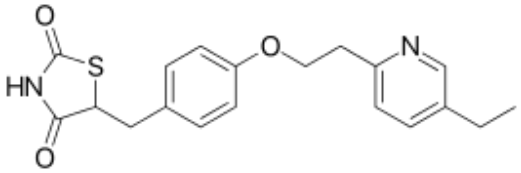
Mechanism of action. Reduces glucose production in the liver by inhibiting gluconeogenesis and glycogenolysis; increases the sensitivity to insulin in muscles, increasing the capture and utilization of glucose in peripheral tissues; reduces the absorption of glucose in the intestine.

Storage. Store at a temperature not higher than 25 °C.

Application. Type II diabetes in case of ineffectiveness of diet therapy and exercise regime, especially in overweight patients.

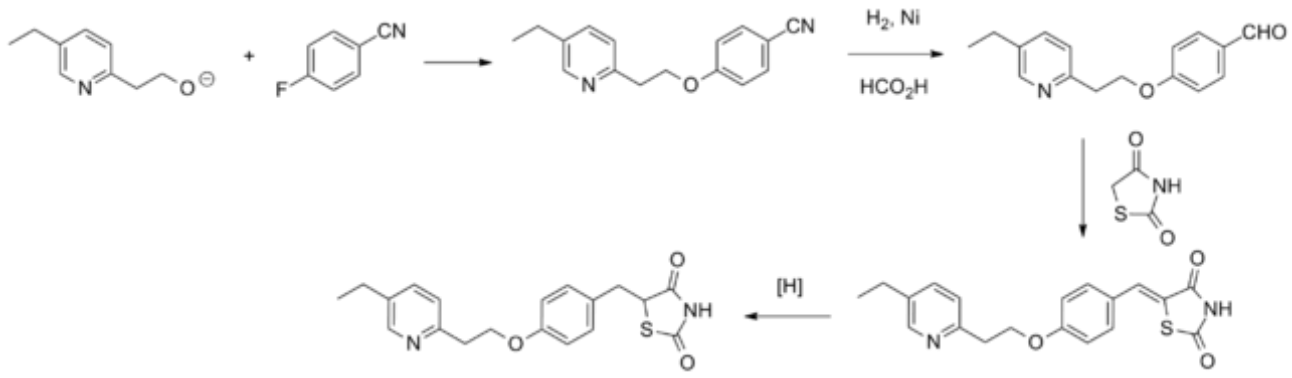
Thiazalidinedione derivatives

Pioglitazone (Pioglar)



Mechanism of action. Highly selective agonist of γ-receptors that are activated by peroxisome proliferator (γ-PPAR). γ-PPAR receptors are found in adipose, muscle tissues and in the liver. Activation of PPAR-γ nuclear receptors modulates the transcription of insulin-sensitive genes involved in glucose control and lipid metabolism. Pioglar reduces insulin resistance in peripheral tissues and in the liver, as a result of which the consumption of insulin-dependent glucose increases and the release of glucose from the liver decreases. Unlike sulfonylurea derivatives, pioglitazone does not stimulate insulin secretion by β-cells of the pancreas.

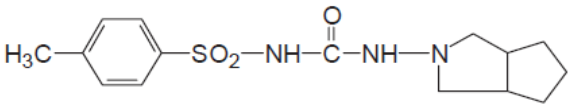
Synthesis.



Application. Treatment of type II diabetes.

Derivatives of sulfonylureas

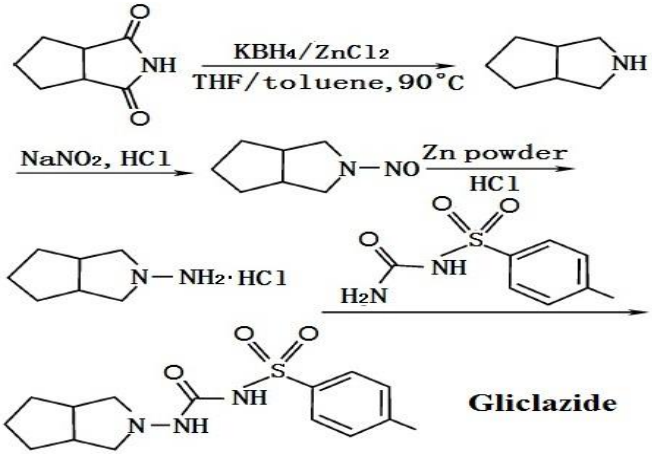
Gliclazide (diabeton, predian)



1-(3-Азабіцикло[3,3,0]-окти–3-іл)-3-(*n*-толілсульфоніл)-сечовина

Mechanism of action. Gliclazide lowers blood glucose levels by stimulating insulin secretion by the beta cells of the islets of Langerhans. The increase in postprandial secretion of insulin and C-peptide is maintained after 2 years of treatment.

Synthesis.



Properties. White crystalline powder, practically insoluble in water, easily soluble in methylene chloride, moderately soluble in acetone, ethanol.

Identification:according to the IR absorption spectrum of the substance.

IR spectrum, cm-1: 1707, 1162, 920, 667, 1089, 997 (in KBr).

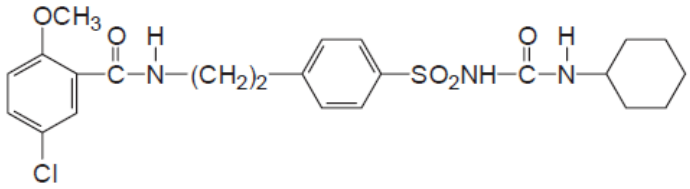
Quantitative definition. It is quantified by non-aqueous acidimetric titration with potentiometric fixation of the titration end point.

Storage. Store in a place protected from light, at a temperature not higher than 25ºC.

Application. Antidiabetic agent belonging to the class of sulfonamides of the II generation; prescribed to diabetics who suffer from obesity.

Prevention of atherosclerosis, prevention of microcirculation disorders, diabetic nephropathy, diabetic retinopathy.

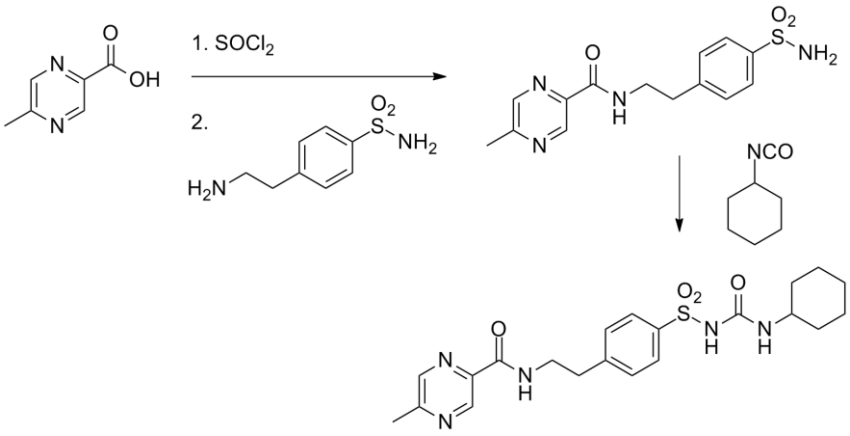
Glibenclamide (Maninil)



1-[[4-[2-[(5-хлор-2-метоксибензоїл)аміно]етил]феніл]сульфоніл]-3-циклогексилсечовина

Mechanism of action. Glibenclamide has a hypoglycemic effect due to an increase in insulin secretion by β-cells of pancreatic islets both in people with normal metabolism and in patients with non-insulin-dependent diabetes mellitus (type 2).

Synthesis

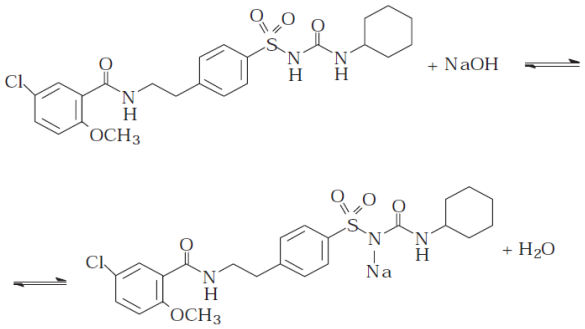


Properties. Crystalline powder of white or almost white color. Practically insoluble in water, moderately soluble in methylene chloride, sparingly soluble in 96% alcohol and methanol.

Identification:

- T. pl., UV- and IR-spectroscopy, TLC;
- a solution of the substance in sulfuric acid should be colorless and show blue fluorescence in UV light. With further addition of chloral hydrate, the color of the solution should change to dark yellow with a brownish tint.

Quantitative definition. Alkalimetry in an alcoholic medium, direct titration, indicator – phenolphthalein, s = 1:

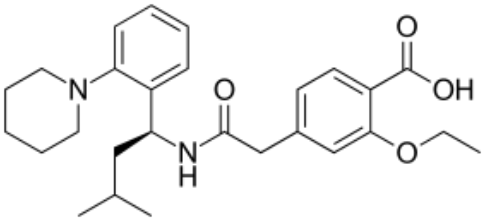


Storage. In a sealed container.

Application. It belongs to the class of sulfonamides of the II generation. Unlike the previous means, it has a higher hypoglycemic activity (the effect is achieved in much smaller doses), is quickly absorbed and is relatively well tolerated.

Derivatives of benzoic acid

Repaglinide (Novonorm)



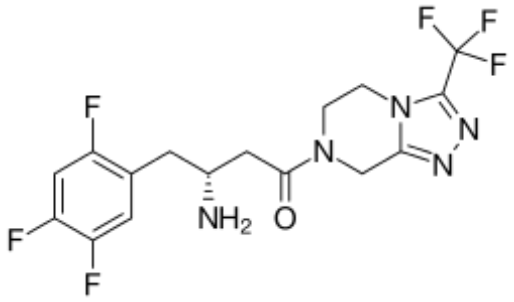
Mechanism of action. Quickly reduces the level of glucose in the blood, stimulating the secretion of insulin by the pancreas, and the effect of the drug depends on the number of functioning β-cells preserved in the islets of the gland; closes ATP-dependent potassium channels in the membrane of β-cells with a special protein, which causes depolarization of β-cells and leads to the opening of calcium channels, which increases the entry of calcium ions into the cell, which stimulate insulin secretion.

Storage. Store at a temperature not higher than 25 °C.

Application. Type II diabetes (non-insulin-dependent diabetes) occurs when diet, weight loss, and exercise fail to control blood glucose levels satisfactorily.

Dipeptidyl peptidase-4 inhibitors

Sitagliptin (januvia)

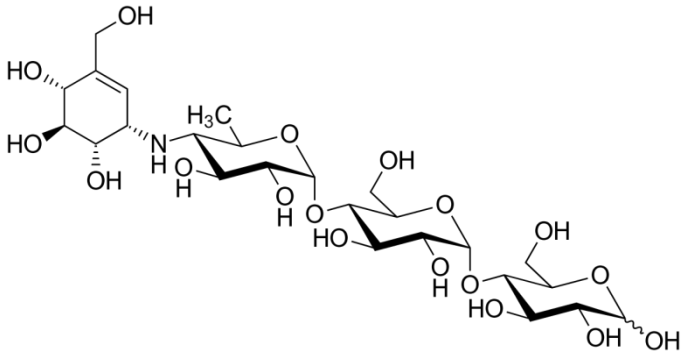


Mechanism of action. Highly selective inhibitor of dipeptidyl peptidase-4 (DPP-4) enzyme. By inhibiting DPP-4, sitagliptin increases the concentration of two known hormones of the incretin family: GLP-1 and glucose-dependent insulinotropic peptide (GIP). Hormones of the incretin family are secreted in the intestine during the day, their level increases in response to food intake. Incretins are part of the internal physiological system of regulation of glucose homeostasis. With a normal or elevated blood glucose level, the hormones of the incretin family contribute to an increase in the synthesis of insulin, as well as its secretion by β-cells of the pancreas due to signaling intracellular mechanisms associated with cyclic AMP.

Application. Type II diabetes.

Inhibitors of α-glucosidase

Acarbose (glucobay)



Mechanism of action. The mechanism of action of the drug consists in the inhibition of intestinal alpha-glucosidases, which are involved in the splitting of di-, oligo- and polysaccharides, which slows down the assimilation of carbohydrates and causes a decrease in the absorption of glucose from saccharides.

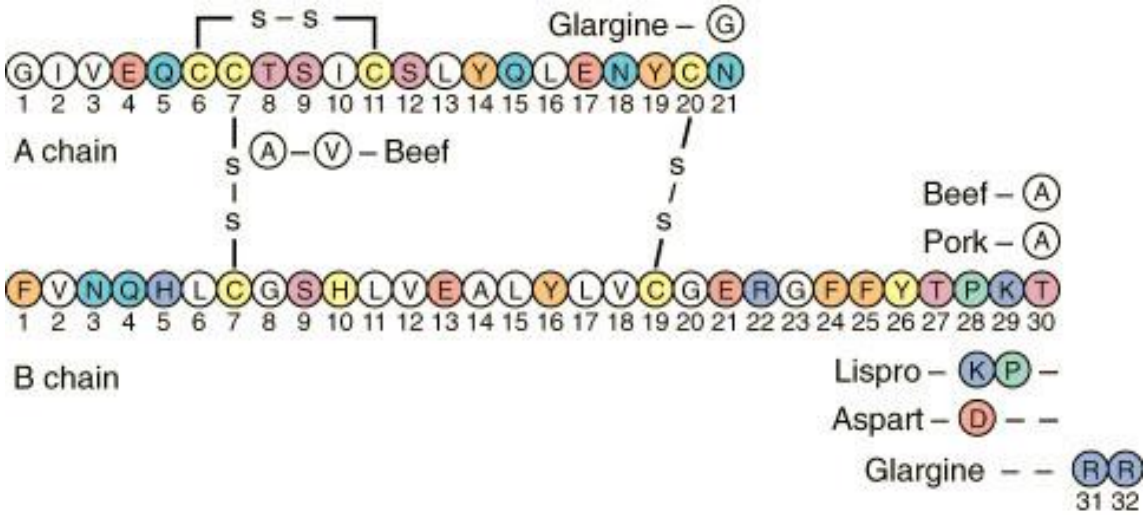
Storage. Store at a temperature no higher than +30 °C, in a dry place protected from light.

Application. Diabetes mellitus type 2 (in case of ineffectiveness of diet therapy, insufficient effectiveness of the appointment of sulfonylurea derivatives against the

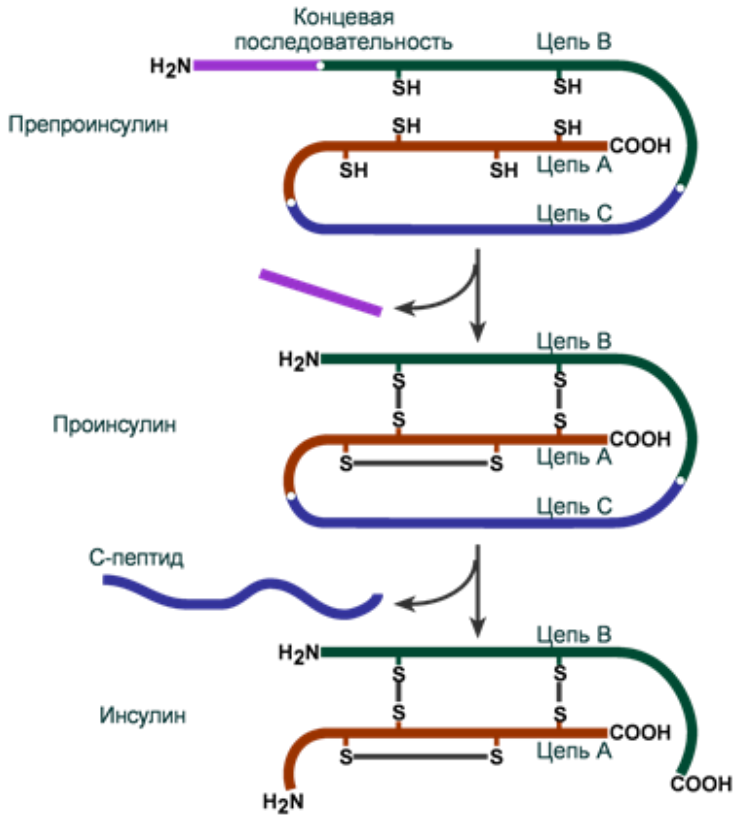
background of a low-calorie diet); type 1 diabetes (as part of combined therapy). Prevention of type 2 diabetes (in patients with impaired glucose tolerance in combination with diet and exercise).

Pancreatic hormone drugs

Insulin– a hormone discovered in 1902 by L.V. Sobolev and preparatively isolated by F. Bunting and I. Best (University of Toronto, Canada) in 1921. Its amino acid sequence was deciphered by F. Sanger (1955). By chemical nature, Insulin is a protein consisting of two polypeptide chains - A and B, connected by two disulfide bonds. The A-chain contains 21, the B-chain – 30 amino acid residues:



Insulinof some animals has a significant similarity in primary structure with human insulin. Bovine insulin differs from human insulin by three amino acid residues, pig insulin by only one amino acid. It is synthesized in the β-cells of the islets of Langerhans of the pancreas from precursor proteins by limited proteolysis: preproinsulin (107 amino acid residues) → proinsulin (84) → I. (51) and C-peptide (33):



The main biological function of insulin is to regulate the level of glucose in the blood. Insulin is the only hormone that lowers the level of glucose in the blood.

Mechanism of action. Interaction of insulin with receptors increases the permeability of the membranes of muscle and fat tissues for glucose, amino acids, K+, Ca2+, Na+. The hormone stimulates glucose utilization in cells in different ways: about 50% of glucose is broken down by glycolysis, 30–40% is converted into lipids, and about 10% is stored in the form of glycogen.

Animal and human insulins are secreted. Animal insulins are obtained from the pancreas of pigs and cattle. In terms of its biological structure, porcine insulin is the closest to human insulin, which differs from it by only one amino acid.

To date, human insulins are considered the best drugs. They are obtained in two ways:

- the first method consists in the "processing" of pork, in which one amino acid is replaced. It is a semi-synthetic human insulin;
- in the second method, with the help of genetic engineering methods, the Escherichia coli is "forced" to synthesize insulin similar to human insulin. The resulting drug is called biosynthetic human insulin.

Classification and preparations of insulins

Short action	Average duration of action	Long acting	Short action	Average duration of action	Long acting
Lisproinsulin Human insulin for injections	Isophane insulin human suspension Insulin-zinc suspension mixed human	Insulin-zinc suspension crystalline	Insulin for injections neutral	Insulin aminoquinuride Insulin-zinc suspension amorphous	Insulin-zinc suspension crystalline

Characteristics of insulin preparations

Insulin-zinc suspension crystalline human			

Insulin analogues

*Insulin analogues*represent a changed chemical structure of the insulin molecule, interact with insulin receptors, but the duration of their action is different from the natural hormone.

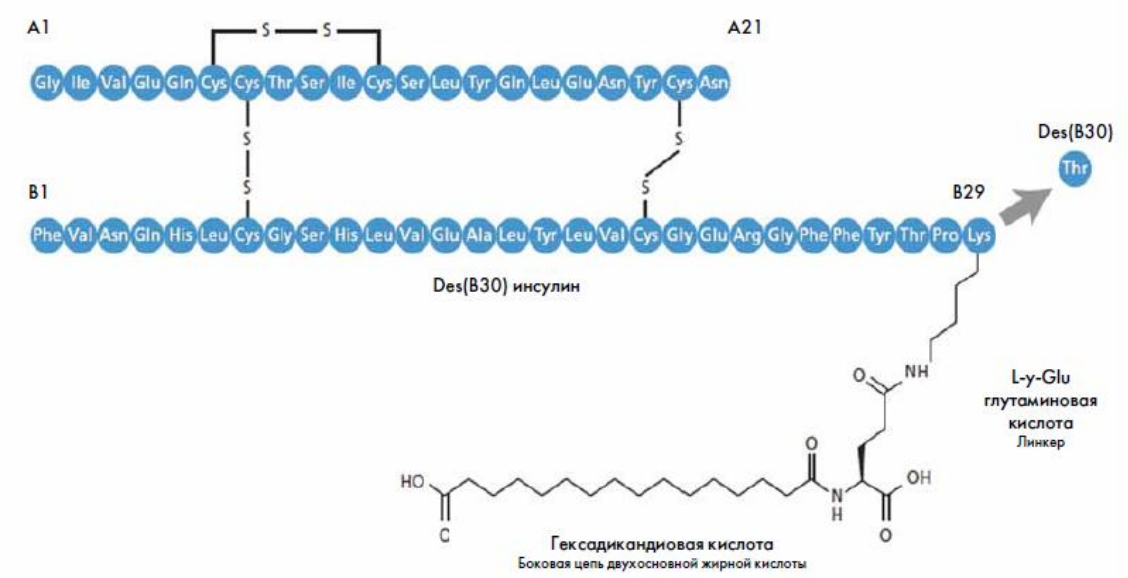
Ultra-short-acting drugs– insulin lispro ("Humaloe"), insulin aspart ("NovoRanid"), insulin glulisine ("Apidra"). In terms of their action, they have the following advantage: the quick onset of action allows insulin to be administered immediately before meals. The duration of action of ultra-short-acting insulins approximately corresponds to the time of the rise in blood sugar levels after a meal.

Long-acting drugs.*Insulin detemir*("Levemir") is a soluble analogue of insulin of medium duration of action, which has a neutral pH. Detemir is an acetylated derivative of human insulin and has a prolonged effect of biological action. The mechanism of prolonged action of insulin detemir is provided by the formation of complexes of insulin hexamers with albumin.

Long-acting drugs. These include Insulin degludec ("Tresiba® Penfill®") - a new insulin of ultra-long action. After subcutaneous administration, degludec forms a depot of soluble multihexamers, which are gradually absorbed into the bloodstream, providing an even, stable hypoglycemic effect lasting more than 42 hours.

*Insulin degludec*is a recombinant acylated DesB30 human insulin, to which a hexadecanedioic fatty acid residue is attached at the LysB29 position through γ-L-glutamic acid (linker).

After subcutaneous injection, as a result of self-association, insulin degludec forms a depot of soluble multihexamers, which gradually, slowly, at a constant rate disintegrate into monomers that are absorbed into the blood and exert metabolic effects. As a result, the half-life (t 1/2) of degludec from the subcutaneous fat depot is increased to 25 hours, which is 2 times more than that of currently used analogues of basal insulin and does not depend on the dose of insulin used.



Application. Insulin is used to treat insulin-dependent diabetes mellitus type 1 (all insulins), hyperglycemic coma (human insulin for injections, neutral insulin for injections, insulin-zinc-crystalline suspension).

In addition, it is prescribed:

- as a means of causing hypoglycemic states in some forms of schizophrenia;
- as an anabolic agent for general exhaustion, reduced nutrition, furunculosis, thyrotoxicosis, stomach diseases, decreased appetite, chronic hepatitis, initial forms of liver cirrhosis.

Storage. Store in the original packaging at a temperature from 2 °C to 8 °C (in the refrigerator).

General material and bulk-methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1. Pharmaceutical analysis of drugs from the group of thyroid hormones
2. Pharmaceutical analysisantithyroid drugs
3. Pharmaceutical analysisantidiabetic drugs
4. Pharmaceutical analysisdrugs of pancreatic hormones

References:

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2. World Health Organization. - [Electronic resource]. - Access mode:http://www.who.int.

3. Pharmaceutical encyclopedia. - [Electronic resource]. – Access mode: http://www.pharmencyclopedia.com.ua.

4. Official website of the International Organization for Standardizationhttp://www.iso.org/iso/home.html

5. Compendium online. [Electronic resource]. - Access mode:https://compendium.com.ua/bad/

6. Medline search database [Electronic resource]. – Access mode: National Library of Medicinehttps://www.nlm.nih.gov/bsd/medline.html

Lecture No. 2

Topic:Steroid hormones and their analogues. Corticosteroids and their synthetic analogues.

Actuality of theme: Pharmaceutical chemistry is a science that studies methods of preparation, structure, physical and chemical properties of medicinal products; relationship between their chemical structure and action on organism; methods of quality control of medicines and changes that occur during their storage, as well as their use in medicine. Therefore, it is urgent to solve the problems facing pharmaceutical chemistry with the help of physical, chemical and physico-chemical methods, which are used both for synthesis, as well as for the analysis of medicinal products.

Goal:the formation of students' knowledge about the peculiarities of the storage of medicinal products, which affect the afferent nervous system, as well as the characteristics, classification, relationship between structure and pharmacological action, mechanism of action, methods of obtaining, methods of analysis, application in medicine. As a result of the lecture, students should learn the properties, methods of analysis of steroid hormones and their analogues, corticosteroids and their synthetic analogues.

Basic concepts:pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

Plan and organizational structure of the lecture:

1.Preparatory stage

1.1.Determination of educational goals.

1.2.Providing positive motivation.

2. The main stage

Presentation of lecture material

Plan:

-Classificationsteroid hormones and their analogues

- General methods of identificationsteroid hormones and their analogues

- General methods of quantitative determinationsteroid hormones and their analogues

-Corticosteroids and their synthetic analogues

3. The final stage

3.1. Summary of the lecture, general conclusions.

3.2. The lecturer's answers to possible questions

3.3. Tasks for self-training of students.

Content of lecture material (lecture text):

Steroid hormones– adrenal cortex hormones (corticosteroids) and sex hormones. The cortex of the adrenal gland secretes about 50 different hormones, of which 8 have a pronounced biological effect and are called corticosteroids. According to the effect on metabolism, the main corticoids are classified into two groups:

- mineralocorticosteroids (mineralocorticoids);
- glucocorticosteroids (glucocorticoids).

Hormones of the adrenal cortex and their synthetic analogues are widely used in clinical practice.

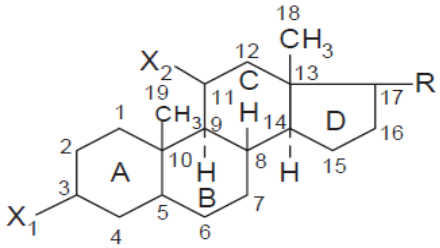
Mineralocorticosteroids participate in the regulation of mineral metabolism, increase blood pressure, tone and improve muscle performance.

Glucocorticoids regulate carbohydrate, protein and fat metabolism.

In turn, sex hormones, which are formed in the gonads and ensure the sexual function of the body, are divided into:

- male sex hormones (androgens);
- female sex hormones (estrogens);
- corpus luteum hormones (gestagens, or luteinizing hormones).

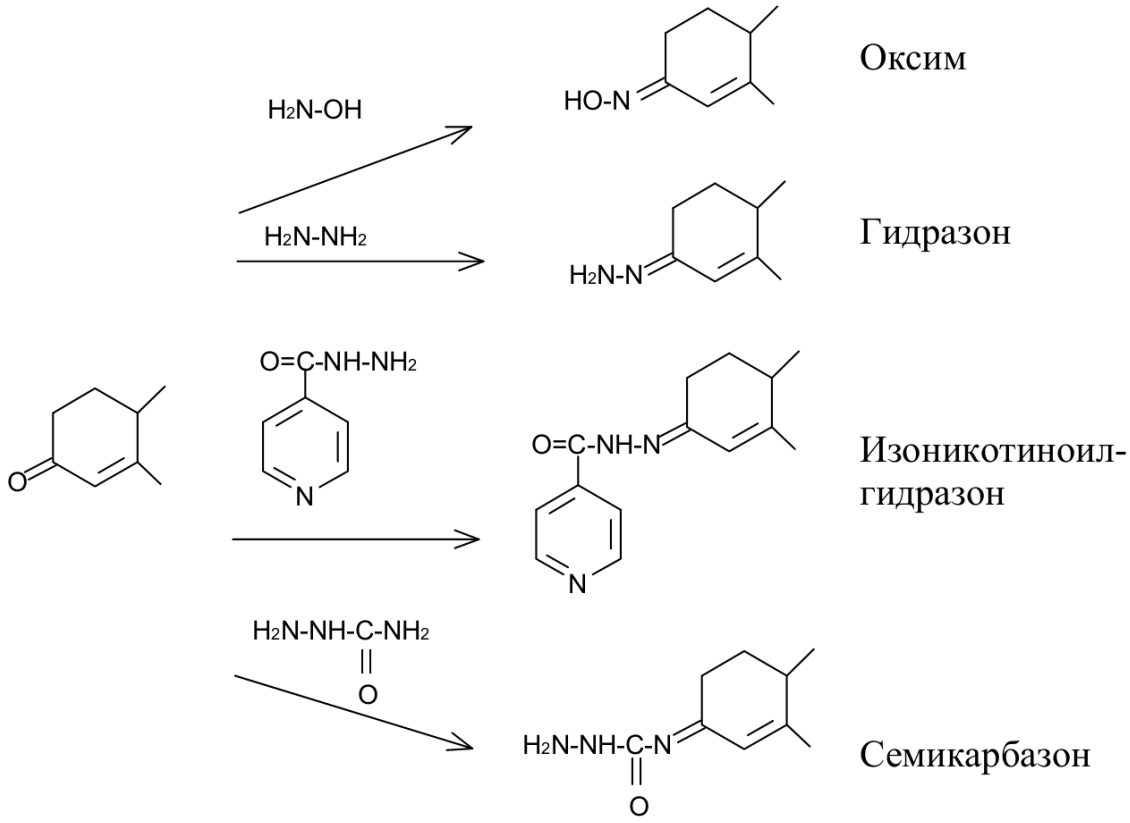
General formula of steroid hormones:



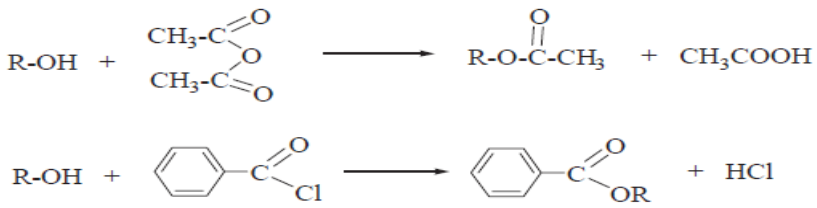
Since there is much in common in the structure of steroid hormones, the methods of their analysis are also largely in common.

Identification.

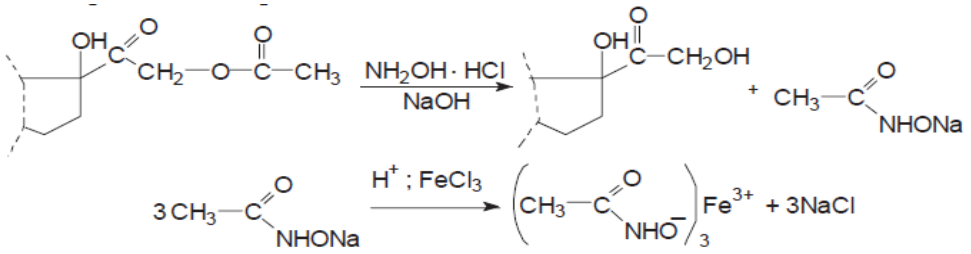
- These compounds are crystalline substances, therefore, T. pl. is determined for them. - one of the indicators of purity and identity.
- Steroid hormones and their analogs are optically active substances, most of them are dextrorotatory isomers. For identification and confirmation of purity, the Ministry of Internal Affairs recommends determining the angle of rotation of solutions of the analyzed compounds in ethanol, chloroform, or dioxane and calculating the specific rotation.
- A common reaction for all steroid hormones and their synthetic analogues is a reaction with concentrated sulfuric acid. When dissolved in it and heated, substances give a specific color, sometimes fluorescence.
- Steroid hormones, which have a keto group in position 3, give a substitution reaction with hydroxylamine hydrochloride, phenylhydrazine, 2,4-dinitrophenylhydrazine, isoniazid - precipitation with a characteristic T. pl. or a characteristic color appears (yellow, orange-red):



- To identify hormones that have a hydroxy group in positions 3 or 17, the reaction of the formation of esters (acetates, benzoates) with a characteristic melting point is often used:



- To identify hormones and their synthetic analogues, which are used in the form of esters (acetates, propionates), the hydroxam test reaction is used:



- Identification of substances is also carried out by IR spectra, which are compared with the spectra given in the pharmacopoeia or with the spectra of standard samples. The TLC method is widely used to identify and determine the presence of foreign impurities

Quantitative definition. For the quantitative analysis of steroid hormones and their analogs, UV spectroscopy of alcohol solutions is widely used. The content of the active substance is determined by the specific absorption index or standard solution.

Corticosteroids and their synthetic analogues

The cortical layer of the adrenal glands produces hormones called corticosteroids. In all hormones of this series, there is always a keto group in position 3 of the steroid cycle, a double bond in position 4. In position 17, all corticosteroids have a labile α-ketol group and therefore they are all reducing agents.

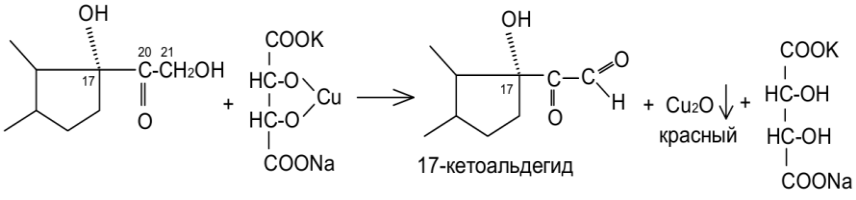
According to their effect on the body, corticosteroids are conventionally divided into two groups:

- mineralocorticoids - deoxycorticosterone acetate (DOXA);
- glucocorticoids - cortisone and hydrocortisone.

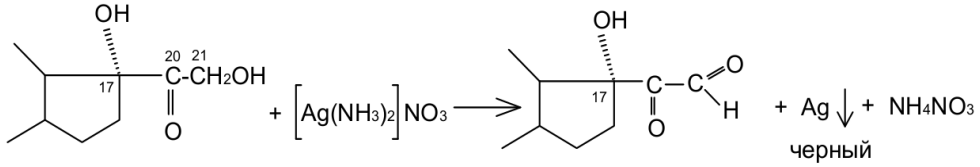
A number of synthetic analogs of cortisone and hydrocortisone have been obtained in order to reduce side effects and enhance anti-inflammatory, desensitizing and antihistamine effects. Thus, by introducing a double bond in position 1, prednisolone was synthesized.

Properties. Adrenocortical hormones and their synthetic analogues are white crystalline substances, which sometimes have a yellowish or cream tint, and are odorless. They are practically insoluble in water, difficult or slightly soluble in most organic solvents. DOXA and cortisone acetate are easily soluble in chloroform. Corticosteroids and their analogues are dextrorotatory optical isomers.

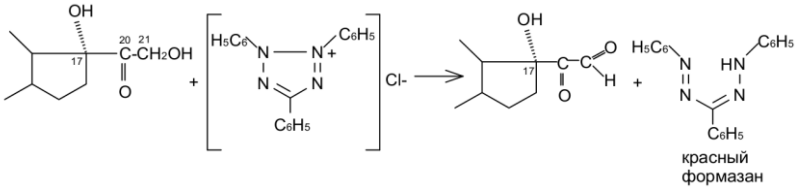
Identification. When a mixture of an alcoholic solution of the substance and a copper-tartrate reagent is heated on a water heater, a red-orange precipitate of copper (I) oxide falls out - reducing properties of the α-ketol group:



An ammonia solution of argentum nitrate ("silver mirror" reaction), phosphoromolybdic acid, ferrum (III) salts can be used as oxidants:

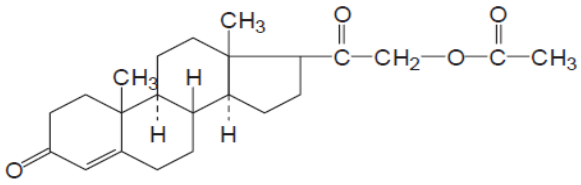


When corticosteroids are oxidized with an ethanolic solution of triphenylterazolium chloride in the presence of a solution of tetramethylammonium hydroxide, red-colored pharmazones are formed as a reduction product:



The reaction is used for identification and quantification by spectrophotometry.

Deoxycorticosterone acetate (DOXA)



Прегнен-4-ол-21-діону-3,20–21-ацетат

Mechanism of action. Retains sodium ions in the body, increases the excretion of potassium by the kidneys, increases the volume of circulating blood; increases tone and improves performance of striated muscles.

Identification:

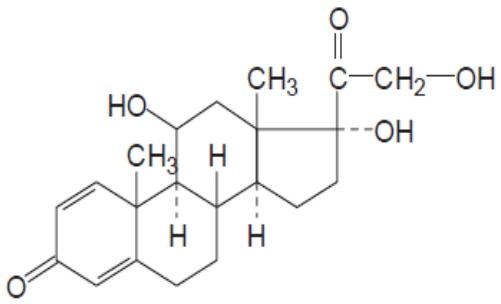
- reduces the copper-tartrate reagent (α-ketol group);
- gives a red-brown color in the reaction of the hydroxam sample (21-acetate);
- upon dissolution in concentrated sulfuric acid and subsequent addition of water, a cherry color with greenish-brown fluorescence appears. After adding chloroform and shaking, the lower layer turns yellow, the upper one turns green (steroid cycle).

Quantitative definition.UV spectrophotometry.

Storage. In a sealed container, protected from light.

Application. For the treatment of Addison's disease, myasthenia, asthenia, general muscle weakness and other diseases.

Prednisone

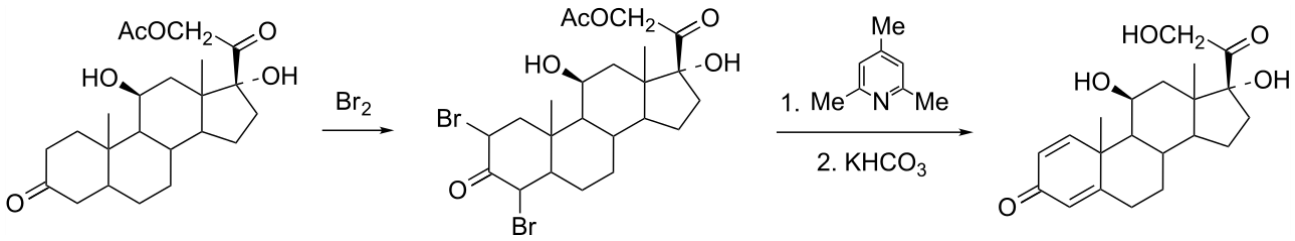


Прегнадієн-1,4-тріол-11β,17α,21-діон-3,20

According to its structure, it is a modified derivative of hydrocortisone with the formation of a double bond between 1 and 2 atoms of the steroid ring, which allowed to increase the anti-inflammatory activity and reduced the mineralocorticoid activity of the drug.

Mechanism of action. Prednisolone, penetrating through the cell membrane, binds to specific cytoplasmic receptors. Then this complex penetrates into the cell nucleus and affects the synthesis of a number of proteins, including enzymes. Inhibits the synthesis and secretion of ACTH and glucocorticoids.

Synthesis:



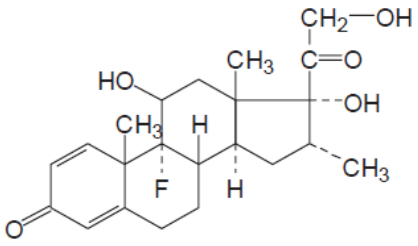
Identification:

- reduces the copper-tartrate reagent (α-ketol group);
- when heating an alcoholic solution of phenylhydrazine with sulfate, it gives a yellow color (keto group in position 3);
- when dissolved in concentrated sulfuric acid – red color with red-brown fluorescence (when exposed to UV light with a wavelength of 365 nm); after adding water, the color pales, yellow fluorescence is visible in UV light (steroid cycle).

Quantitative definition. Spectrophotometry.

Application. The drug has anti-inflammatory, anti-shock, anti-allergic, anti-toxic and immunosuppressive effects.

Dexamethasone

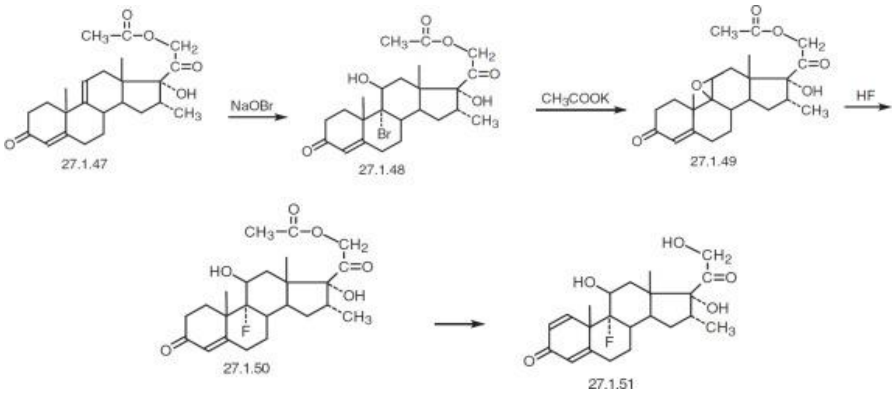


16α-Метил-9α-флюорпреднізолон

It is structurally a fluorinated derivative of hydrocortisone, and is more active than prednisolone or cortisone.

Mechanism of action. The mechanisms of action are mainly associated with inhibition of phospholipase A2 and the arachidonic acid cascade, inhibition of immunoglobulin synthesis, promotion of expression and increased sensitivity of adrenoceptors.

Synthesis.



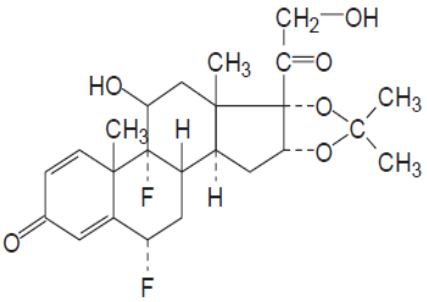
Identification:

- when heating an alcoholic solution of dexamethasone with phenylhydrazine sulfate, a yellow color appears (keto group in position 3);
- when dissolved in concentrated sulfuric acid, a faint red-brown color appears after 5 minutes, which disappears when water is added (steroid cycle);
- UV and IR spectral characteristics are determined, the TLC method is also used.

Quantitative definition. Spectrophotometry.

Application. The drug has anti-inflammatory, anti-allergic and immunosuppressive effects. The anti-inflammatory activity is 20-40 times higher than the activity of hydrocortisone.

Fluocinolone acetonide (Sinaflan)



6α, 9α-Дифлюор-16α-гідроксипреднізолон-16,17-ацетонід

Mechanism of action. It is believed that this agent affects the inflammatory process by suppressing the production of prostaglandins and leukotrienes as a result of reducing the activity of phospholipase A2 and reducing the release of arachidonic acid from the phospholipids of the cell membrane.

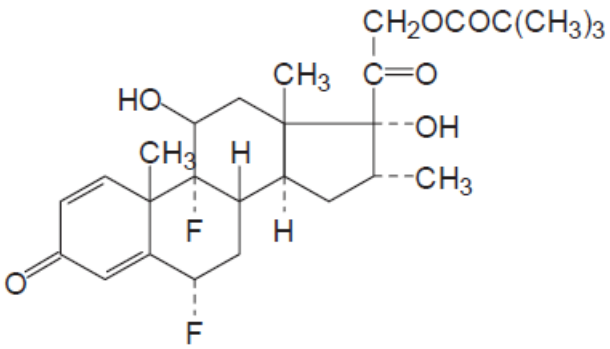
Identification:IR spectroscopy, thin-layer chromatography.

Quantitative definition.

Spectrophotometrically by reaction products with triphenyltetrazolium chloride.

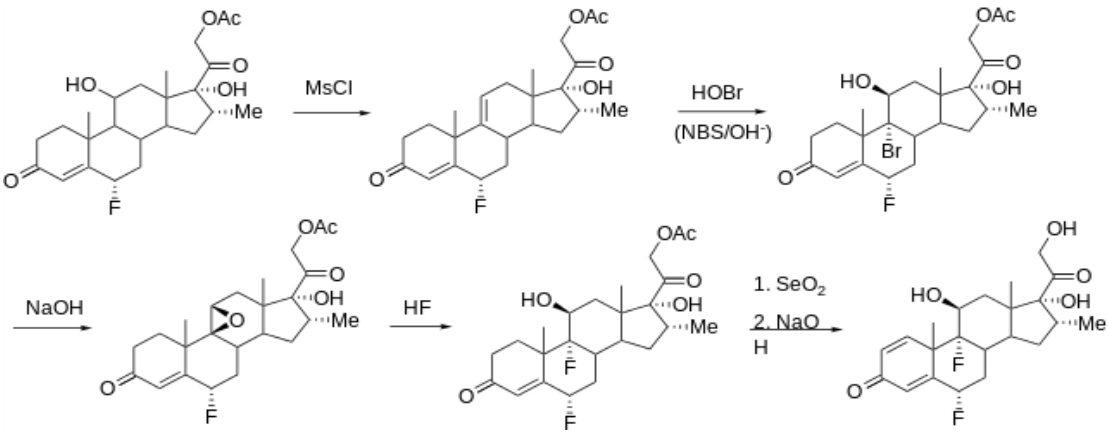
Application. Pronounced local anti-inflammatory, anti-allergic, anti-pruritic effect.

Flumethasone pivalate



6α, 9α-Дифлюор-16α-метилпреднізолон-21-триметилацетат

Synthesis.



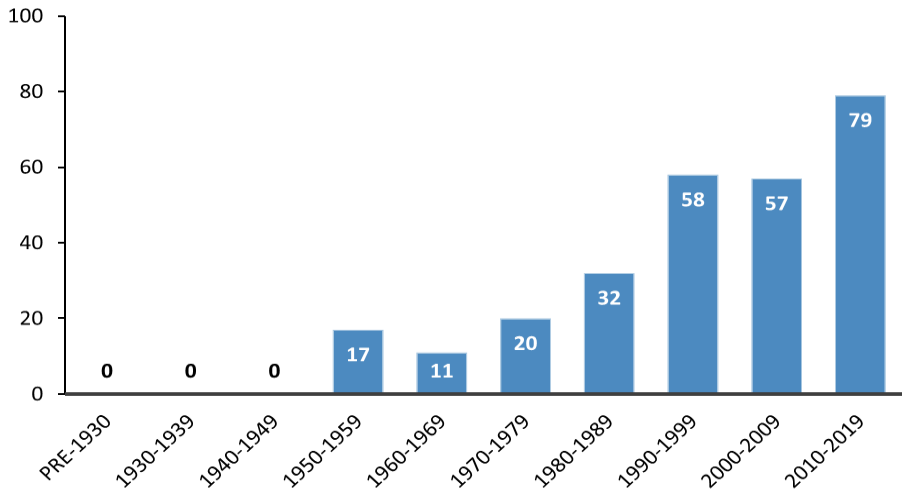
Identification:

- identify by the IR absorption spectrum of the substance;
- according to the color reaction with sulfuric acid (the pink color disappears when water is added);
- by the TLC method in the system water - methanol (1.2 : 8), mixed with the system ether - methylene chloride (15 : 77). Revealed with an alcoholic solution of sulfuric acid (λmax = 365 nm);
- in the presence of fluoride ions (preliminarily obtained by burning the preparation with MgO and extracting from the dry residue with a dilute HCl solution) using a solution of alizarin and zirconyl nitrate (the red color changes to yellow).

Quantitative definition. Spectrophotometrically (for alcohol solutions λmax = 239 nm).

Application. Pronounced local anti-inflammatory, anti-allergic, anti-pruritic effect.

Fluocinolone acetonide (sinaflan) and flumethasone pivalate, containing fluorine atoms in the 9 α- and 6 α-positions, have very high anti-inflammatory activity (150–300 times greater than the activity of hydrocortisone). However, they are practically not absorbed when applied topically and therefore, unlike other corticosteroids, do not cause side effects.



Fluoride-containing organic medicinal products approved by the US Food and Drug Administration by the end of 2019

The first fluorinated drug was introduced into practice in 1955, and with the exception of 1960−1969 and 2000−2009, the number of fluorinated drugs approved has increased every decade since then, as summarized by the statistics presented in the figure.

Organofluorine compounds, due to the masking effect mistakenly included by the body in exchange processes, in many cases show biological activity, which consists in inhibiting various stages of metabolism. Therefore, for example, fluorine-containing steroids show significantly higher anti-inflammatory activity compared to non-fluorinated analogues.

General material and bulk-methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1.Classificationsteroid hormones and their analogues

2.General methods of identificationsteroid hormones and their analogues

3.General methods of quantitative determinationsteroid hormones and their analogues

4. Pharmaceutical analysisCorticosteroids and their synthetic analogues

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3. Pharmaceutical encyclopedia. - [Electronic resource]. – Access mode: http://www.pharmencyclopedia.com.ua.

4. Official website of the International Organization for Standardizationhttp://www.iso.org/iso/home.html

5. Compendium online. [Electronic resource]. - Access mode:https://compendium.com.ua/bad/

6. Medline search database [Electronic resource]. – Access mode: National Library of Medicinehttps://www.nlm.nih.gov/bsd/medline.html

Lecture No. 3

Topic:Sex hormones, anabolic steroids and their analogues. Birth control. Estrogens of nonsteroidal structure.

Actuality of theme: Pharmaceutical chemistry is a science that studies methods of preparation, structure, physical and chemical properties of medicinal products; relationship between their chemical structure and action on organism; methods of quality control of medicines and changes that occur during their storage, as well as their use in medicine. Therefore, it is urgent to solve the problems facing pharmaceutical chemistry with the help of physical, chemical and physico-chemical methods, which are used both for synthesis, as well as for the analysis of medicinal products.

Goal:the formation of students' knowledge about the peculiarities of the storage of medicinal products, which affect the afferent nervous system, as well as the characteristics, classification, relationship between structure and pharmacological action, mechanism of action, methods of obtaining, methods of analysis, application in medicine. As a result of the lecture, students should learn the properties and methods of analysissex

hormones, anabolic steroids and their analogues, contraceptives, estrogens of a non-steroidal structure.

Basic concepts:pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

Plan and organizational structure of the lecture:

1.Preparatory stage

1.1.Determination of educational goals.

1.2.Providing positive motivation.

2. The main stage

Presentation of lecture material

Plan:

-Classificationsex hormones

-Anabolic steroids and their analogues

-Birth control

- Estrogens of nonsteroidal structure

3. The final stage

3.1. Summary of the lecture, general conclusions.

3.2. The lecturer's answers to possible questions

3.3. Tasks for self-training of students.

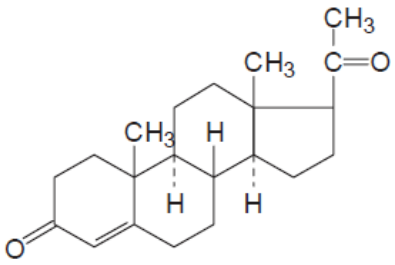
Content of lecture material (lecture text):

Progestogenic hormones and their semisynthetic analogs

Progestogenic hormones (hormones of the corpus luteum) and their semi-synthetic analogues, as well as corticosteroids, in most cases:

- have methyl groups in positions 10 and 13;
- have a keto group in position 3;
- have an unsaturated bond in position 4;
- do not have an oxygen function in position 11;
- unlike corticosteroids, in position 17, instead of an α-ketol group, they have acetyl or hydroxy and ethynyl groups.

Progesterone



Прегнен-4-діон-3,20

Properties. White crystalline powder. Practically insoluble in water, soluble in ethanol and ether, very easily soluble in chloroform.

Identification:

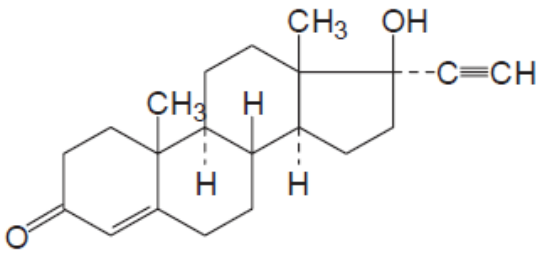
- IR spectrophotometry, TLC;
- a solution of LZ in concentrated H2SO4 acquires a yellow color with green fluorescence after adding water. After the addition of chloroform, the color disappears (steroid cycle);
- when heating an alcoholic solution of progesterone with m-dinitrobenzene and sodium hydroxide, a pink color appears, turning into red-brown;
- for identification, the decomposition temperature of 2,4-dinitrophenylhydrazone obtained during quantitative determination (keto group in position 3) is determined.

Quantitative definition. Gravimetry by products of interaction with 2,4-dinitrophenylhydrazine or spectrophotometry in ethanol solution at λ = 241 nm.

Storage. In a sealed container, protected from light.

Application. Progestogenic drug.

Pregnin



Прегнен-4-ін-20-ол-17β-он-3; або 17α-етинілтестостерон

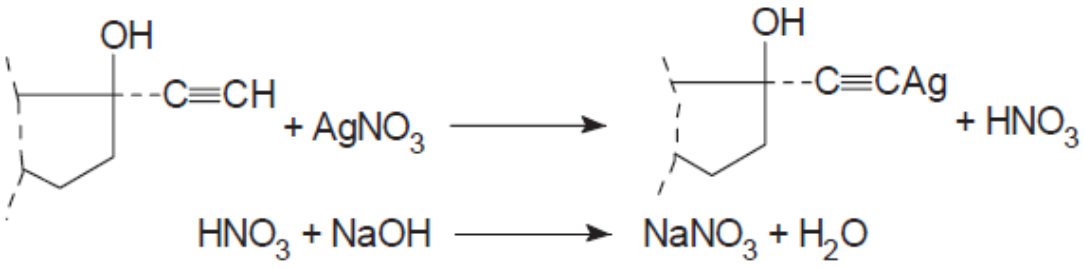
Properties. White or slightly yellowish crystalline odorless powder. Practically insoluble in water, very slightly soluble in ethanol and ether, slightly soluble in chloroform.

Identification:

- IR spectrophotometry, TLC;
- upon dissolving pregnin in concentrated H2SO4 and adding water – crimson color with green fluorescence. After adding chloroform and stirring, the lower layer turns orange, the upper layer is almost colorless (steroid cycle);
- determine the melting point of the oxime (keto group in position 3).

Quantitative definition.

1. Alkalimetry by substitute. To the solution of the substance in THF, add a solution of AgNO3 and the released HNO3, titrate with a NaOH solution according to bromocresol green or potentiometrically, s = 1:



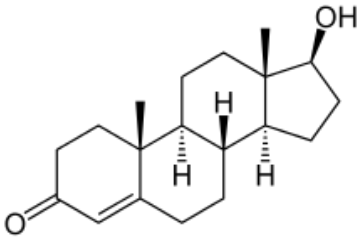
2. Spectrophotometry in an alcohol solution at λ = 241 nm compared to the standard.

Storage. In a sealed container, protected from light.

Application. Progestogenic agent. It is 5-6 times less active than progesterone, but retains its activity when taking tablets sublingually.

Androgenic hormones and semi-synthetic anabolic substances

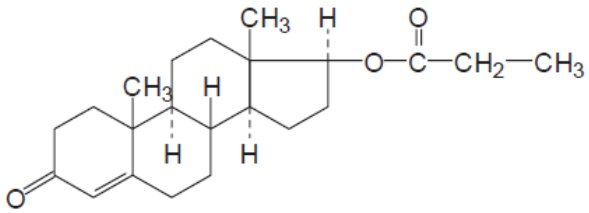
Androgenic hormones are produced by male gonads (testicles) during puberty. Testosterone, which is an endogenous male sex hormone, in addition to specific androgenic action, like all androgens, affects nitrogen metabolism and can be considered as an endogenous anabolic hormone:



It has been established that the effect of testosterone becomes longer after esterification with aliphatic acids. Esters create a kind of depot at the point of introduction, from which they are gradually absorbed, while testosterone is quickly excreted from the body by the

kidneys. One of the most active and stable testosterone esters during storage is testosterone propionate.

Testosterone propionate

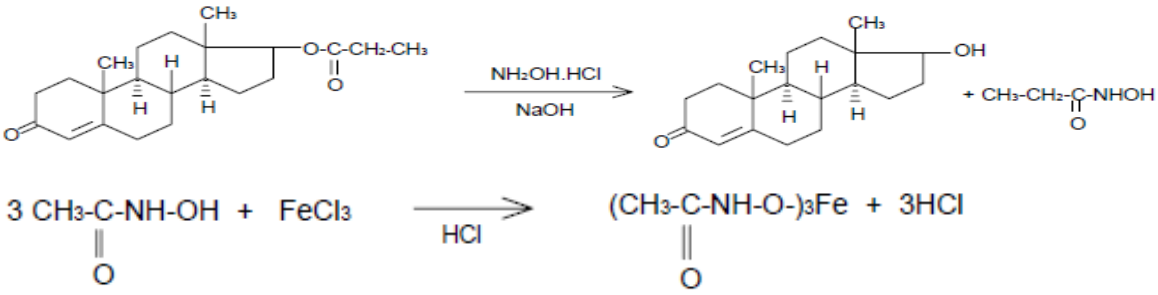


Андростен-4-он-3-олу-17β-пропіонат

Properties. White crystalline powder. Practically insoluble in water, very slightly soluble in chloroform, easily soluble in ethanol and ether.

Identification:

- identified by the IR absorption spectrum; determine T.pl.;
- install T. pl. oxime (166–171 °C; keto group in position 3) and testosterone – a product of alkaline hydrolysis (150–156 °C);
- as testosterone ester propionate gives a red-brown color in the reaction of the hydroxam test (17 β-propionate):

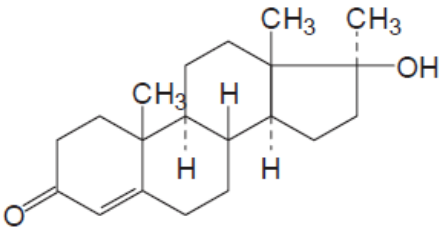


Quantitative definition. Spectrophotometry.

Storage. In a sealed container, protecting from moisture and light.

Application. Androgenic medicine for the treatment of climacteric, vascular and nervous disorders, as well as oncological diseases of the breast and ovaries in women.

Methyltestosterone

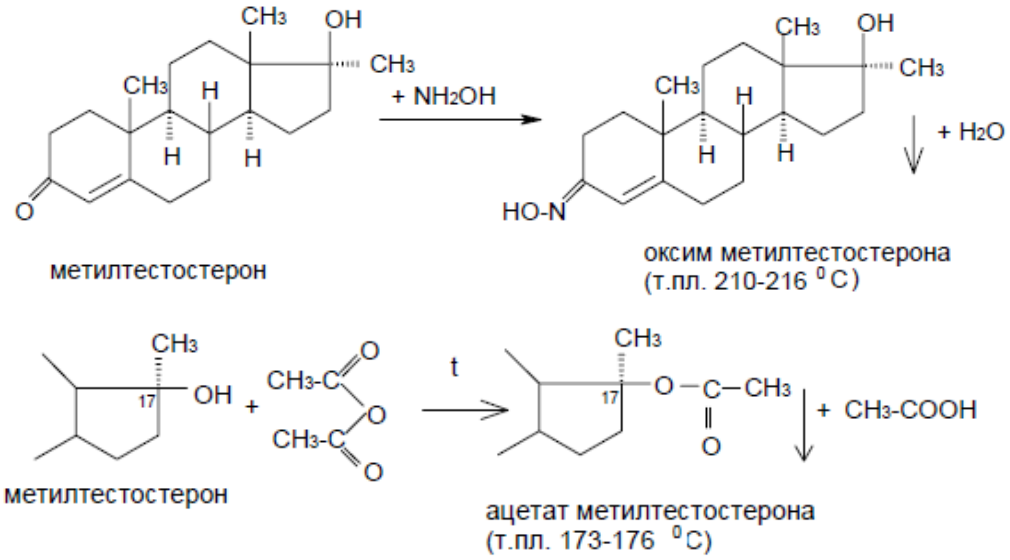


17α-Метиландростен-4-ол-17β-он-3

Properties. Odorless white crystalline powder. Practically insoluble in water, sparingly soluble in ether, sparingly soluble in oils, soluble in acetone, easily soluble in ethanol.

Identification:

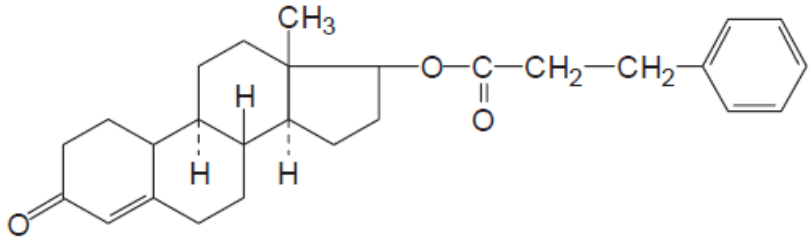
- when the drug is dissolved in concentrated H2SO4, an orange-yellow color appears; after adding water – orange-yellow color with green fluorescence (steroid cycle);
- for identification, the melting point of oxime (keto group in position 3) and acetate (oxy group in position 17) is also determined:



Storage. In a closed container, protecting from moisture and light.

Application. Androgenic drug, a synthetic analogue of testosterone. It is 2-3 times less active than testosterone propionate, but remains active when taken orally and under the tongue. Sexual underdevelopment, functional disorders in the sexual sphere, menopause in men; dysfunctional uterine bleeding in the pre-menopausal and climacteric periods, breast and ovarian cancer.

Phenobolin



17β-Гідрокси-19-нор-4-андростен-3-он-17β-фенілпропіонат,
або (19-нортестостерону фенілпропіонат)

Mechanism of action. Stimulates the synthesis of nucleic acids and protein in the body (activating reparative processes in bone and muscle tissue), has a positive effect on nitrogen metabolism (retaining nitrogen in the body, reducing urea excretion by the kidneys).

Properties. White, sometimes with a cream shade, crystalline powder. Practically insoluble in water, sparingly soluble in ethanol, easily soluble in chloroform and acetone.

Identification:T. pl. (95–99 °C), IR spectrum, TLC.

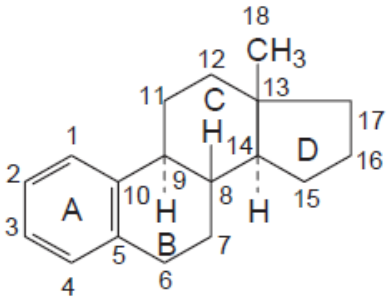
Quantitative definition. Spectrophotometry.

Storage. In a place protected from light.

Application. Anabolic steroid. After a single injection, the effect lasts 7–15 days. Phenobolin is 2 times weaker in its androgenic effect, and 2-5 times more active than testosterone in its anabolic effect.

Estrogen hormones and their analogues

Estrogens(lat. oestrogena) – natural female sex hormones and drugs with female sex hormone activity. The structure of estrogen hormones is based on the hydrocarbon estrone:

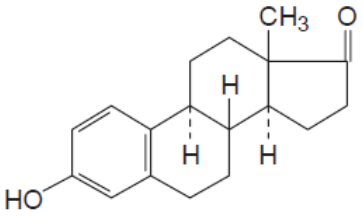


A characteristic structural feature of estrogens, which distinguishes them from other steroid hormones, is:

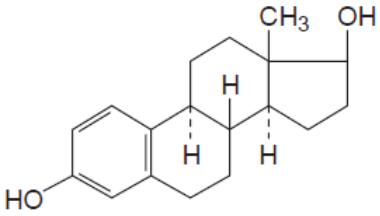
- aromatic ring A;
- phenolic hydroxyl must be present in position 3;

- estrogens do not have a methyl group in the 10 position.
- in position 17 there must be an oxygen function - a keto group (estrone) or a hydroxyl group (estradiol, ethinylestradiol).

The natural hormones of this series are:



естрон



естрадіол

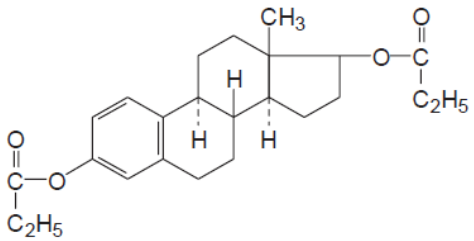
Estradiol has approximately twice as much activity, but is quickly inactivated and excreted from the body.

Estradiol esters (benzoate and dipropionate) are slowly absorbed, slowly excreted and have a long-lasting effect on the body.

Ethinylestradiol, like pregnin, has an ethynyl radical in position 17. Its introduction leads to a significant increase in activity. In addition, ethinyl estradiol is not destroyed in the gastrointestinal tract and is effective when taken orally.

Mechanism of action.E. selectively accumulate in the target organs - the uterus, vagina, mammary glands, anterior lobe of the pituitary gland, liver, where they bind to the specific extranuclear protein estrophilin, receptors of the plasma membranes of the target cells, forming hormone-receptor complexes with them. They penetrate into the nucleus, activate DNA and RNA synthesis, affect protein synthesis.

Estradiol dipropionate



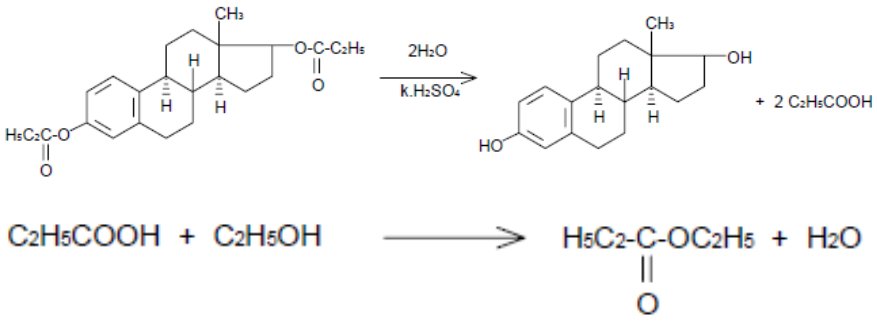
Естратрієн-1,3,5(10)-діолу-3,17β-дипропіонат

Properties. White crystalline powder. Practically insoluble in water, sparingly soluble in alcohol and oils.

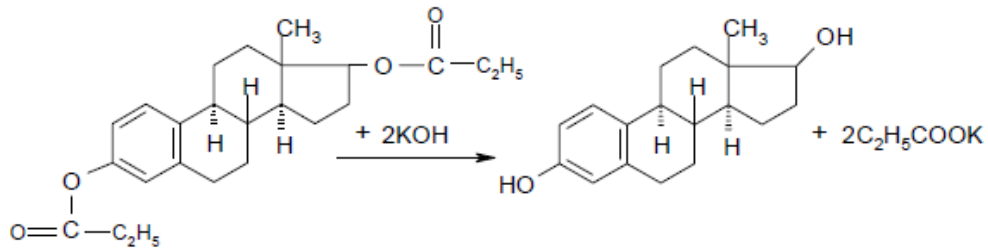
Identification:

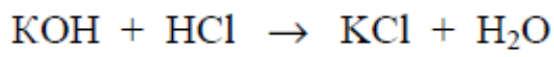
- physicochemical methods: IR and UV spectrophotometry;
- after alkaline hydrolysis, estradiol is isolated, for which T. pl. is determined;

- estradiol dipropionate is hydrolyzed under the influence of concentrated H2SO4. Further heating in the presence of ethanol leads to the formation of ethyl ester of propionic acid, which has a characteristic smell:



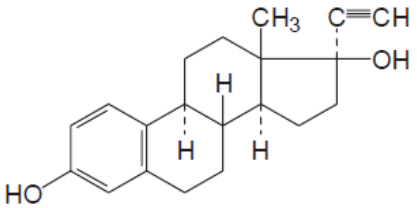
Quantitative definition. Alkalimetry, reverse titration. The substance is hydrolyzed with an alcoholic solution of potassium hydroxide, the excess of which is titrated with a solution of hydrochloric acid against phenolphthalein, s = ½:





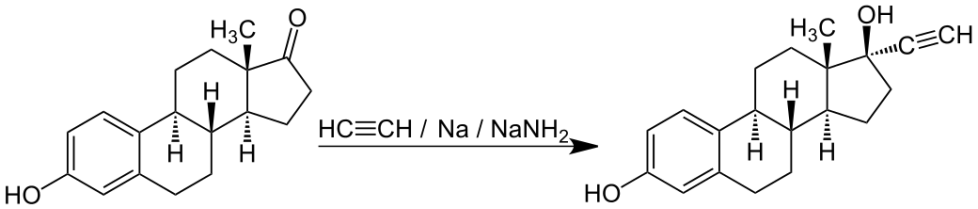
Application. Pathological conditions caused by insufficient ovarian function; prevention and treatment of osteoporosis; carcinoma of the prostate gland.

Ethinylestradiol



17α-Етинілестратрієн-1,3,5(10)-діол-3,17β

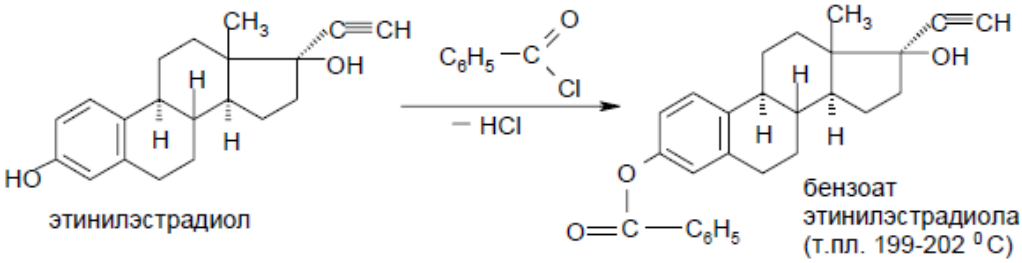
Synthesis.



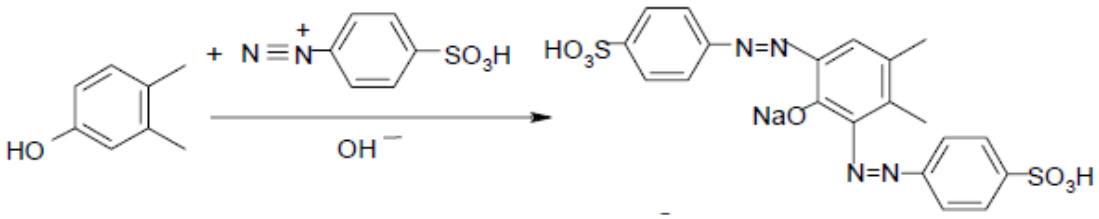
Properties. White or creamy-white fine crystalline powder without odor. Practically insoluble in water, sparingly soluble in alkali metal hydroxide solutions, soluble in alcohol, chloroform, easily soluble in acetone, dioxane, and ether.

Identification:

- when dissolved in concentrated H2SO4, an orange-red color appears with yellow-green fluorescence in reflected light (steroid cycle). When adding a solution of ferrum (III), ammonium sulfate and water, the solution darkens and a reddish-brown precipitate falls out;
- use IR and UV spectrophotometry, TLC;
- determine the melting point of benzoate (phenolic hydroxyl):



Quantitative definition. Alkalimetry according to the substituent (see pregnin), or spectrophotometry or photocolorimetry according to the formation of a bis-diazo compound in an alkaline medium upon interaction with a diazo reagent:



Storage. In a place protected from light.

Application. Estrogenic medicine. Used orally. It is a part of birth control pills.

Synthetic compounds of estrogenic action

Substances that have estrogenic activity were found not only among steroid but also among aromatic compounds. It is assumed that the estrogenic effect depends on the presence of aromatic nuclei in the molecule. An important role belongs to hydroxyl and ketone groups, capable of forming H-bonds and interacting with proteins in the body.

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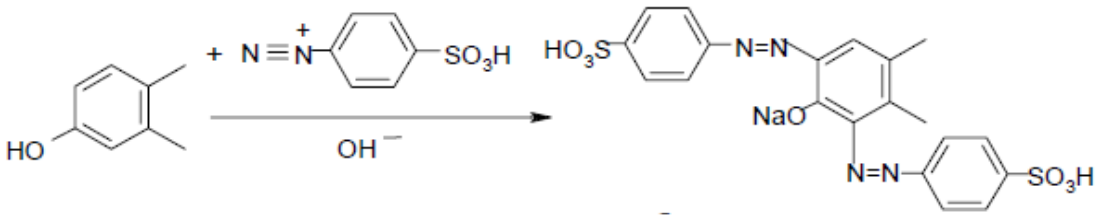

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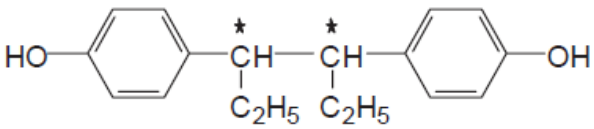
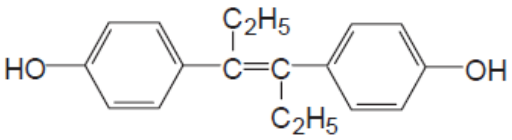
The distance between functional groups is important for the manifestation of estrogenic action. It was established that the distance between OH groups (at positions 3 and 17) in estradiol is 1.1 nm, in the meso-form of sinestrol - 1.2 nm, in the trans-isomer of diethylstilbestrol - 1.22 nm. However, the cis-isomer of diethylstilbestrol, the distance between hydroxyls in which is 0.75 nm, is physiologically inactive.

Sinestrol Diethylstilbestrol



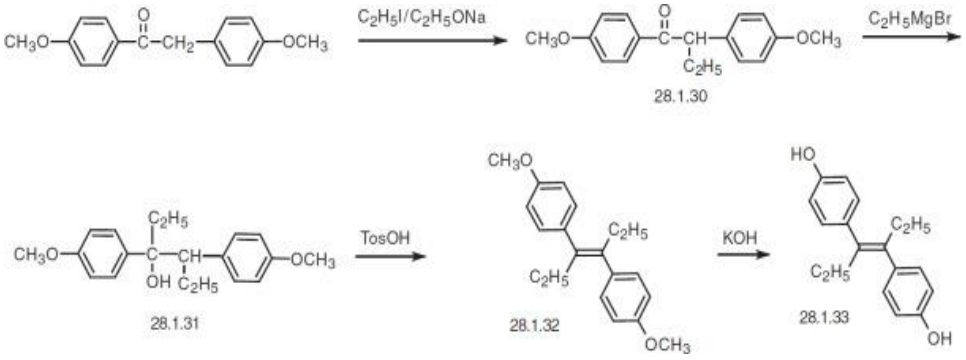
Мезо-3,4-ди-(*n*-гідроксифеніл)-гексан



транс-3,4-Ди-(*n*-гідроксифеніл)-гексен-3

Properties. Synthetic estrogens (sinestrol and diethylstilbestrol) are white crystalline powders (sinestrol may have a yellowish tint) without odor. Practically insoluble or very slightly soluble in water. Sinestrol is easily soluble in ethanol, diethylstilbestrol is slightly soluble in chloroform.

Synthesis of diethylstilbestrol

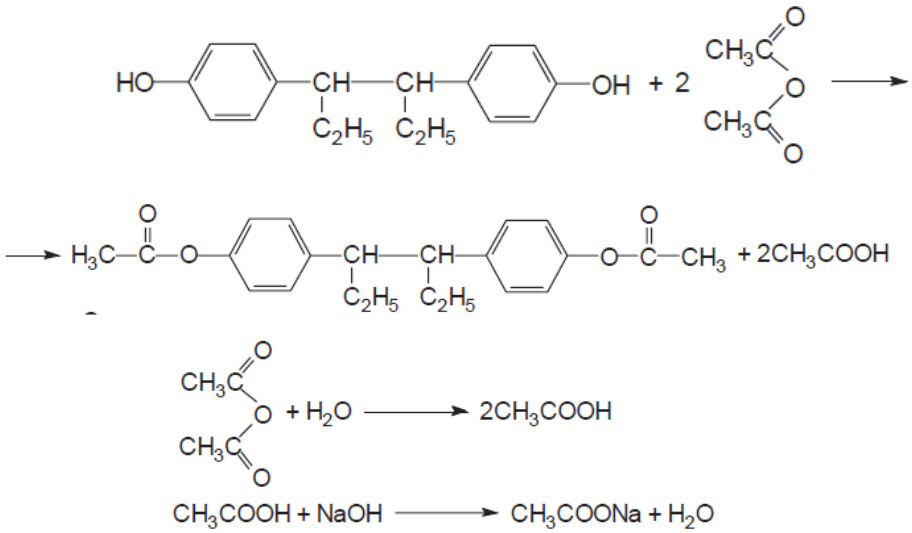


Identification:

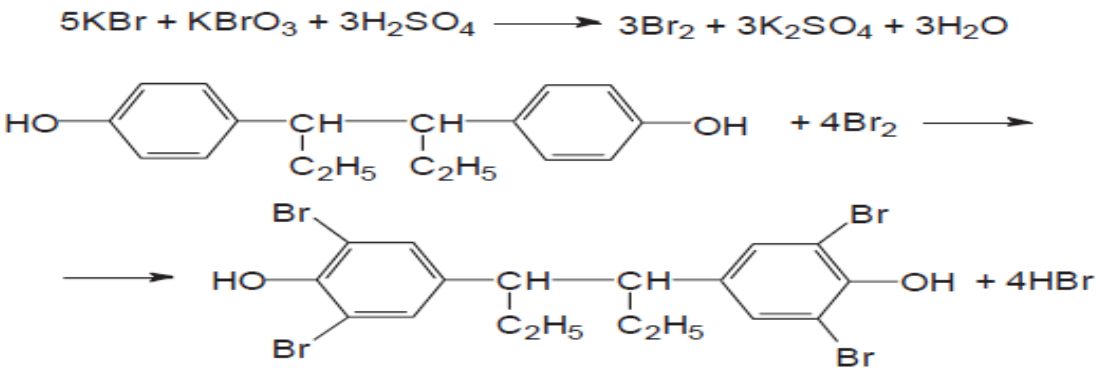
- upon interaction of a chloroform solution of sinestrol with concentrated H2SO4 in the presence of formalin, the chloroform layer turns cherry-red (phenyl radicals). A solution of diethylstilbestrol in concentrated H2SO4 has an orange color, which gradually disappears after dilution with water;
- when bromine water is added to a solution of sinestrol in glacial acetic acid, a yellow precipitate is released (see quantitative definition). Diethylstilbestrol with bromine water in the presence of liquid phenol forms an emerald-green color when heated; after adding a few grains of sugar and heating, the color changes to dark blue, and then to brownish-cherry;
- the presence of phenolic hydroxyls in molecules of medicinal substances can be detected with the help of ferrum (III) chloride. AND recommends this reaction for the identification of diethylstilbestrol, the alcoholic solutions of which are colored green, which gradually turns yellow.
- UV spectrophotometry is used for identification;
- synthetic estrogens can be identified and quantified by the esterification reaction. During the interaction of sinestrol and diethylstilbestrol with acetic anhydride or benzoyl chloride, diacetates (dibenzoates) are formed, which have a characteristic melting point.

Quantitative definition.

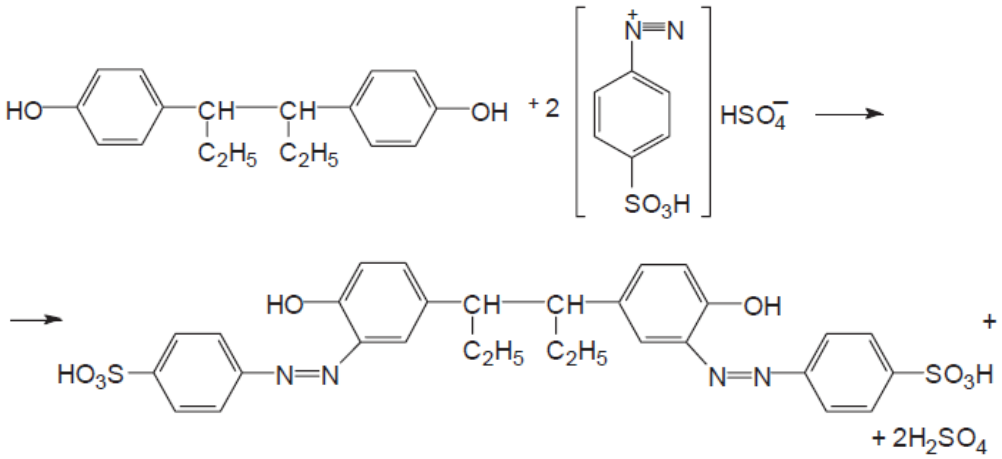
1. Acetylation method. It is based on obtaining esters when heated with acetic anhydride in the presence of pyridine. The excess of acetic anhydride is converted into acetic acid and the amount of acid is titrated with NaOH solution, the indicator is phenolphthalein, s = 1/2. In parallel, a control experiment is conducted:



2. Quantitative determination of sinestrol in an oil solution is carried out after extraction with an aqueous solution of sodium hydroxide by the method of reverse bromatometry with a control experiment, s = 3/4:



3. Sinestrol and diethylstilbestrol can be determined photometrically by the reaction of the azo compound with diazotized sulfanilic acid:



Storage. In a sealed container that protects against light.

Application. In terms of their pharmacological effect, they are close to natural hormones. When taken orally, they are not destroyed in the gastrointestinal tract and are quickly

absorbed. It is prescribed in the form of tablets of 2 mg and intramuscularly in the form of oil solutions (0.1 and 2–3%) for the treatment of malignant neoplasms.

Birth control

Antifertility (contraceptive) drugs (lat. anticoncipientia, s. Contraceptiva <contra - against and conceptio - conception) - drugs to prevent pregnancy. Contraception is a birth control method that interrupts the natural course of events from conception to birth.

*Chemical contraceptives*are called spermicides. Modern spermicides consist of two components: a chemical that destroys the outer shell of sperm and inhibits their motility, or ability to penetrate the egg shell during fertilization, and a base. For most spermicides, the active ingredients are nonoxylon-9, octoxylon, menfegol, and benzalkonium chloride. Spermicides are produced in the following dosage forms: creams, gels, jellies, foams, suppositories, tablets, dissolvable films, tampons.

*Intrauterine*LP - intrauterine spirals (IUDs) are divided into two groups - copper-containing and hormone-releasing IUDs. Copper-containing IUDs are made of polyethylene with the addition of a silver or gold vein, lavsanethylene bactericidal winding, copper-containing threads with antimicrobial action. The contraceptive effect of copper-containing IUDs is based on the sharp acceleration of the egg's progress through the fallopian tubes, as a result of which it does not have time to mature.

The mechanism of action of hormone-releasing IUDs consists in increasing the viscosity of cervical mucus, inhibiting the proliferation of the endometrium, and reducing the activity of spermatozoa. The system has only a local effect, the hormone is not absorbed into the systemic bloodstream, so it is free from the side effects of systemic hormonal drugs and provides high contraceptive effectiveness.

Hormonal contraception(HC) are oral contraceptives (hormonal birth control pills); injectable contraceptives (contraceptive injections); subcutaneous implants (capsules inserted subcutaneously). The composition of HA includes analogues of two natural female sex hormones produced by the ovaries, estrogen and progesterone.

Long-acting hormonal contraceptives(injectable) create a depot of the contraceptive drug in the body for a certain period. After that, the drug is gradually absorbed into the blood, and a contraceptive effect occurs. After that, the drug is gradually absorbed into the blood, and a contraceptive effect occurs. The drug is administered intravenously once every

3 months, contains only one progesterone hormone. In addition, the drug thickens cervical mucus, which makes it difficult for sperm to enter the uterus, and changes the mucous membrane of the uterus in such a way that pregnancy becomes practically impossible. The triple action mechanism of injectable contraceptives makes them one of the most reliable. Effectiveness when observing the terms of the injection is 98%.

*Subcutaneous implants*are silicone capsules containing low doses of progestagen. Capsules are injected subcutaneously in the area of the shoulder. The mechanism of action is similar to the mechanism of action of injectable contraceptives. The drug is valid for 5 years. During this time, the hormone is gradually absorbed into the blood, causing a reliable contraceptive effect (about 99%).

General material and bulk-methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1.Classificationsex hormones

2. Pharmaceutical analysisAnabolic steroids and their analogues

3. Pharmaceutical analysisContraceptives

4. Pharmaceutical analysisEstrogens of nonsteroidal structure

References:

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4. Pharmaceutical chemistry: Textbook for students. higher pharmacy education closing and pharmacy Faculty of Medical Sciences for students higher pharmacy education closing / In general ed. P.O. Bezuglio - Kind. 3rd edition, revised. – Vinnytsia, NOVA KNYGA, 2017. - 456 p.
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7. Nizhnyk H.P. Pharmaceutical chemistry: a textbook (University I-III years) H.P. Nizhnyk — 2nd ed., ed. - All-Ukrainian specialized publishing house "Medytsyna", 2015. - 352p.
8. Pharmaceutical chemistry. Analysis of medicinal substances by functional groups: study guide / O.O. Tsurkan, I.V. Nizhenkovska, O.O. Glushachenko. - 3rd edition - All-Ukrainian specialized publishing house "Medytsina", 2019. - 152 p.
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11. Pharmaceutical chemistry. General and special pharmaceutical chemistry. Medicines of an inorganic nature: laboratory-practical classes. Study guide / L.G. Mishina - Vinnytsia: PP "TD "Edelweiss and K"", 2010. - 384 p.
12. Analytical chemistry and instrumental methods of analysis / A.I. Gab, D.B. Shakhnin, V.V. Malyshev -Ukraine University, 2018- 396 p.

Electronic information resources:

1. Specialized medical online publication for doctors, pharmacists, pharmacists, students of medical and pharmaceutical universities. - [Electronic resource]. - Access mode:http://www.morion.ua.
2. World Health Organization. - [Electronic resource]. - Access mode:http://www.who.int.

3. Pharmaceutical encyclopedia. - [Electronic resource]. – Access mode: http://www.pharmencyclopedia.com.ua.
4. Official website of the International Organization for Standardizationhttp://www.iso.org/iso/home.html
5. Compendium online. [Electronic resource]. - Access mode:https://compendium.com.ua/bad/
6. Medline search database [Electronic resource]. – Access mode: National Library of Medicinehttps://www.nlm.nih.gov/bsd/medline.html

Lecture No. 4

Topic: Vitamins.

Actuality of theme: Pharmaceutical chemistry is a science that studies methods of preparation, structure, physical and chemical properties of medicinal products; relationship between their chemical structure and action on organism; methods of quality control of medicines and changes that occur during their storage, as well as their use in medicine. Therefore, it is urgent to solve the problems facing pharmaceutical chemistry with the help of physical, chemical and physico-chemical methods, which are used both for synthesis, as well as for the analysis of medicinal products.

Goal:the formation of students' knowledge about the peculiarities of the storage of medicinal products, which affect the afferent nervous system, as well as the characteristics, classification, relationship between structure and pharmacological action, mechanism of action, methods of obtaining, methods of analysis, application in medicine. As a result of the lecture, students should learn the properties and methods of medical analysis meansfrom the group of vitamins.

Basic concepts:pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

Plan and organizational structure of the lecture:

1.Preparatory stage

1.1.Determination of educational goals.

1.2.Providing positive motivation.

2. The main stage

Presentation of lecture material

Plan:

-Classification of vitamins

-Aliphatic vitamins

-Vitamins of the alicyclic series

-Aromatic vitamins

- Vitamins of the heterocyclic series

3. The final stage

3.1. Summary of the lecture, general conclusions.

3.2. The lecturer's answers to possible questions

3.3. Tasks for self-training of students.

Content of lecture material (lecture text):

Vitamins(lat. vita life + aminus - that is, nitrogen-containing substances necessary for life) - low molecular weight organic substances of various chemical structures, which are biological catalysts of chemical reactions that take place in a living cell, necessary for normal metabolism and vital activity of the body.

The term Vitamins was proposed in 1911–1912 by the Polish scientist K. Funk.About 30 vitamins and vitamin-like compounds are known today. Human and animal bodies do not synthesize vitamins or synthesize them in insufficient quantities (nicotinic acid) and therefore must receive them with food.

Classification. As individual vitamins were discovered, they were labeled with letters of the Latin alphabet (eg A, B, C, etc.). With the selection of new Vitamins in an individual state, they began to notice the similarity of their structure and the difference in biological action, so they began to add numerical indices to the letters (B1, B2, K1, etc.). Classification by physical properties was also introduced, according to which all vitamins are divided into two groups: water-soluble and fat-soluble.

Aliphatic vitamins

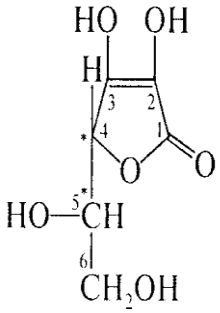
Polyoxy-γ-lactone derivatives of unsaturated carboxylic acids include ascorbic acid. It is widely distributed in nature. The plant life is especially rich in it: fresh vegetables, fruits, sweet potatoes, etc. In industry, ascorbic acid is synthesized from D-glucose.

Pangamic acid (vitamin B15) belongs to aliphatic vitamins, derivatives of gluconic acid esters. Calcium salt is also used in medicine. Pangamic acid is part of rice bran, yeast, blood, and liver. According to its chemical structure, it is an ester of D-gluconic and dimethylaminoacetic acids.

Pantothenic acid belongs to vitamins of the aliphatic series, derivatives of β-amino acids. Yeast, coffee, liver and egg yolk are rich in it. Chemically, pantothenic acid is an amide formed by β-alanine and α,γ-dioxy-β,β-dimethylbutyric (pantoic) acid.

Calcium salt of pantothenic acid is used in medical practice.

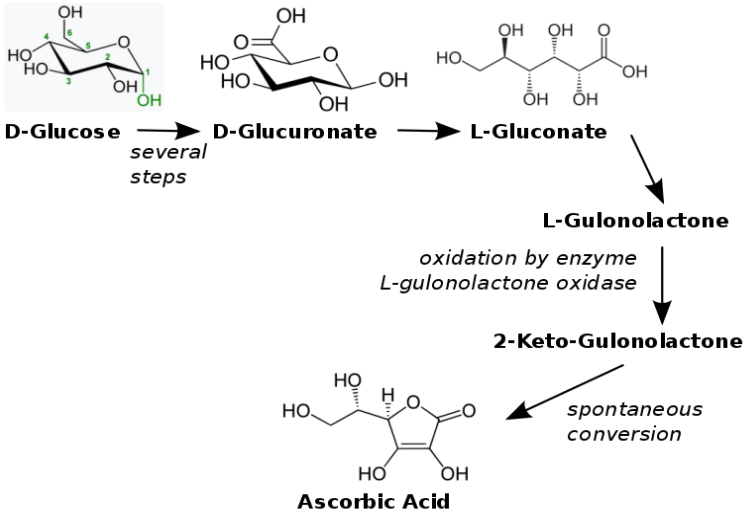
Ascorbic acid (Acidum ascorbsnscum)



γ-Лактон-2,3-дегідро-*L*-гулонової кислоти

Mechanism of action. Ascorbic acid (vitamin C) as an antioxidant, metabolic and redox-regulating agent increases the body's adaptive capabilities and strengthens its resistance to infections.

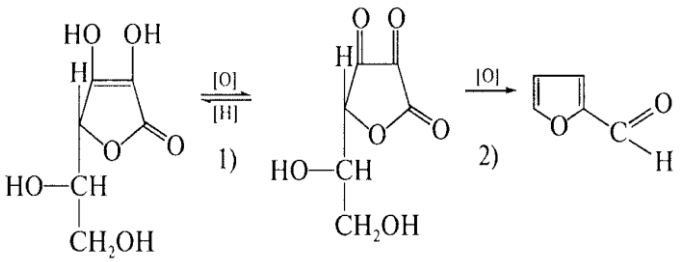
Synthesis.



Properties. Crystalline powder of white or almost white color or colorless crystals that change color under the influence of air and moisture. Easily soluble in water, soluble in 96% alcohol, practically insoluble in ether. Melts at a temperature of about 190 °C with decomposition. Due to the enediol group, it exhibits both reducing and acidic properties.

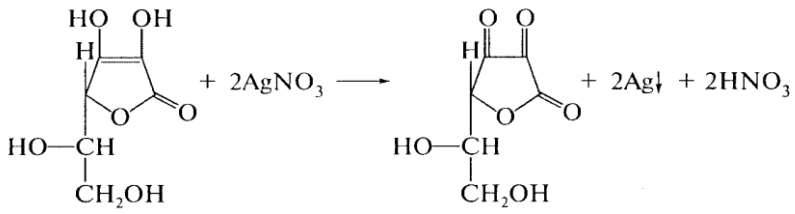
Ascorbic acid is oxidized in two stages:

- reversible process of oxidation to dehydroascorbic acid;
- an irreversible process that eventually leads to furfural:

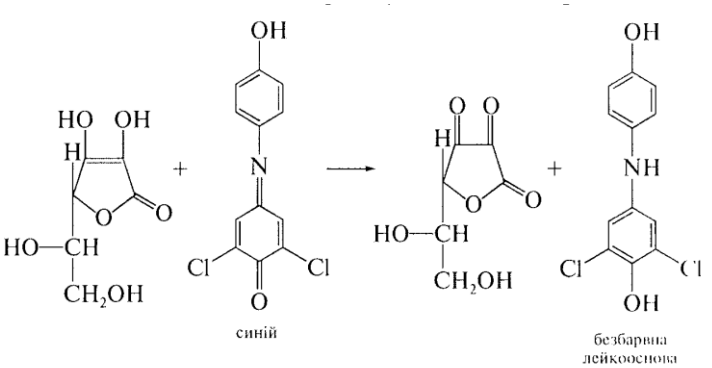


Identification:

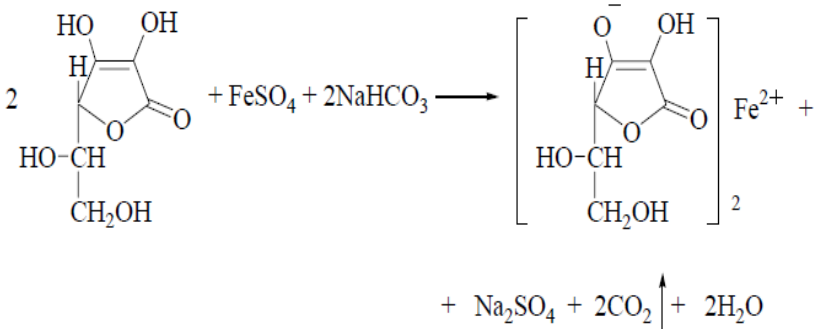
- a solution of AgNO3 is added to the solution of LZ - a dark precipitate of Ag falls out:



- when adding 1 drop of 2,6-dichlorophenolindophenol solution to the ascorbic acid solution, its blue color disappears:

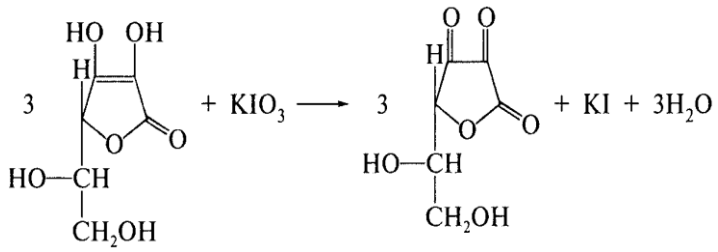


- ascorbic acid with FeSO4 in the presence of NaHCO3 forms iron ascorbate, colored purple:

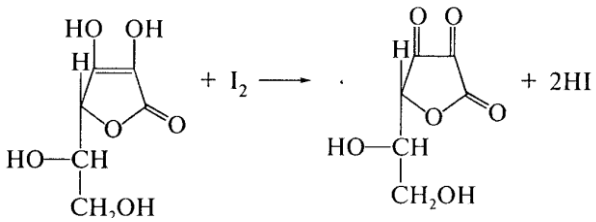


Quantitative definition.

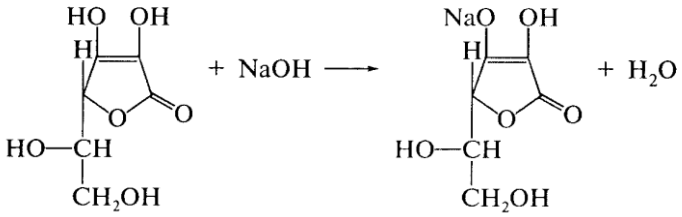
1. Iodometry, direct titration in an acidic environment in the presence of potassium iodide, the indicator is starch, s = 3:



2. Iodometry, direct titration without indicator, s = 1/2:



3. Alkalimetry, direct titration, indicator – phenolphthalein, s = 1:



4. Titration with sodium 2,6-dichlorophenolindophenolate solution, s = 1/2. The method is used to determine the content of ascorbic acid in vegetable raw materials.

Storage. In a well-stoppered dark glass container. Released in powders, tablets or dragees, injection solutions.

Application. For preventive and therapeutic purposes in scurvy (scurvy), bleeding of various etiologies, infectious diseases and intoxications, liver and kidney diseases.

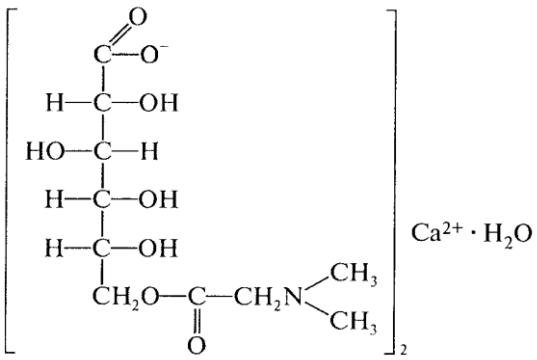
L. Pauling and vitamin C

Linus Pauling (Linus Pauling, 1901–1994) is an American chemist, also known for his research in crystallography, molecular biology and medicine, laureate of the Nobel Prizes in Chemistry (1954) and Peace (1962).

In the book "Vitamin C and the Common Cold", published in 1970, Pauling laid out his evidence in support of the therapeutic properties of vitamin C. In the early 1970s, he formulated the theory of orthomolecular medicine (" the right molecules in the right amounts"), which emphasized the importance of vitamins and amino acids.

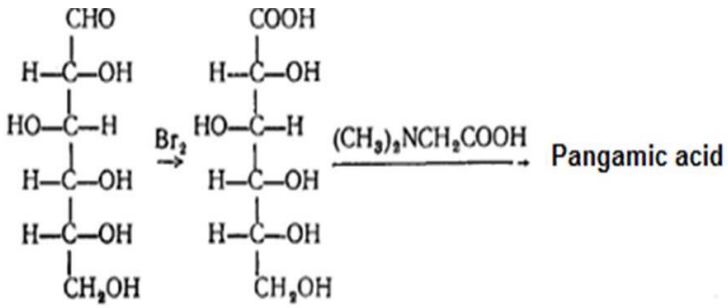
L. Pauling proposed to increase the daily dose of vitamin C consumption by 100-200 times (up to 10 g), assuming that such extremely high doses are optimal for health. Pauling believed that taking vitamin C in large doses could help cure many different diseases, including cancer. Several experiments in model animal cell cultures have shown that vitamin C can destroy some tumor cells (cells in model cell cultures that have regenerated). However, no such effect was found in living human organisms: systematic meta-reviews of clinical studies with hundreds of thousands of patients demonstrate that taking vitamin C and other antioxidant supplements for all types of tumors of the digestive system does not affect tumor development and does not improve patient survival.

Calcium pangamate (Calcii pangamas, vitamin B15)



Mechanism of action. Stimulates cellular metabolism. It is a source of active methyl groups and calcium ions for biosynthetic processes. Improves lipid metabolism, increases oxygen assimilation by tissues, increases the content of creatine phosphate in muscles and glycogen in muscles and liver, eliminates the phenomenon of hypoxia.

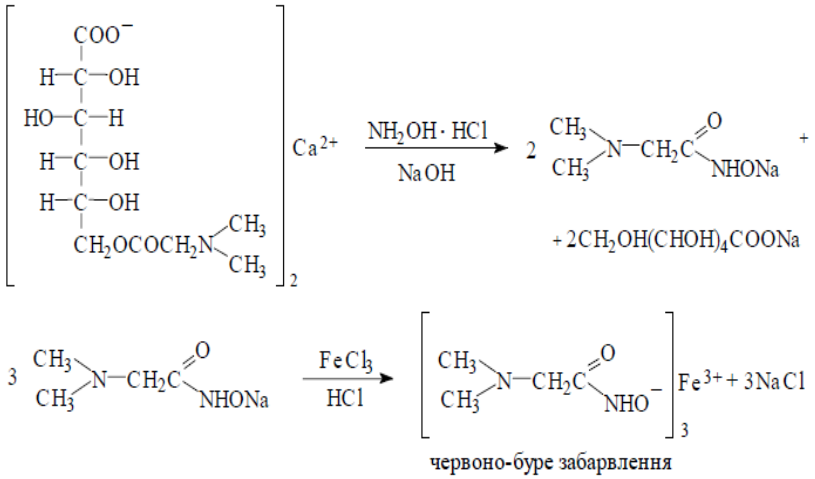
Synthesis



Properties. White, sometimes with a yellowish tinge, crystalline powder with a characteristic smell. Hygroscopic. Easily soluble in water and practically insoluble in organic solvents.

Identification:

- by IR spectroscopy;
- the substance reacts to calcium ions;
- the remainder of gluconic acid is confirmed by reaction with ferrum(III) salts to form a light green color;
- when heating a solution of the substance with NaOH, the smell of amines is felt;
- reaction of formation of colored ferrum hydroxamate (ester group):



червоно-буре забарвлення

Quantitative definition. Given that the substance, in addition to calcium pangamate, contains 25% calcium gluconate and 6% calcium chloride, the content is quantified:

1. nitrogen - by the method of acidimetry in a non-aqueous medium (3.6–4.2%);

2. calcium - by the complexonometry method (5.8–7.4%);

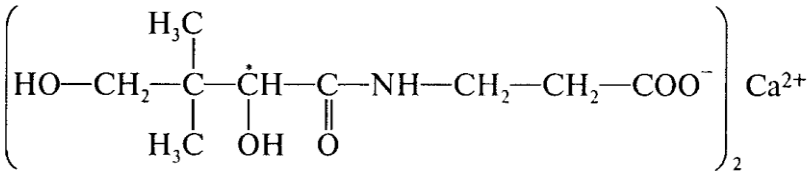
3. chlorides - by the method of reverse argentometry according to Folgard (no more than 2.2%);

4. amount of carboxyl groups - by the method of ion exchange chromatography (11.0–15.0%).

Storage. In a dry place, in well-stoppered glasses.

Application. With various forms of atherosclerosis, liver cirrhosis, alcoholism and other diseases. Used in the form of tablets. Calcium pangamate has a positive effect on metabolism - it improves lipid metabolism, increases the assimilation of oxygen by tissues.

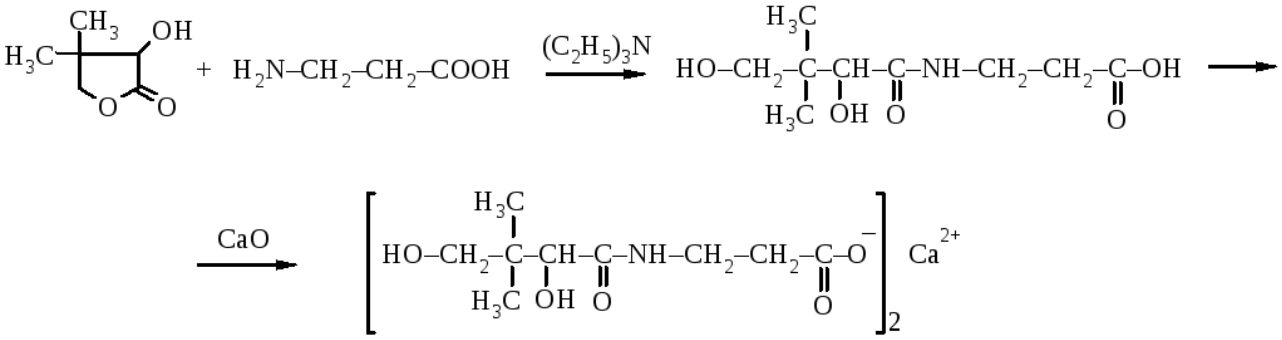
Calcium pantothenate (Calcii pantothenas, vitamin B5)



Кальцієва сіль *D*-(+)-α,γ-діокси-β,β-диметилбутирил-N-амід-β'-амінопропіонової кислоти

Mechanism of action. After being absorbed in the intestines, vitamin B5 participates in the synthesis of acetyl coenzyme A. The main function of acetyl CoA is that it is an acceptor and carrier of acid (acyl) residues. This coenzyme (A-CoA) is necessary for the normal course of many metabolic processes: it participates in the oxidative decarboxylation of keto acids (for example, pyruvic acid, α-ketoglutaric acid), in the synthesis of citric acid (included in the cycle of tricarboxylic acids), corticosteroids, and acetylcholine. With its participation, the synthesis of fatty acids, cholesterol, and sex hormones is carried out.

Synthesis.

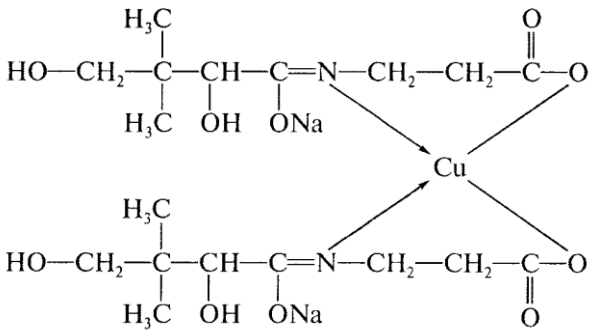


Properties. White fine crystalline powder without odor. Easily soluble in water, very slightly soluble in organic solvents.

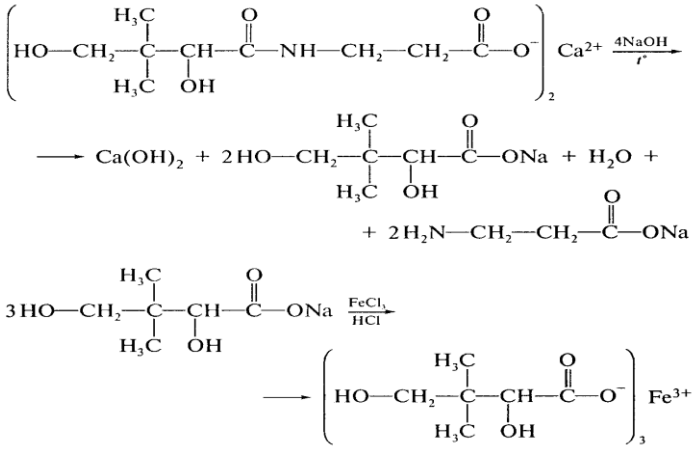
Identification:

- specific rotation from +25 to +28 o (5% aqueous solution);

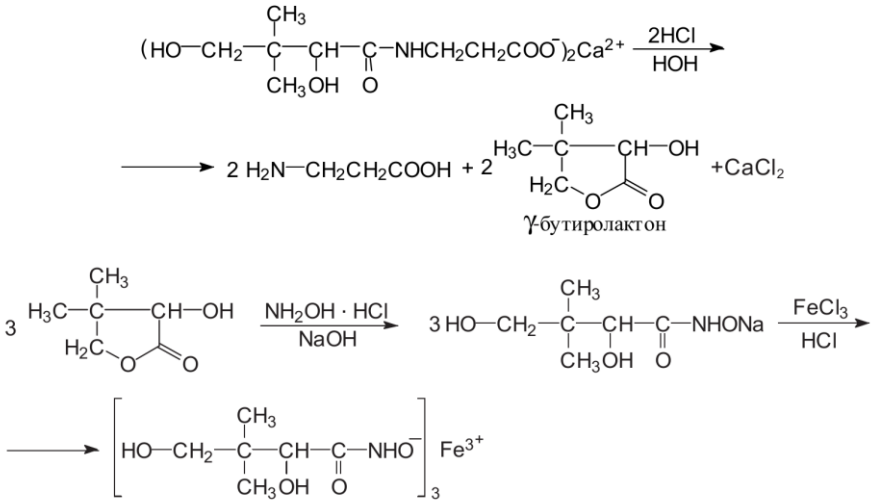
- the substance reacts to calcium ions;
- with a solution of copper(II) sulfate in an alkaline medium, the substance forms a blue complex (β-alanine):



- the residue of α,γ-dihydroxy-β,β-dimethylbutyric acid is determined after alkaline hydrolysis. The substance is boiled with NaOH solution, after cooling it is acidified with hydrochloric acid and FeCl3 solution is added – a yellow color is formed:



- reaction of formation of colored ferrum hydroxamate:



Quantitative definition.

The content of calcium cations (8.2–8.6%) is determined complexometrically, and the nitrogen content (5.7–6.0%) is determined by the method of determining nitrogen in organic compounds.

Storage. In a dry place at room temperature, in well-stoppered glasses.

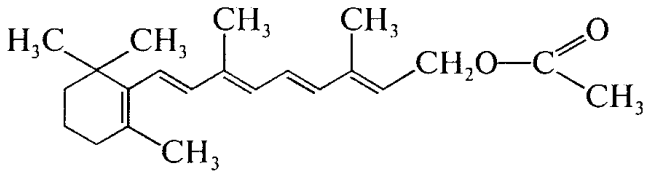
Application.

For the treatment of neuralgia, eczema, allergies, polyneuritis and other diseases associated with metabolic disorders, as well as inflammatory processes.

Vitamins of the alicyclic series

Alicyclic vitamins include retinols (vitamins of group A) and calciferols (vitamins of group D). At the heart of the retinol molecule is a trimethylcyclohexane ring connected to a tetraenol conjugated chain, which ends with a hydroxyl or aldehyde group. Retinol was obtained from the liver of fish in 1909. In 1928, Euler established that in some plants there are substances that have provitamin activity, that is, they are precursors of vitamins. Provitamins of vitamin A are α-, β- and γ-carotenes.

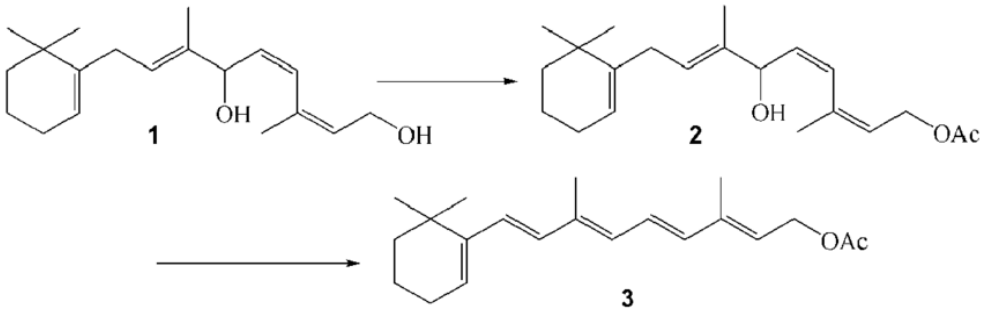
Retinol acetate (Retinoli acetas)



транс-9,13-Диметил-7-(1,1,5-триметилциклогексен-5-іл-6)-нонатетраен-7,9,11,13-олу-15 ацетат

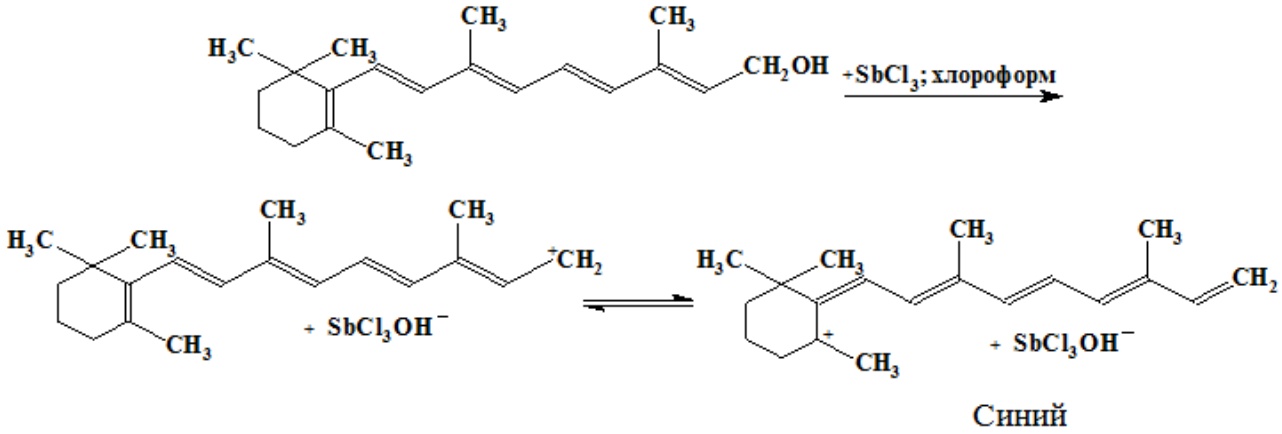
Mechanism of action. Enhances the proliferation of epitheliocytes, rejuvenates the cell population, stimulates the synthesis of rhodopsin in the retina, improves the regeneration process, has an antioxidant, immunomodulatory effect.

Synthesis.



Properties. White or pale yellow crystals with a faint odor. Extremely unstable under the influence of air oxygen and light. Practically insoluble in water, soluble in 96% alcohol, chloroform, ether and oils.

Identification:color reaction with stibium(III) chloride in a chloroform medium - a blue color appears:

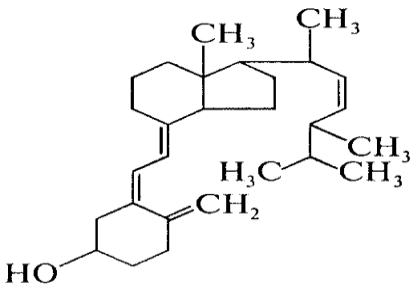


Quantitative definition.UV spectrophotometric method.

Storage. Due to the fact that the substance is easily oxidized, it is stored in ampoules sealed in a stream of nitrogen, protected from light, at a temperature not higher than +5 °C. Retinol acetate oil solutions are stored in dark glass filled to the top, well-stoppered glasses at a temperature no higher than +10 °C.

Application. With vitamin deficiency, skin diseases and lesions, eye diseases. Retinol acetate is prescribed in the form of dragees, granules, oil solutions internally, intramuscularly and locally.

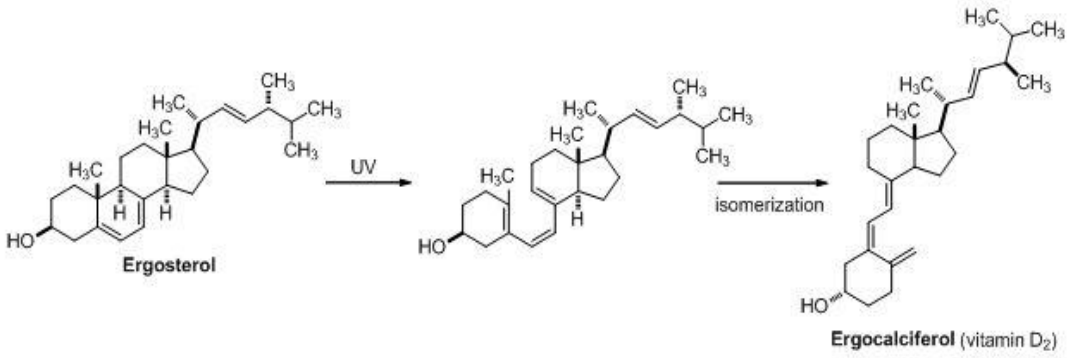
Ergocalciferol (Ergocalciferolum)



24-Метил-9,10-секохолеста-5,7,10(19),22-тетраен-3 β-ол

Mechanism of action. Regulates the exchange of phosphorus and calcium in the body, promotes their absorption in the intestines due to the increase in the permeability of its mucous membrane and adequate deposition in bone tissue. The action of ergocalciferol is enhanced with simultaneous intake of calcium and phosphorus compounds.

Synthesis



Properties. White or slightly yellowish crystalline powder or white or almost white crystals. Practically insoluble in water, easily soluble in 96% alcohol, soluble in fatty oils. Sensitive to air, heat and light. Solutions in volatile solvents are unstable and should be used immediately after preparation. In solutions, temperature- and time-dependent reversible isomerization to preergocalciferol is possible. The activity of the substance is determined by both components. The solution of ergocalciferol in oil is a clear, oily liquid from light yellow to dark yellow in color.

Identification:

- by IR spectroscopy;
- upon interaction with a solution of stibium (III) chloride in the presence of acetyl chloride, an orange-pink color is formed.

Quantitative definition. It is carried out by the method of liquid chromatography.

Storage. Ergocalciferol is stored in an airtight container, under nitrogen, in a place protected from light, at a temperature of 2 to 8 °C. The contents of the opened container should be used immediately.

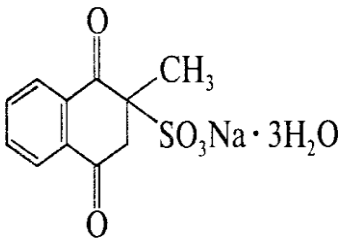
Application. In medical practice, alcohol (0.5%) and oil (0.125%) solutions of vitamin D2 are used for the prevention and treatment of rickets, as well as bone diseases associated with calcium metabolism disorders.

Aromatic vitamins

Aromatic vitamins include derivatives of 2-methyl-1,4-naphthoquinone (group K vitamins). They have an antihemorrhagic effect and participate in the formation of prothrombin.

In medical practice, a synthetic analogue of group K vitamins is used - Vikasol.

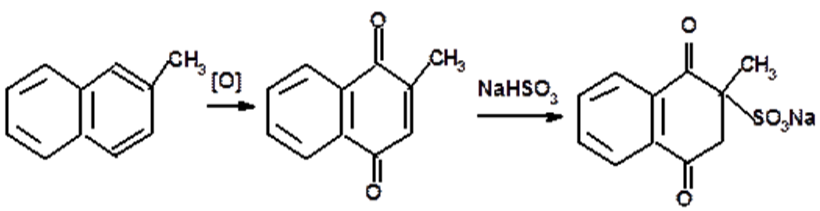
Vikasol (Vikasolum)



Натрію 2,3-дигідро-2-метил-1,4-нафтохінон-2-сульфонат

Mechanism of action. Stimulates the synthesis of prothrombin and proconvertin, enhances the synthesis of II, VII, IX, X coagulation factors and, as a result, increases blood coagulation. It has hemostatic properties, since vitamin K deficiency leads to increased bleeding.

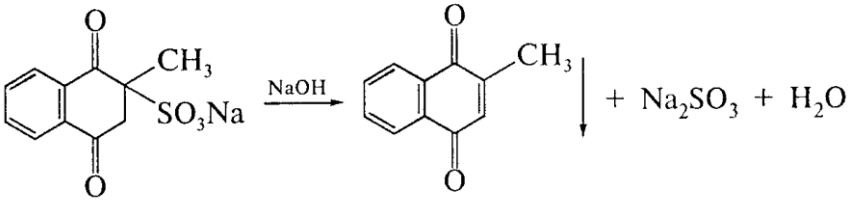
Synthesis.



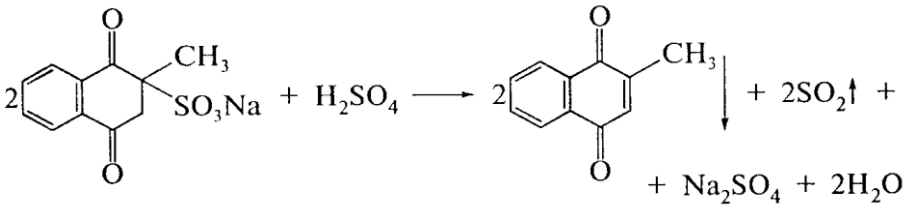
Properties. White, sometimes with a yellowish tinge, odorless crystalline powder. Easily soluble in water, hardly soluble in alcohol, very slightly soluble in ether.

Identification:

- upon interaction with a NaOH solution, a precipitate of 2-methyl-1,4-naphthoquinone falls out, which is extracted with chloroform, purified from impurities, and the melting point is determined (104–107 °C):



- when Vikasol interacts with concentrated sulfuric acid, the smell of sulfur (IV) oxide (sulfur gas) is felt:



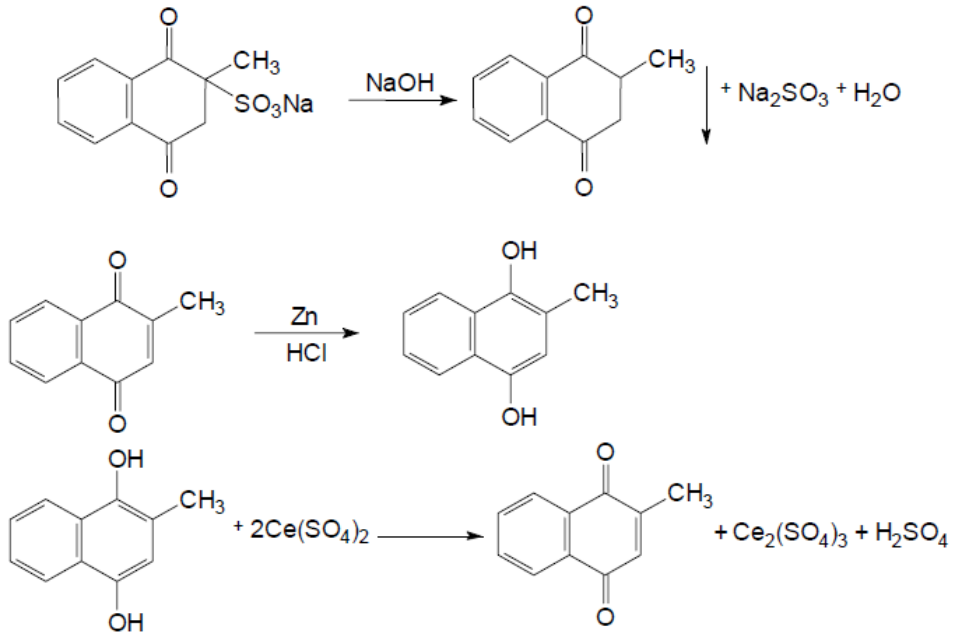
- the substance reacts to sodium ions.

Specific impurities. Sodium bisulfite and 2-methyl-1,4-naphthohydroquinone-3-sulfonate.

Sodium bisulfite is determined quantitatively by the iodometric method (no more than 2% is allowed).

2-Methyl-1,4-naphthohydroquinone-3-sulfonate is determined using o-phenanthroline - no precipitate should form (impurity is unacceptable).

Quantitative definition. Cerimetry, direct titration, indicator – o-phenanthroline, s = 1/2. Interaction with sodium hydroxide precipitates 2-methyl-1,4-naphthoquinone, which is extracted with chloroform. After removal of chloroform, it is reduced in an acidic medium to 2-methyl-1,4-dihydroxynaphthalene, which is then titrated with a solution of cerium (IV) sulfate until a green color appears:



Storage. In a well-closed container that protects from light.

Application. To increase blood clotting in case of various bleedings. Available in powders, tablets and solutions.

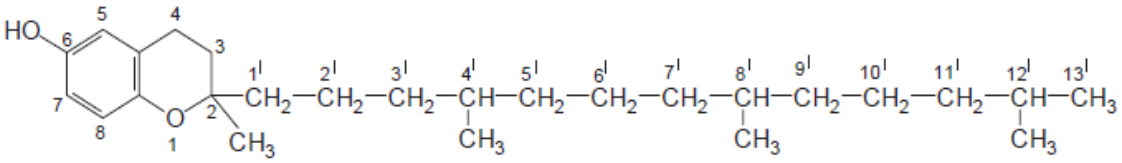
Vitamins of the heterocyclic series

Chromane derivatives

Vitamins of the heterocyclic series, derivatives of chroman (vitamins of group E - tocopherols), are contained in oils, as well as in the green parts of plants, especially in young sprouts of cereals. They are also found in small amounts in milk, butter, egg yolks, meat, and fats.

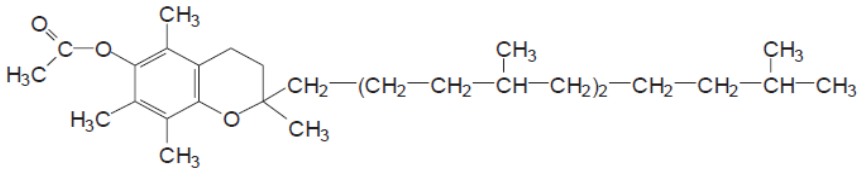
In industry, vitamin E is obtained from natural sources or as a result of synthesis.

The structure of group E vitamins is based on the tocol molecule:



Tocopherols differ in the number of methyl groups in the chroman core; there are seven natural vitamins of group E. The most active is α-tocopherol. Tocopherol acetate is used in medical practice.

Tocopherol acetate (Tocopheroli acetas)



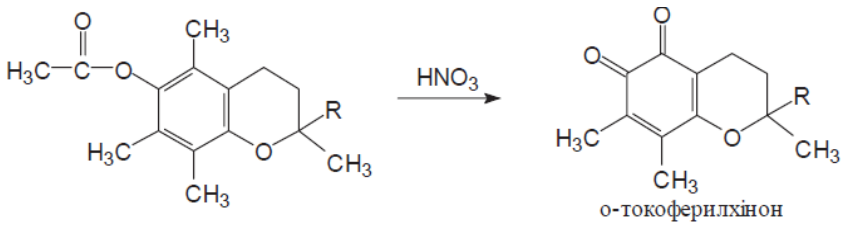
(±)-2,5,7,8-Тетраметил-2-(4',8',12'-триметилтридецил)-6-ацетоксихроман

Mechanism of action. Blocks the participation of oxygen in the oxidation of polyunsaturated fatty acids, participates in phosphorylation processes. Supports the normal function of the gonads. It inhibits the synthesis of cholesterol, reduces the oxygen demand of the myocardium, improves blood supply to tissues, including of the myocardium, and has an antioxidant effect, prevents the increase in capillary permeability and fragility.

Properties. Light yellow, transparent, thick, oily liquid with a weak odor. Practically insoluble in water, soluble in 95% alcohol and very easily soluble in ether, acetone, chloroform and oils. Under the influence of light, tocopherol acetate oxidizes and darkens.

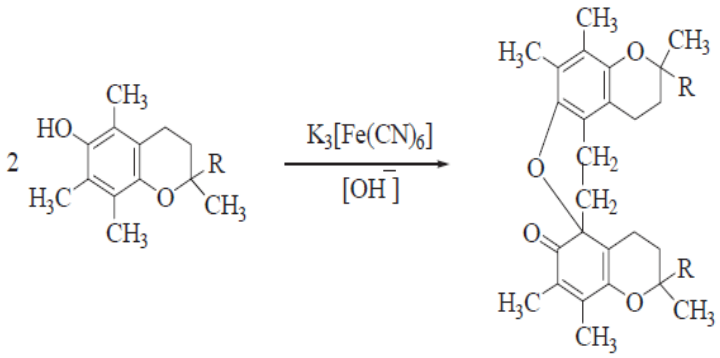
Identification:

- oxidation with fuming nitric acid, when heated on a water heater - a red-orange color appears:

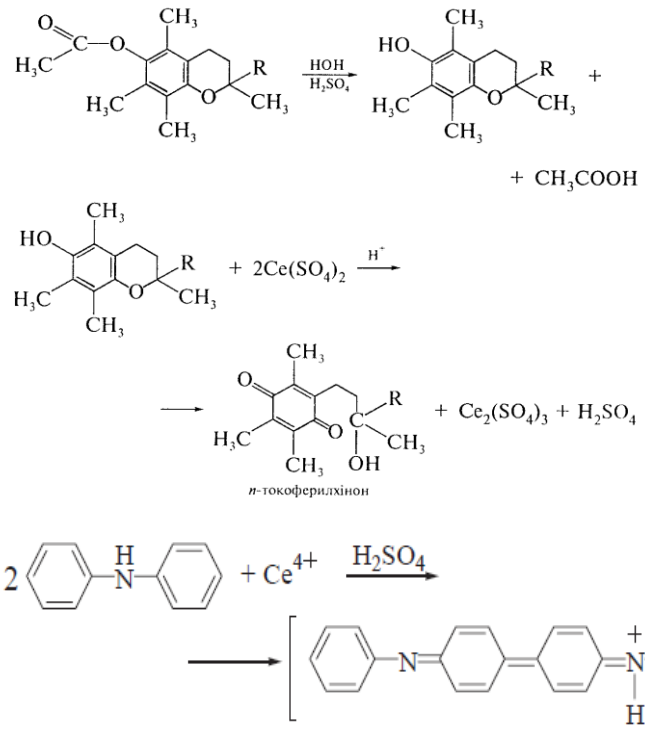


о-токоферилхінон

- tocopherol acetate is hydrolyzed with a solution of KOH in absolute alcohol (when heated), then concentrated sulfuric acid is added - the smell of ethyl acetate is felt;
- upon oxidation of potassium tocopherol with hexacyanoferrate (III) in an alkaline medium, colored di-α-tocopherol is formed:



Quantitative definition. Cerimetry, direct titration after hydrolysis, indicator – diphenylamine, s = 1/2:

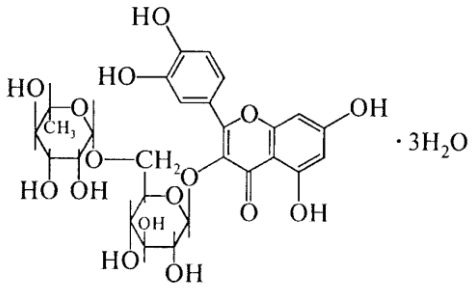


In parallel, a control experiment is conducted.

Storage. In hermetically closed, filled to the top jars made of dark glass, in a cool place, protected from light.

Application. For nervous diseases, muscular dystrophies, sclerosis, to improve vision, for radiation sickness, an alcohol or oil concentrate with a content of 0.3 to 2% α-tocopherol is used, an ampoule solution containing 0.05; 0.1 and 0.2 g of α-tocopherol in 1 ml of oil, as well as dragees.

Rutin (Rutinum)



3-Рутинозид кверцетину, або 3-рамноглюкозил-3,5,7,3',4'-пентаоксифлавон

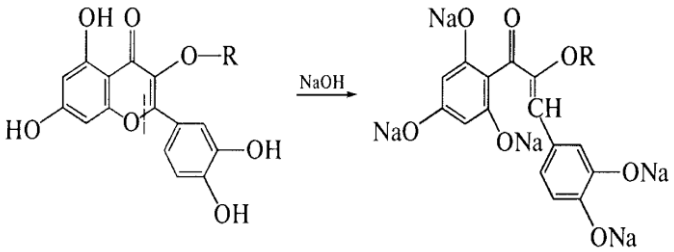
Mechanism of action. Promotes the transformation of ascorbic acid into dehydroascorbic acid and prevents further transformation of the latter into diketogulonic acid. Therefore, most of the effects of rutin are mediated by ascorbic acid.

Properties. Greenish-yellow fine crystalline powder without smell and taste. Practically insoluble in water, sparingly soluble in alcohol, sparingly soluble in boiling alcohol, practically insoluble in acid solutions, ether, chloroform, acetone and benzene, soluble in dilute alkali solutions.

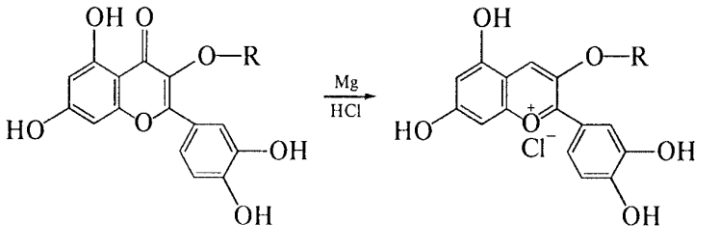
Rutin is a glycoside and upon acid hydrolysis it gives the aglycone quercetin and the disaccharide rutinose, which consists of glucose and rhamnose.

Identification:

- when the substance is dissolved in sodium hydroxide solution, a yellow-orange color appears. As a result of the reaction, the flavonoid turns into a chalcone:



- rutin is reduced in an acidic medium, thus pyrylium salts are formed, which have a red color (cyanine reaction):



- the remaining glucose is detected after acid hydrolysis by reaction with Fehling's reagent;
- the presence of absorption maxima in the UV spectrum at 259 and 362.5 nm.

Quantitative definition. Spectrophotometry.

Storage. In a sealed container that protects against light.

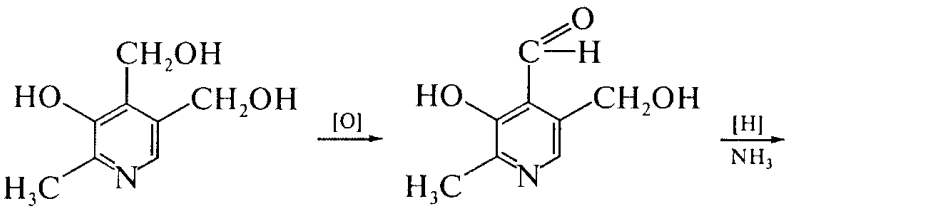
Application. Rutin regulates the permeability of blood vessels, enhances the action of ascorbic acid. It is used for the prevention and treatment of hypo- and avitaminosis P, as well as for the treatment of diseases associated with impaired vascular permeability and capillary damage. Tablets containing rutin and ascorbic acid are produced under the name "Ascorutin".

Pyridine derivatives

Vitamins derived from pyridine include nicotinic acid and amide (vitamins PP) and oxymethylpyridine vitamins (group B6).

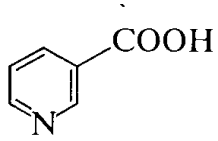
Nicotinic acid, or β-pyridinecarboxylic acid, was first obtained synthetically by K. Huber in 1867 during the oxidation of nicotine with chromic acid. Its vitamin properties were discovered in 1937-1938. The natural raw material does not contain nicotinic acid itself, but nicotinamide, which is part of many enzymes. Thus, nicotinic acid is a provitamin of nicotinamide.

Vitamins of the B6 group are represented by related substances: pyridoxol (pyridoxine), pyridoxal and pyridoxamine, which are successively transformed into each other:



піридоксол піридоксаль піридоксамін

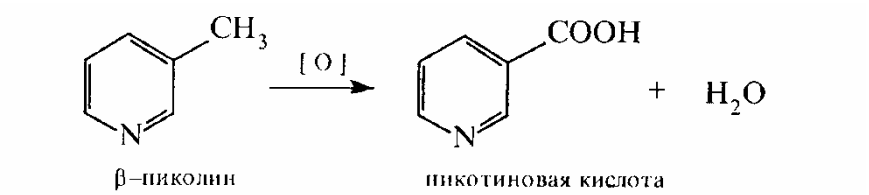
Nicotinic acid (Acidum nicotinicum)



Піридин-3-карбонова кислота

Mechanism of action. Nicotinic acid is a prosthetic group of enzymes codehydrase I and codehydrase II - enzymes that transfer hydrogen and carry out redox processes. Codehydrase II is also involved in phosphate transport. Insufficiency of nicotinic acid leads to pellagra. Nicotinic acid improves carbohydrate metabolism, dilates blood vessels.

Synthesis.

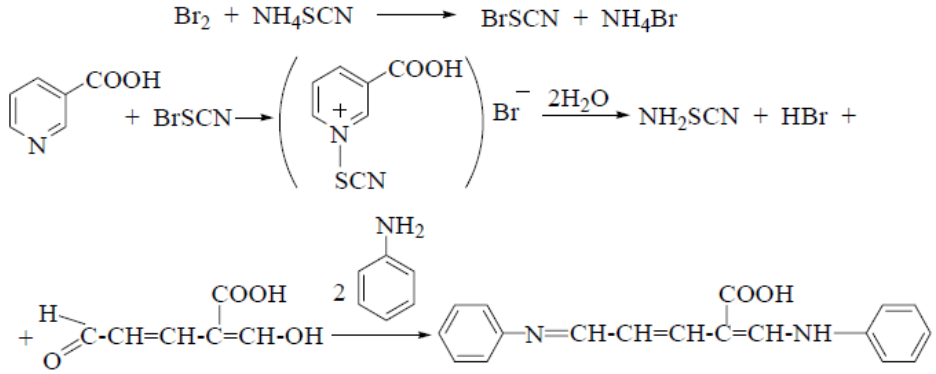


β–пиколин никотиновая кислота

Properties. White crystalline powder without odor, slightly acidic in taste. Hardly soluble in water and 95% alcohol, soluble in hot water, very slightly soluble in ether. Soluble in acids and bases.

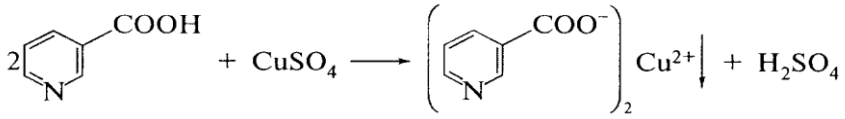
Identification:

- physicochemical methods: determination of temperature, IR spectroscopy;
- the substance, upon interaction with a cyanobromide solution and the subsequent addition of an aniline solution, forms a yellow color:

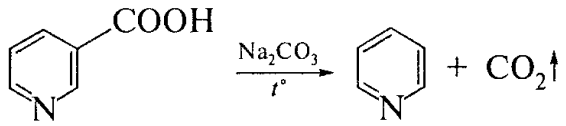


Non-pharmacopoeial reactions:

- reaction to the pyridine cycle with 2,4-dinitrochlorobenzene;
- formation of blue-colored cuprum nicotinate:

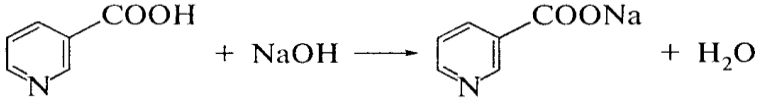


- when the substance is heated with anhydrous sodium carbonate, the smell of pyridine appears:

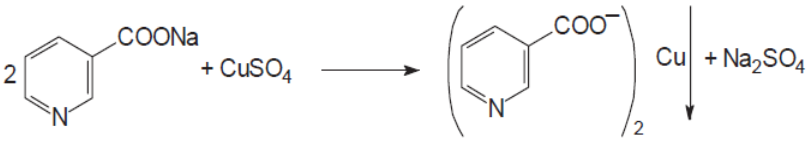


Quantitative definition.

1. Alkalimetry, direct titration, the indicator is phenolphthalein, s = 1. In parallel, a control experiment (SFU) is carried out:



2. In solutions for injections, the quantitative content of nicotinic acid is determined by the cupriiodometric method after neutralization with sodium hydroxide solution, the indicator is starch, s = 2:



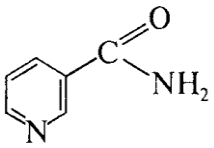
$2CuSO_4 + 4KI \longrightarrow Cu_2I_2\downarrow + I_2 + 2K_2SO_4$

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

Storage. In a sealed container that protects against light.

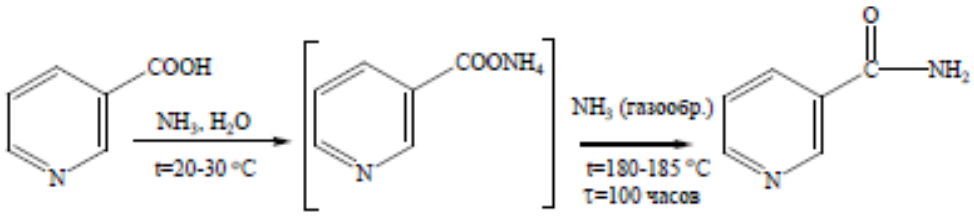
Application. Antipelagic agent. Nicotinic acid has a vasodilating and hypocholesterolemic effect, therefore it is prescribed for liver diseases, spasms of blood vessels in the limbs, kidneys, brain, and infectious diseases. Causes a side effect: redness of the face, feeling of a rush of blood to the head.

Nicotinamidum (SFU)



Амід нікотинової кислоти

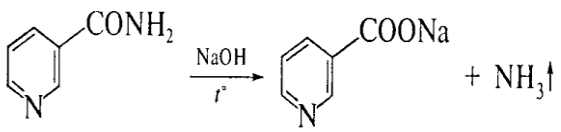
Synthesis.



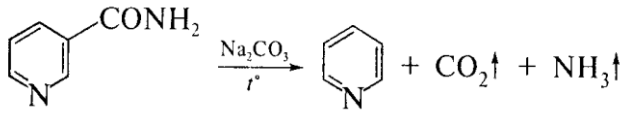
Properties. White fine crystalline powder with a very weak odor, bitter taste. Easily soluble in water and alcohol, soluble in glycerol, very slightly soluble in ether and chloroform

Identification:

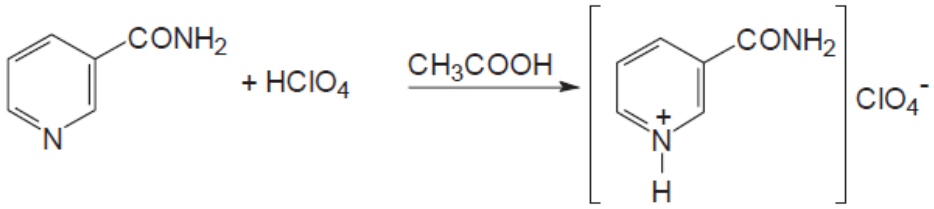
- by physical and chemical methods: determination of temperature, IR spectroscopy;
- release of ammonia when heating the substance with NaOH solution:



- Schiff's base formation reaction upon interaction with cyanobromide reagent and aniline;
- Non-pharmacopoeial reaction. Nicotinamide decomposes when heated with crystalline sodium carbonate - the smell of pyridine appears:



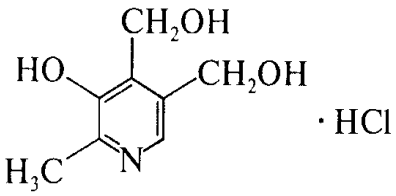
Quantitative definition. Acidimetry in a non-aqueous medium, the indicator is crystal violet, s = 1:



Storage. In a tightly closed container that protects from light.

Application. Similar to nicotinic acid, but it does not cause adverse reactions.

Pyridoxine hydrochloride (Pyridoxini hydrochloridum) (SFU)



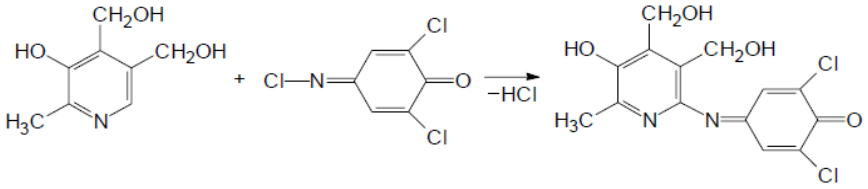
2-Метил-3-окси-4,5-ді-(оксиметил)-піридину гідрохлорид

Mechanism of action. Stimulates hematopoiesis. In its phosphorylated form, it is part of enzymes that participate in the processes of decarboxylation, transamination of amino acids, as well as in lipid metabolism. Necessary for normal functioning of the central nervous system.

Properties. White fine crystalline powder without odor, bitter in taste. Easily soluble in water, poorly soluble in 95% alcohol, practically insoluble in ether.

Identification:

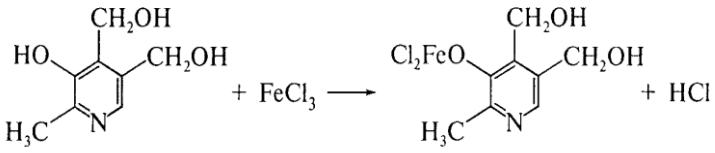
- by physical and chemical methods: IR and UV spectroscopy, TLC (2,6-dichloroquinone chlorimide is used as a developer):



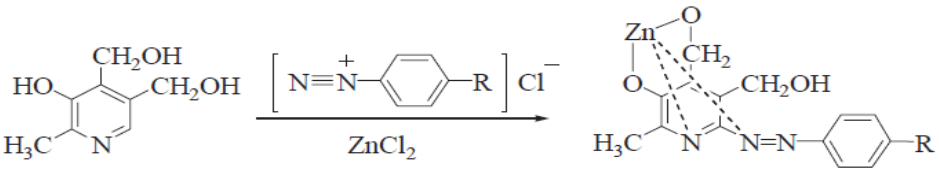
- the substance gives characteristic reactions to chlorides.

Non-pharmacopoeial reactions:

- upon interaction with a solution of ferrum (III) chloride, a red color is formed, which disappears when sulfuric acid is added (reaction to phenolic hydroxyl):

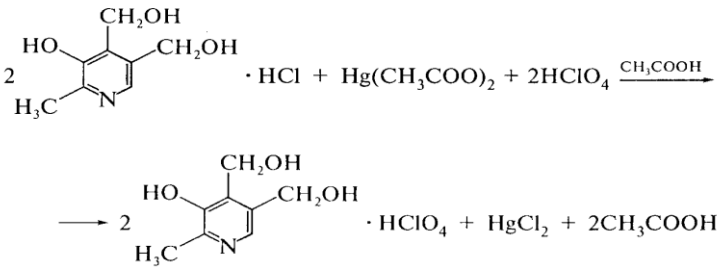


- pyridoxine reacts with azo compounds with diazonium salts. The formed azo dyes give colored complexes with salts of heavy metals, in particular zinc:

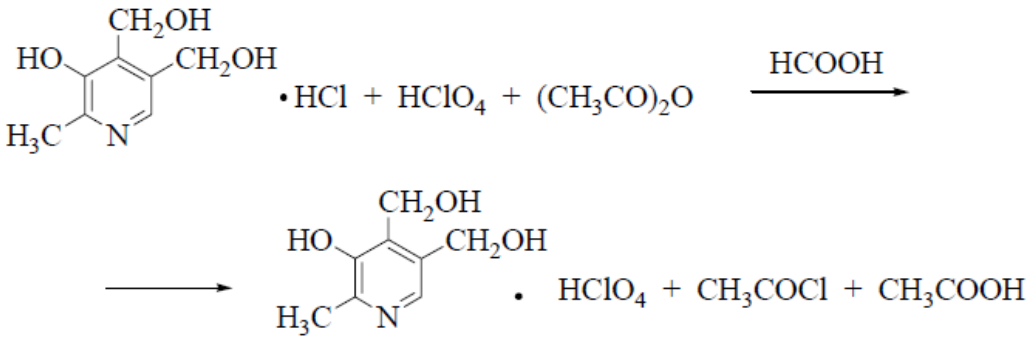


Quantitative definition.

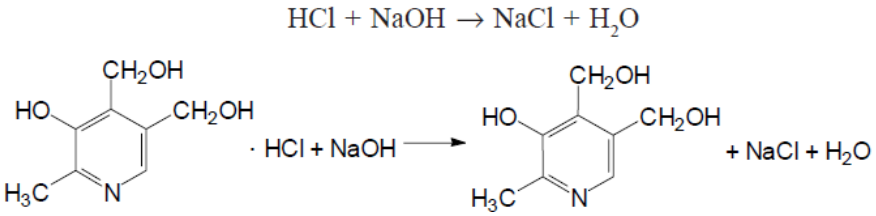
1. Acidimetry in a non-aqueous environment in the presence of mercury (II) acetate, the indicator is crystal violet, s = 1. In parallel, a control experiment is carried out:



2. Acidimetry in a non-aqueous medium in a mixture of formic acid and acetic anhydride potentiometrically, s = 1. In parallel, a control experiment is carried out:



3. Alkalimetry, direct titration in a mixture of 0.01 M solution of hydrochloric acid and 96% alcohol potentiometrically (SFU). The difference in titrant volumes between two potential jumps on the titration curve is taken into account:

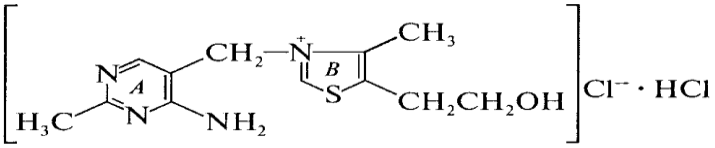


Storage. In well-stoppered dark glass jars.

Application. With various forms of parkinsonism, chorea, acute and chronic hepatitis.

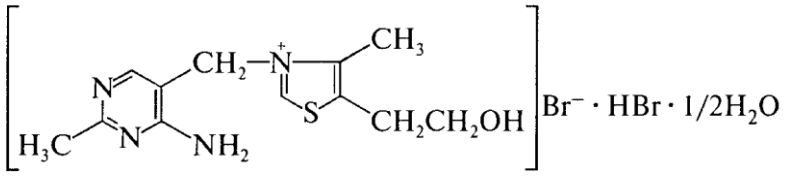
Pyrimidine and thiazole derivatives

The molecule of pyrimidine-thiazole vitamins (B1 - thiamines) consists of two heterocycles - pyrimidine (A) and thiazole (B), connected to each other by a methylene group:



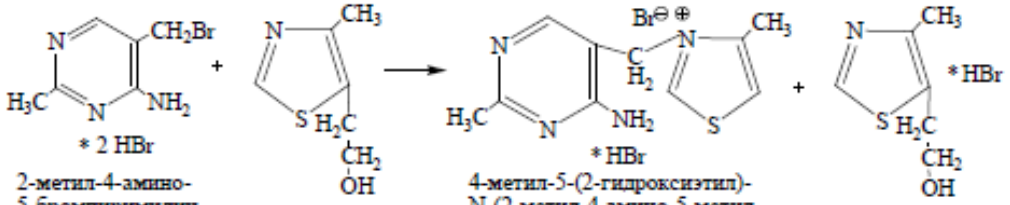
Thiamine hydrobromide, thiamine hydrochloride, diphosphoric ester of thiamine hydrochloride (cocarboxylase) are used in medical practice.

Thiamini hydrobromidum (Thiamini hydrobromidum)



4-Метил-5-β-оксіетил-N-(2'-метил-4'-аміно-5'-метилпіримідил)-тіазолію броміду гідробромід

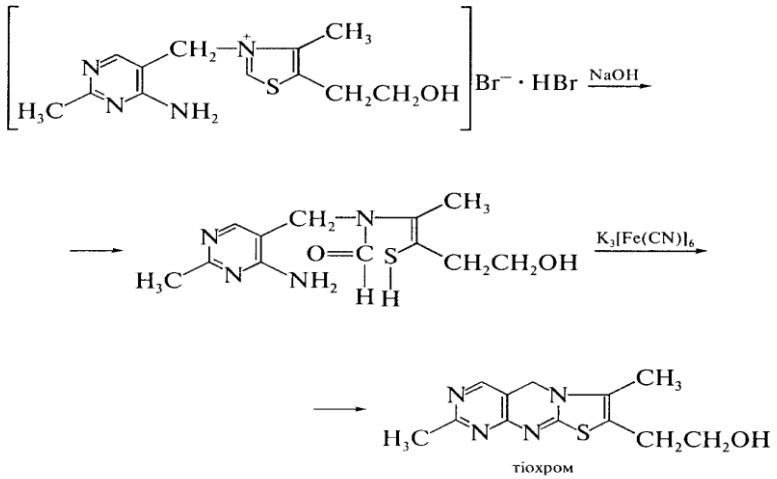
Synthesis.



Properties. White, sometimes with a slightly yellowish tinge, crystalline powder with a weak characteristic smell. Easily soluble in water and methyl alcohol, sparingly soluble in ethyl alcohol, practically insoluble in ether.

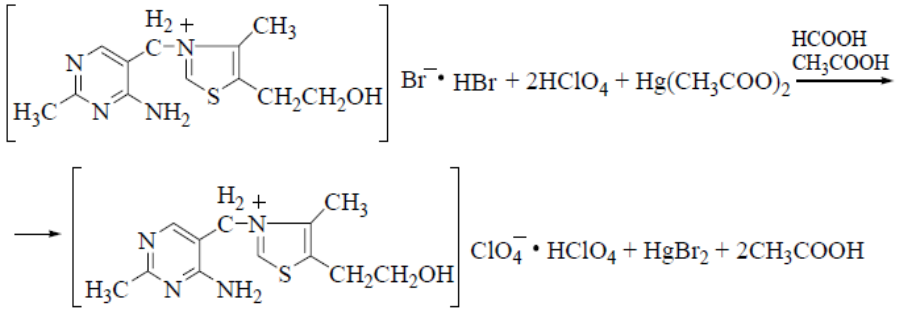
Identification:

- by IR spectroscopy;
- oxidized by potassium ferricyanide in an alkaline environment with the formation of thiochrome, which is extracted with isoamyl or butyl alcohol, blue fluorescence in UV light:
- the substance gives characteristic reactions to bromides.



Quantitative definition.

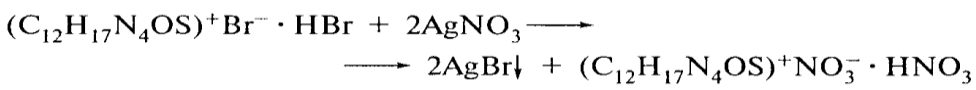
1. Acidimetry in a non-aqueous medium in the presence of mercury (II) acetate potentiometrically, s = 1/2 (SFU):



2. Gravimetry after precipitation of the medicinal substance with silicotungstic acid. Sediment composition: $SiO_2 \cdot 12WO_3 \cdot 2C_{12}H_{17}BrN_4OS$. The mass of the precipitate multiplied by 0.25 (gravimetric factor) corresponds to the amount of thiamine bromide.

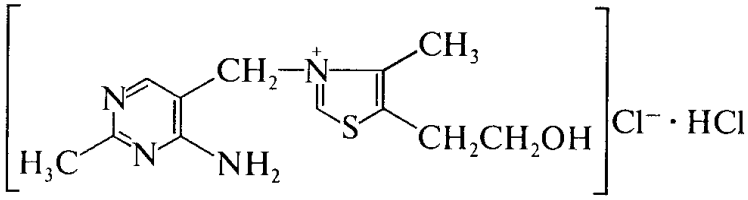
3. Alkalimetry, direct titration, indicator – bromophenol blue or phenolphthalein, s = 1.

4. Argentometry according to the Fayance method, the indicator is bromothymol blue, s = 1/2:



Storage. In a hermetically sealed container that protects against light.

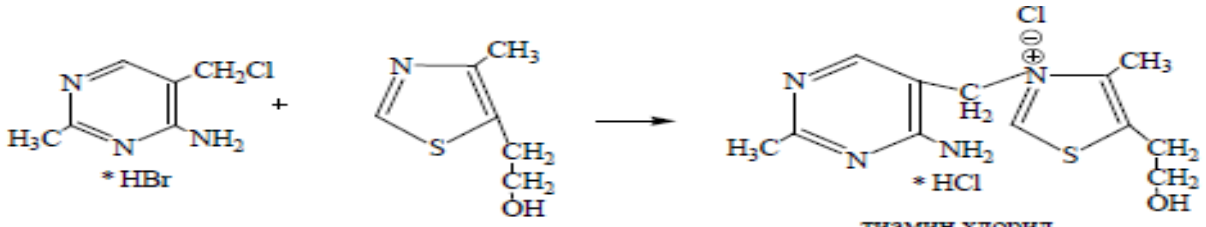
Thiamine hydrochloride (Thiamini hydrochloridum)



4-Метил-5-β-оксіетил-N-(2'-метил-4'-аміно-5'-метилпіримідил)-тіазолію хлориду гідрохлорид

Mechanism of action. As a result of phosphorylation, thiamine pyrophosphate is formed, which is a coenzyme of numerous decarboxylases that participate in the metabolism of pyruvate, alpha-ketoglutarate; also plays an important role in carbohydrate metabolism. Reduces vitamin B1 deficiency, has a metabolic, immunostimulating, antioxidant, ganglioblocking effect.

Synthesis.



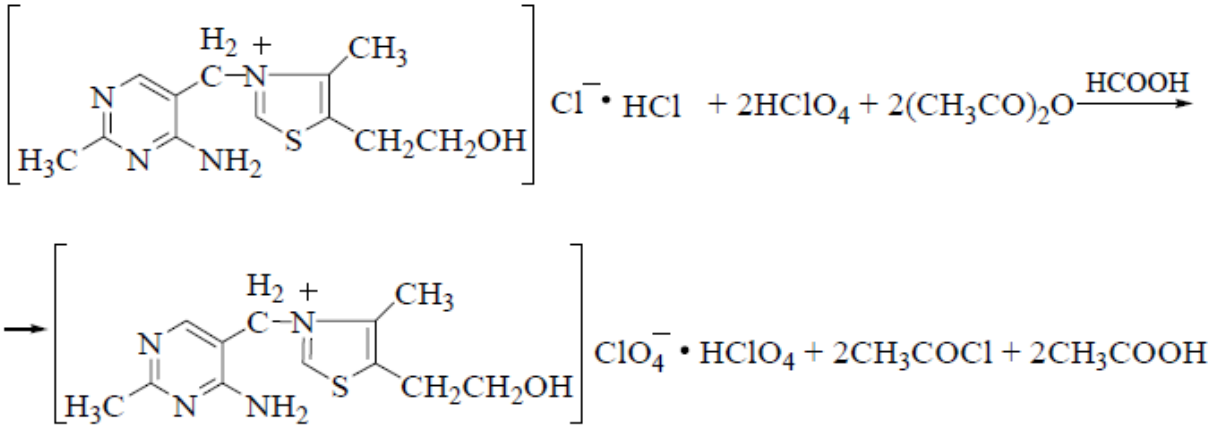
Properties. White or almost white crystalline powder or colorless crystals. Easily soluble in water, soluble in glycerin, sparingly soluble in 96% alcohol.

Identification:

- by IR spectroscopy;
- the formation of thiochrome is analogous to thiamine bromide;
- the substance gives characteristic reactions to chlorides.

Quantitative definition.

1. Acidimetry in a non-aqueous medium in a mixture of formic acid and acetic anhydride potentiometrically, s = ½ (SFU):

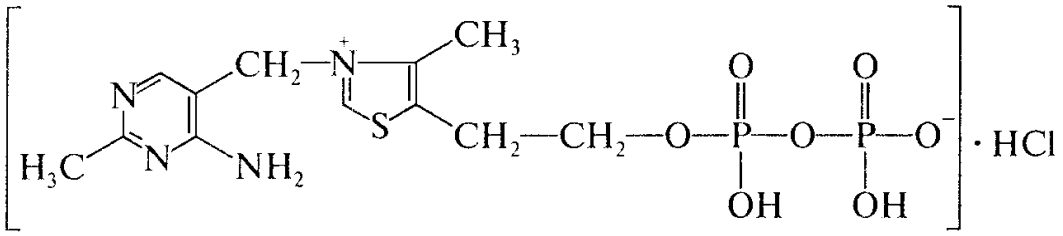


2. Alkalimetry in a mixture of 0.01 M solution of hydrochloric acid and 96% alcohol potentiometrically (SFU). The difference in titrant volumes between two potential jumps on the titration curve is taken into account, s = 1/2.

Storage. Similar to thiamine bromide.

Application. Hypovitaminosis and vitamin B1 deficiency; malabsorption in the intestines, starvation, chronic alcoholism, liver dysfunction; pregnancy, period of breastfeeding, period of intensive growth, neuritis, radiculitis, neuralgia, peripheral paresis and paralysis, myocardiodystrophy, intoxication, spasm of peripheral vessels, heart failure; intestinal atony, dermatoses, eczema, psoriasis, ringworm, thyrotoxicosis.

Cocarboxylase (Cocarboxylasum)



Дифосфорного ефіру тіаміну гідрохлорид

Mechanism of action. It is a constituent non-protein part (coenzyme) of enzymes that regulate metabolic processes. It is formed in the body from thiamine as a result of its phosphorylation. It plays a particularly important role in carbohydrate metabolism.

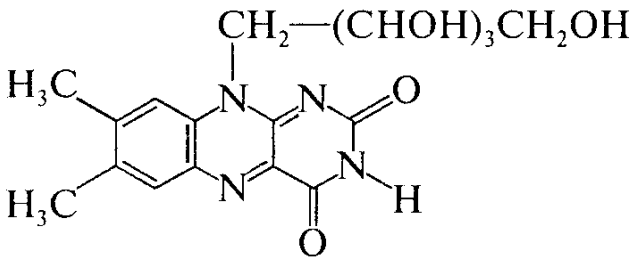
Application. It is prescribed for arrhythmia, coronary insufficiency and other cardiovascular diseases.

Derivatives of isoalloxazine

For the first time, isoalloxazine vitamins (vitamin B2) were isolated from milk serum. The name of vitamin B2 "riboflavin" comes from the fact that it contains the residue of a polyatomic alcohol, a derivative of ribose sugar, and its solutions have a yellow color (Latin flavus - yellow).

Riboflavin is found in milk whey, liver, kidneys, baker's and brewer's yeast; in cereals - millet, barley; in vegetables - spinach and tomatoes.

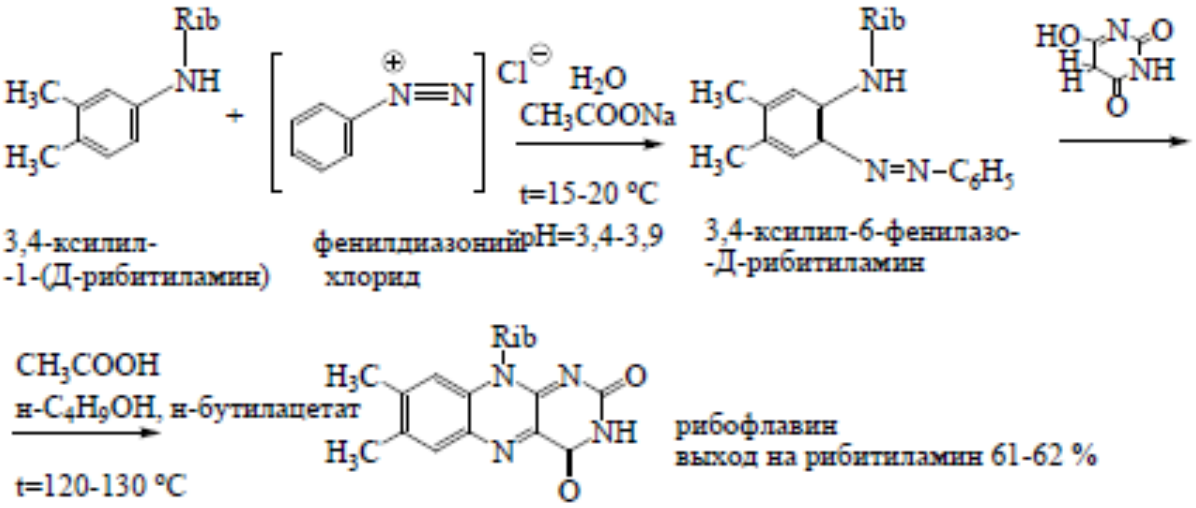
Riboflavin (Riboflavinum)



6,7-Диметил-9-(1-*D*-рибітил)-ізоалоксазин

Mechanism of action. Regulates redox processes, participates in the processes of protein, fat, and carbohydrate metabolism, maintenance of normal visual function of the organ of vision, synthesis of hemoglobin and erythropoietin, increases the content of glycogen in the liver and improves its antitoxic function.

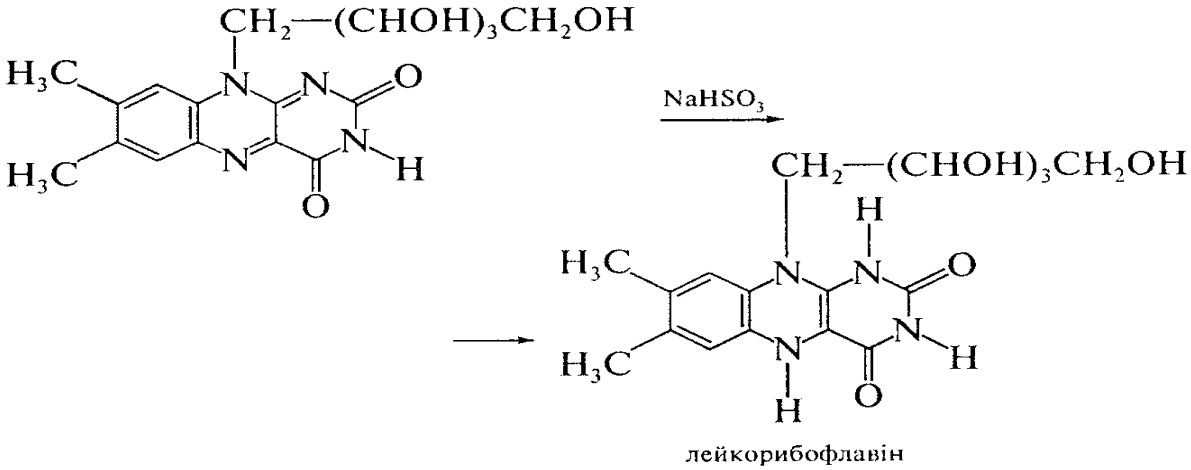
Synthesis.



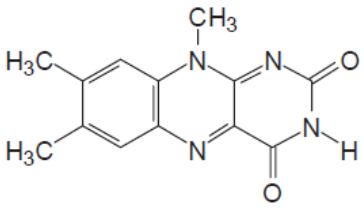
Properties. Yellow-orange crystalline powder with a weak specific smell, bitter taste. Unstable to light. Slightly soluble in water, practically insoluble in 95% alcohol, ether, acetone, benzene and chloroform, soluble in alkali solutions.

Identification:

- by physical and chemical methods: determination of specific rotation, IR spectroscopy, TLC;
- the solution of the substance has a pale greenish-yellow color in the transmitted light, and an intense yellowish-green fluorescence in the reflected light, which disappears when solutions of mineral acids or alkali metal hydroxides (SFU) are added.
- When sodium hydrosulfite is added, both the fluorescence and the color of the solution disappear:



Purity test. Define lumiflavin, which is formed as a result of changes in the chemical structure of the substance under the influence of light and an alkaline environment:



Determination of lumiflavin admixture is carried out by the TLC method: it is based on its solubility in chloroform (riboflavin is insoluble in chloroform) - the color of the filtrate should not exceed the standard.

Quantitative definition.

1. Spectrophotometry (SFU).
2. Photocolorimetry.
3. Fluorometry.
4. Alkalimetry by substitution after oxidation of potassium with periodate.
5. Alkalimetry by substituent after interaction with $AgNO_3$ solution, s=1.

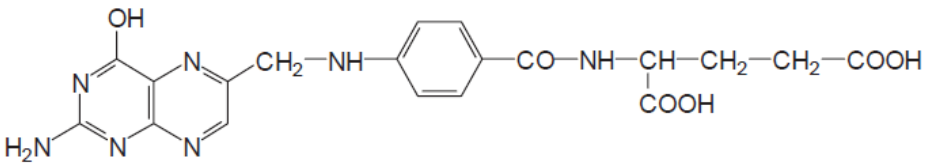
Storage. In a closed container, protected from light.

Application. Hypo- and avitaminosis B_2, hemeralopia, conjunctivitis, keratitis, iritis, clouding of the cornea, cataracts, ulcers that do not heal for a long time, radiation sickness, hypotrophy, asthenia, hepatitis, liver cirrhosis, gastrointestinal tract dysfunction, anemia, leukemia

Derivatives of pterin

Pteric vitamins, which include folic acid (vitamin B), are found in the green leaves of spinach, parsley, and lettuce; in legumes and cereals (wheat, rye, corn), as well as in yeast, liver. Folic acid plays an important role in hematopoietic processes and is also a factor in the growth of microorganisms.

Folic acid (Acidum folicum)



(2S)-2-[[4-[[(2-Аміно-4-оксо-1,4-дигідроптеридин-6-іл)метил]аміно] бензоїл]аміно]пентандіонова кислота

Mechanism of action. Folic acid belongs to group B vitamins and is synthesized in the human body by intestinal microflora. After taking the drug, folic acid is reduced to

tetrahydrofolic acid, which is a coenzyme involved in various metabolic processes. It is necessary for the normal development of other blood cells, including the formation and maturation of megaloblasts and the formation of normoblasts. In combination with vitamin B12 (cyanocobalamin), it stimulates the process of hematopoiesis, partially - erythropoiesis. Participates in the synthesis of amino acids (including methionine, serine, glycine and histidine), nucleic acids, purines, pyrimidines, participates in choline metabolism.

Properties. Crystalline powder of yellowish or orange color. Practically not soluble in water and most organic solvents. Dissolves in dilute acids and alkali solutions. Decomposes under the influence of light, hygroscopic.

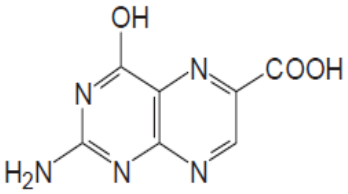
Folic acid is an amphoteric compound: the main properties are due to pteridine nitrogens, acidic - carboxyl groups and hydroxyl in position 4.

Identification:

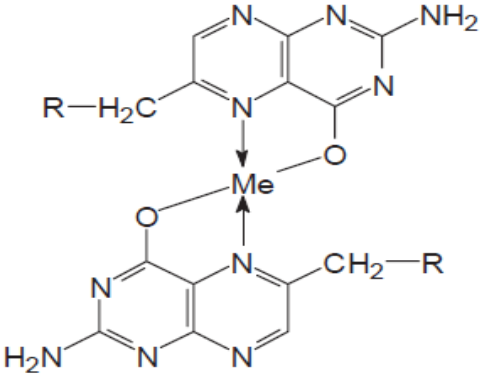
- by physical and chemical methods: determination of specific rotation, liquid chromatography, TLC.

Non-pharmacopoeial reactions:

- oxidation reaction under the influence of potassium permanganate with the formation of pteridine-6-carboxylic acid (2-amino-4-hydroxy-6-pteridinecarboxylic acid), which has blue fluorescence in UV light:



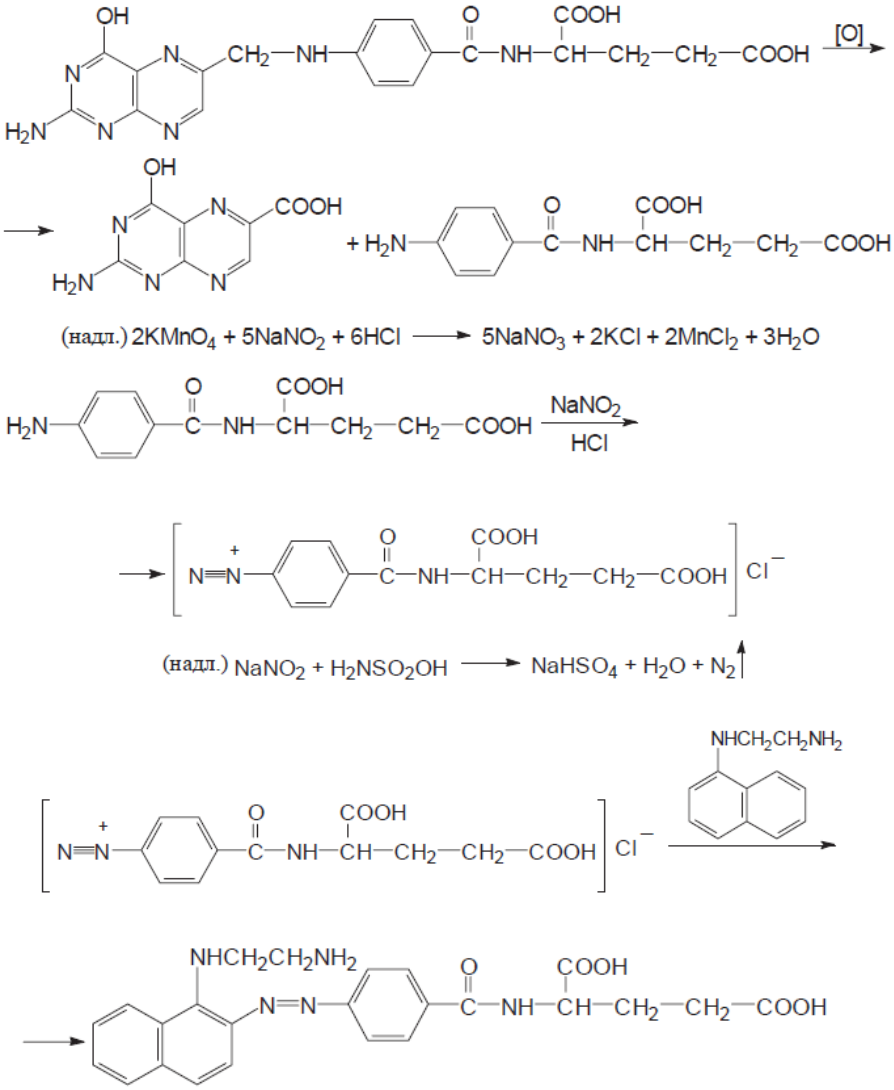
- determination of UV-spectral characteristics of folic acid;
- forms insoluble colored complexes with salts of heavy metals: with CuSO4 – green, with Co(NO3)2 – dark yellow, with FeCl3 – red-yellow.



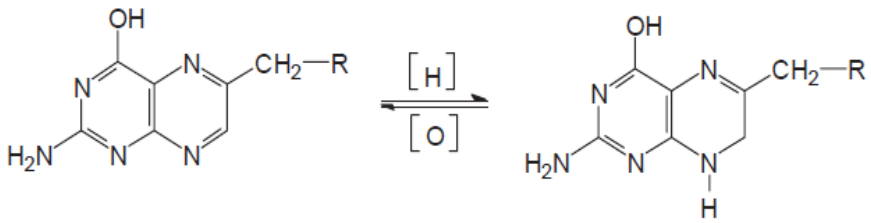
Quantitative definition.

1. By the method of liquid chromatography (LC).

2. Photocolorimetric method:



3. Polarographic method. The ability of folic acid to be reduced in sodium carbonate medium to 7,8-dihydrofolic acid is used:



7,8-Dihydrofolic acid is easily oxidized to folic acid even by air oxygen, so the polarographic cell is constantly blown with nitrogen.

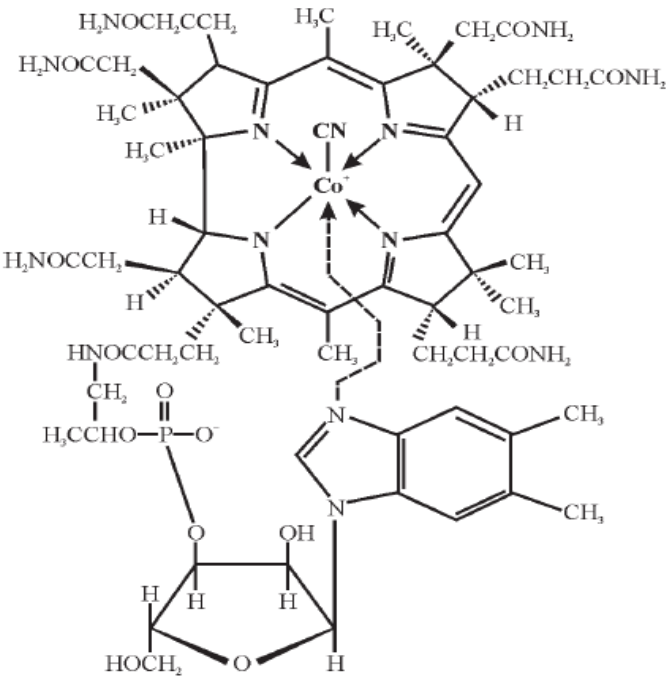
Storage. In a well-closed container that protects from light.

Application. To increase erythropoiesis, in some types of anemia, including anemia and leukopenia caused by drugs and ionizing radiation.

Root derivatives

Corinthic vitamins (group B_{12}) have been found in natural products of animal origin, mainly in internal organs. So, the richest source of vitamin B_{12} is the entrails of fish, its content is high in whale liver and even higher in mollusk meat. In the body of humans and animals, B_{12} is synthesized by intestinal microflora and accumulates in the liver, kidneys, and intestinal walls.

Cyanocobalamin (Cyanocobalaminum)



Mechanism of action. In the body (mainly in the liver), it is converted into a coenzyme form - adenosylcobalamin, or cobamamide, which is the active form of vitamin B_{12}. Cobamamide is part of numerous enzymes, including reductase, which reduces folic acid to tetrahydrofolic acid. Cobamamide is necessary for normal hematopoiesis, because it contributes to the maturation of erythrocytes.

Activates the blood coagulation system, lowers the level of cholesterol in the blood. It has a positive effect on the function of the liver and nervous system. Increases the ability of tissues to regenerate.

Extraction Vitamin B_{12} (cyanocobalamin) is obtained from waste in the production of streptomycin and chlortetracycline antibiotics.

Properties. Crystalline powder of dark red color, odorless, hygroscopic. Hardly soluble in water, soluble in 95% alcohol, practically insoluble in ether, chloroform, acetone.

Identification:

- determination of UV spectral characteristics;
- cobalt ions are determined after mineralization by fusion with potassium hydrosulfate by interaction with sodium 1-nitroso-2-naphthol-3,6-disulfonate - a red color appears.

Quantitative definition. Spectrophotometry.

Storage. In a well-closed container, in aseptic conditions, in a place protected from light.

Application. With malignant anemia, various types of anemia, diseases of the liver, nervous system, skin diseases, etc.

General material and bulk-methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1. Classification of vitamins
2. Pharmaceutical analysisAliphatic vitamins
3. Pharmaceutical analysisAlicyclic vitamins
4. Pharmaceutical analysisAromatic vitamins
5. Pharmaceutical analysisVitamins of the heterocyclic series

References:

Main:

1. State Pharmacopoeia of Ukraine: in 3 volumes / Derz. medical service of Ukraine funds, Ukr. of science pharmacopoeia medicine quality center means - 2nd edition. - Kh.: Ukr. of science pharmacopoeia medicine quality center means, 2015. - Vol. 1. - 1128 p.

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4. Pharmaceutical chemistry: Textbook for students. higher pharmacy education closing and pharmacy Faculty of Medical Sciences for students higher pharmacy education closing / In general ed. P.O. Bezuglio - Kind. 3rd edition, revised. – Vinnytsia, NOVA KNYGA, 2017. - 456 p.
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6. European Pharmacopoeia. Third Edition. Supplement, 2008. Council of Europe Strasbourg.
7. Nizhnyk H.P. Pharmaceutical chemistry: a textbook (University I-III years) H.P. Nizhnyk — 2nd ed., ed. - All-Ukrainian specialized publishing house "Medytsyna", 2015. - 352p.
8. Pharmaceutical chemistry. Analysis of medicinal substances by functional groups: study guide / O.O. Tsurkan, I.V. Nizhenkovska, O.O. Glushachenko. - 3rd edition - All-Ukrainian specialized publishing house "Medytsina", 2019. - 152 p.
9. Hudoyarova O.S. Pharmaceutical chemistry. - Vinnytsia: "Nilan-LTD" LLC, 2018. - 194p.
10. Medicinal chemistry: education. manual for students of higher educational institutions / I.S. Hrytsenko, S.G. Taran, L.O. Transition, etc.; for general I.S. Hrytsenko - Kharkiv: NFaU: Golden Pages, 2017. - 552p.
11. Pharmaceutical chemistry. General and special pharmaceutical chemistry. Medicines of an inorganic nature: laboratory-practical classes. Study guide / L.G. Mishina - Vinnytsia: PP "TD "Edelweiss and K"", 2010. - 384 p.
12. Analytical chemistry and instrumental methods of analysis / A.I. Gab, D.B. Shakhnin, V.V. Malyshev -Ukraine University, 2018- 396 p.

Electronic information resources:

1. Specialized medical online publication for doctors, pharmacists, pharmacists, students of medical and pharmaceutical universities. - [Electronic resource]. - Access mode:http://www.morion.ua.

2. World Health Organization. - [Electronic resource]. - Access mode:http://www.who.int.

3. Pharmaceutical encyclopedia. - [Electronic resource]. – Access mode: http://www.pharmencyclopedia.com.ua.

4. Official website of the International Organization for Standardizationhttp://www.iso.org/iso/home.html

5. Compendium online. [Electronic resource]. - Access mode:https://compendium.com.ua/bad/

6. Medline search database [Electronic resource]. – Access mode: National Library of Medicinehttps://www.nlm.nih.gov/bsd/medline.html

Lecture No. 5

Topic:Anorexigenic means. Sorbents, antidotes and complexons. Anti-ulcer drugs. Means for the treatment of alcoholism.

Actuality of theme: Pharmaceutical chemistry is a science that studies methods of preparation, structure, physical and chemical properties of medicinal products; relationship between their chemical structure and action on organism; methods of quality control of medicines and changes that occur during their storage, as well as their use in medicine. Therefore, it is urgent to solve the problems facing pharmaceutical chemistry with the help of physical, chemical and physico-chemical methods, which are used both for synthesis, as well as for the analysis of medicinal products.

Goal:the formation of students' knowledge about the peculiarities of the storage of medicinal products, which affect the afferent nervous system, as well as the characteristics, classification, relationship between structure and pharmacological action, mechanism of action, methods of obtaining, methods of analysis, application in medicine. As a result of the lecture, students should learn the properties and methods of analysisanorexic agents, sorbents, antidotes and complexes, anti-ulcer drugs, drugs for the treatment of alcoholism.

Basic concepts:pharmaceutical chemistry, qualitative analysis, quantitative analysis, State Pharmacopoeia of Ukraine, physicochemical methods of analysis, impurities, express analysis.

Plan and organizational structure of the lecture:

1.Preparatory stage

1.1.Determination of educational goals.

1.2.Providing positive motivation.

2. The main stage

Presentation of lecture material

Plan:

- Anorexic agents

-Sorbents, antidotes and complexons

-Anti-ulcer drugs

- Means for the treatment of alcoholism

3. The final stage

3.1. Summary of the lecture, general conclusions.

3.2. The lecturer's answers to possible questions

3.3. Tasks for self-training of students.

Content of lecture material (lecture text):

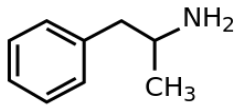
Anorexigenic means

Anorexigenic drugs(Greek an - negative part + órexis - appetite), a group of drugs that suppress appetite and are used to treat obesity.

Classification. Anorexigenic drugs are divided into:

- drugs affecting the catecholaminergic system (CNS stimulants) - amphetamine, fepranon, dezopimon;
- drugs acting on the catecholaminergic and serotonergic systems - sibutramine. These drugs cause an effect on the central mechanisms of appetite regulation located in the hypothalamus, activate the work of the satiety center and reduce the work of the hunger center.

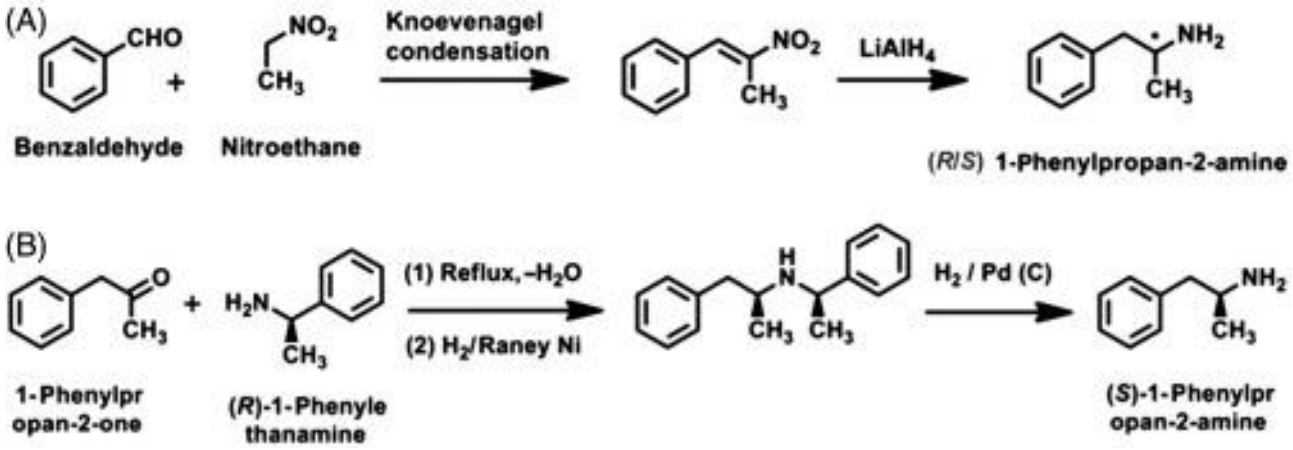
Amfetamini sulfate (Amfetamini sulfas)



1/2H2SO4

Mechanism of action. The drug enhances the release of norepinephrine and dopamine from nerve endings and inhibits their reuptake. This leads to stimulation of central adreno- and dopamine receptors and inhibition of the hunger center. In addition to the anorexic effect, it has a psychostimulant effect and a pronounced peripheral sympathomimetic effect.

Synthesis.



Properties. White powder, easily soluble in water, sparingly soluble in alcohol, practically insoluble in ether.

Identification:

- by the amount of specific optical rotation;
- by the IR absorption spectrum of the substance;
- when the substance is heated with a solution of formaldehyde in concentrated sulfuric acid, an orange color is formed, which turns into dark brown;
- the substance reacts to sulfates:

$+ BaCl_2 \rightarrow BaSO_4\downarrow$

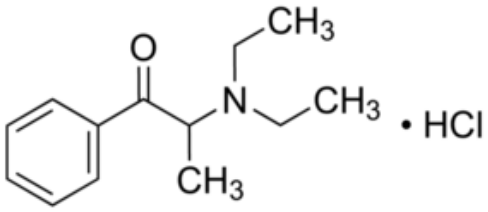
Quantitative definition. By the method of acidimetry in a non-aqueous environment (anhydrous acetic acid) potentiometrically.

Storage. Store in a well-closed container, in a place protected from light.

Application. For narcolepsy, mental depression, to increase mental and physical performance in healthy people. Due to possible side effects, it is used very rarely.

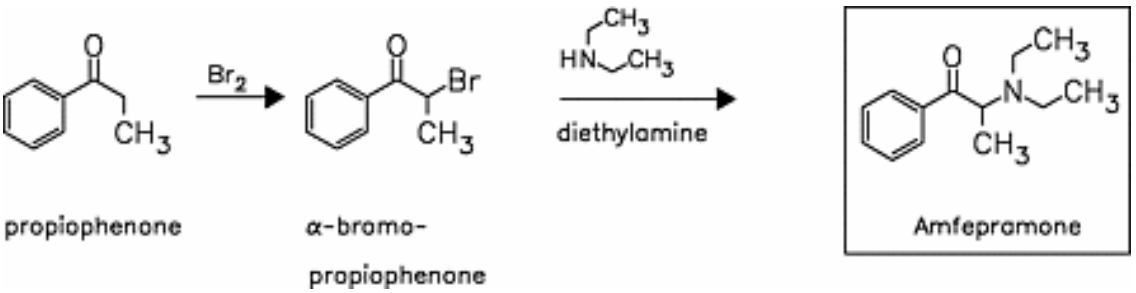
Side effects. Dizziness, chills, nausea, anorexia, insomnia, tachycardia, arrhythmia, arterial hypertension, allergic reactions.

Fepranon (Pherranonum)



Mechanism of action. Stimulates the satiety center and inhibits the hunger center; stimulates the cortex of the large hemispheres of the brain, has practically no peripheral adrenostimulating effect. Increases metabolism (to a small extent), helps to reduce body weight.

Synthesis.

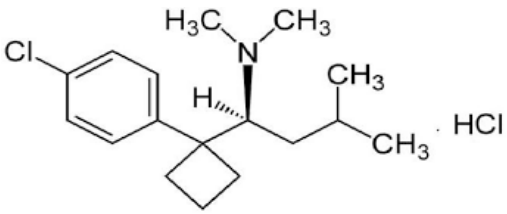


Properties. White or white with a slightly creamy shade crystalline powder with a bitter taste. Easily soluble in water and alcohol.

Storage. In a dry place protected from light.

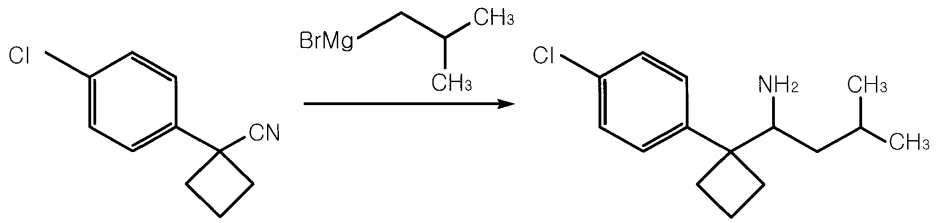
Application. Treatment of alimentary obesity (caused by excessive food consumption).

Sibutramine (Sibutramine)



Mechanism of action. It is caused by the selective inhibition of the reuptake of serotonin and norepinephrine, to a lesser extent - dopamine. Accelerates the onset and prolongs the feeling of satiety, which leads to a decrease in food consumption. Increases energy expenditure due to stimulation of thermogenesis through the indirect activation of β3-blockers. It affects both sides of the energy balance and contributes to weight loss.

Synthesis.



Properties. Crystalline powder from white to cream color. Solubility in water: 2.9 mg/ml at pH 5.2.

Storage. In a dry place at a temperature not higher than 25 °C.

Application. Complex supportive therapy of overweight patients with alimentary obesity.

Sorbents

Sorbents– solid bodies or liquids capable of absorbing gases, vapors and dissolved substances. Solid sorbents are called adsorbents. Sorbents that form a chemical compound with the absorbed substance are called chemosorbents.

The term "enterosorption" ("entero" - inside) was proposed in 1983 by Ukrainian scientists to denote a new method of sorption therapy, which consisted in the daily oral intake of highly active synthetic coal of spherical granulation.

Classification. According to the physicochemical (pharmaceutical) principle, enterosorbents are classified as:

- by dosage form and physical properties – granules, powders, tablets, pastes, gels, suspensions, colloids, encapsulated materials, food additives, fibers. Application sorbents are used in the form of bandages, napkins, etc.;
- by chemical structure – activated carbon, silica gels, zeolites, aluminum gels, oxide and other inorganic sorbents, food fibers, organo-mineral and composite sorbents;
- by sorption mechanisms - adsorbents, absorbents, ion-exchange materials, complex-forming sorbents, sorbents with catalytic properties;
- by selectivity - non-selective, selective mono-, bi- and polyfunctional sorbents. Some experts consider the most acceptable chemical classification for enterosorbents:
- carbon enterosorbents of I–IV generations;
- enterosorbents based on natural and synthetic resins, synthetic polymers and indigestible lipids;
- silicon-containing enterosorbents, including silicon organosorbents, aerosols and clays;

- natural organic enterosorbents based on dietary fibers, hydrolyzed lignin, chitin, pectins and alginates;
- combined enterosorbents, which include two or more types of the mentioned enterosorbents.

Carbon enterosorbents

Activated carbon (Carbo activatus)

Pharmacological properties. Adsorbent. It has great surface activity and high sorption capacity. Absorbs toxic substances, salts of heavy metals, alkaloids and glycosides, medicinal substances from the digestive tract, promoting their elimination from the body. Adsorbs gases on its surface. BA in tablets has a lower adsorption capacity compared to powder, but is more convenient to use. The drug is not toxic. BA is not absorbed, it is well removed from the body through the intestines.

Receiving. They are obtained by pyrolysis of hardwood wood without air access. To increase the adsorption capacity, coal is treated with superheated steam at 800 °C. Then the coal is treated with solutions of zinc chloride, magnesium chloride, sodium hydroxide or phosphoric acid with subsequent heating to 300–400 °C. Next, the coal is thoroughly washed with water to remove impurities and dried. The medicine contains micropores - visible under a microscope d = 10–1 to 10–3 cm; ultrapores - invisible under a microscope d = 9.2·10–7 cm. Ultrapores play a major role in adsorption processes. Their total surface per 1 g of activated carbon is more than 1000 m2.

Purity test. Since the drug is used in large doses, the AED pays great attention to the purity of activated carbon. The content of impurities of chlorides, sulfates, heavy metals, ferrum, arsenic is regulated. There should be no sulfides or cyanides. Determine the adsorption capacity of carbon activated with methylene blue and the degree of grinding.

Storage. In the original packaging, separately from substances and materials that emit vapors and gases, at a temperature not higher than 25°C.

Application. Food toxic infections, acute poisoning by food, household and industrial poisons, alkaloids, medicinal preparations, salts of heavy metals; dyspepsia, flatulence; preparation for X-ray studies.

Karbolong

Pharmacological properties. Carbolong provides effective absorption of endo- and exotoxins, gases, alkaloids and other chemical compounds due to their physical sorption in the pores and their subsequent removal from the body with the mass of the sorbent as part of the intestinal contents. Carbolong stimulates motility and improves blood circulation in the intestines. Unlike ordinary activated carbon, Carbolong has a prolonged effect (36–48 hours) and exhibits high adsorption activity during the entire time of passage through the digestive tract.

Receiving.(Ukrainian consortium "Ekosorb", Kyiv) The preparation is made on the basis of granulated activated carbon, which, in turn, is obtained from the seeds of apricots, plums, peaches, walnut or coconut shells. These raw materials are burned without access to oxygen, and then activated. The obtained activated carbon goes through several stages of processing in order to remove minor impurities of substances that pose a potential threat to the body.

Storage. In a dry place at a temperature not higher than 30 °C, separate from substances and materials that emit gases and vapors.

Application. Acute poisoning by household, industrial and food poisons, drugs, alkaloids, salts of heavy metals, dyspepsia, flatulence, food toxic infections.

Silica-containing enterosorbents

White coal

Pharmacological properties."White Coal®" is an enterosorbent, the active substance of which is silicon dioxide (SiO_2) with a particle size of 7-10 nm, which allows you to reach an active sorption surface area of 300-400 m2 per 1 g. The high dispersity of silicon dioxide provides a large active sorption surface and sorption capacity of the drug. The non-porous structure of silicon dioxide particles ensures a high rate of sorption. The lack of pores also explains the weak sorption of low molecular weight compounds, including minerals and vitamins.

It has significant adsorption activity for protein substances, which helps to remove from the body exo- and endotoxins, toxic products of incomplete decomposition of large organic compounds, pathogenic antigens and allergens of microbial or other origin. It actively

absorbs pathogenic microflora in the intestines - up to 1010 microbial bodies per 1 gram of substance, which provides pronounced antimicrobial and antidiarrheal effects.

Silicon dioxide shows chemical and microbiological stability: it does not decompose in organic solvents and biological fluids, including gastric juice, and the structure of its particles does not change when the pH changes.

Storage. In the original packaging at a temperature not higher than 25 °C.

Application. In 2017, "White Coal®" tablets, which have been known since the year of their creation (2008), received the status of a medicinal product.

As monotherapy or in complex therapy: acute intestinal diseases (salmonellosis, food poisoning); acute diarrhea of various etiology; exogenous intoxication with household and industrial toxins (alkaloids, salts of heavy metals, other substances), drugs, with alcohol and food overload.

Silix (Atoxil)

Pharmacological properties. Silix is an inorganic polymer with the general formula (SiO2)n, has high chemical purity, homogeneity, biological and thermal stability, and is physiologically harmless. The size of the particles varies from 5 to 20 nm, in connection with which the drug is considered highly dispersed silica. The preparation of sorption action. Through adsorption, it binds and removes from the body toxins of exogenous and endogenous origin, food and bacterial allergens, microbial endotoxins, toxic products formed during the breakdown of proteins in the intestines.

Storage. Store at a temperature not higher than 25 °C.

Application. In complex therapy of acute intestinal infections of any genesis, including food toxic infections, in case of diarrhea of non-infectious origin, dysbacteriosis, purulent-septic diseases, in case of acute poisoning by potent and toxic substances, including medicines and ethyl alcohol, with exo- and endogenous intoxications that develop acutely (influenza, ARVI, etc.); with food and drug allergies, with viral hepatitis and chronic renal failure.

Antidotes

Antidotes(Greek anti – against + didonai – to give) – drugs that have the ability to eliminate or weaken the specific effects of a xenobiotic due to its immobilization (e.g.

chelating agents), concentration reduction (adsorbents) or countermeasures at the level of effective systems (pharmacological antagonists). A. are used to treat poisoning. The best therapeutic effect is when A. is administered immediately or in the first hours after the poison enters the body.

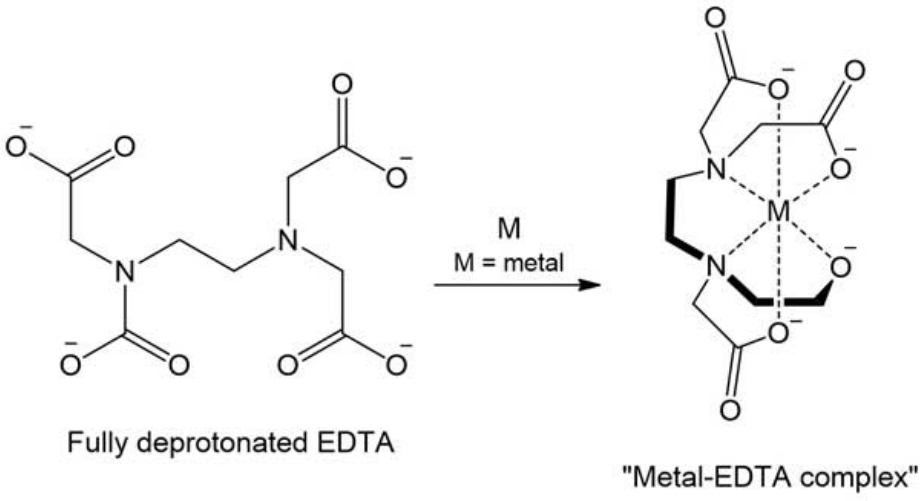
Classification. Has a conditional character; in clinical toxicology:

- Adsorbents whose action is based on physical processes.
- Chemical preparations that neutralize poison as a result of a chemical reaction (reducing agents, oxidizers, chelating agents, etc.).
- Antidotes that form in the body compounds with a high affinity to the toxicant (amyl nitrite, methylene blue, sodium nitrite).
- Biochemical (metabolic, toxic-kinetic) substances that have the ability to modify the metabolism of poison.
- Pharmacological antagonists that compete with poison in the action on enzymes, receptors and physiological systems.
- Immunological antidotes.

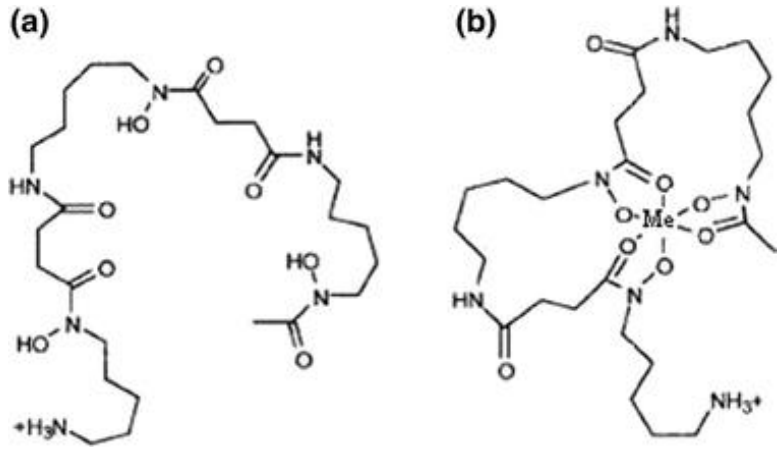
Complexons

The most effective antidotes for acute poisoning are complexones - chelating compounds (deferoxamine, sodium calcium edetate, penicillamine, unitiol).

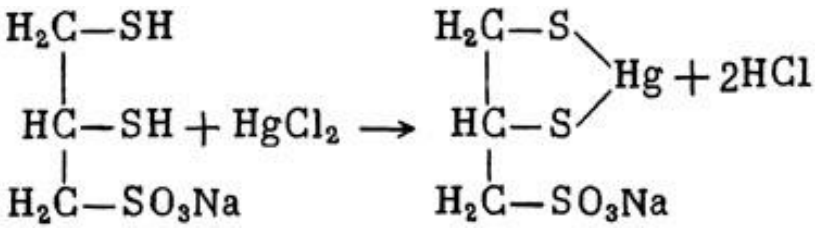
Mechanism of action. Due to the presence of such functional groups as –OH, –CH and –HH in their structure, complexons can donate electrons to bond with metal cations, i.e. form coordination-covalent bonds:



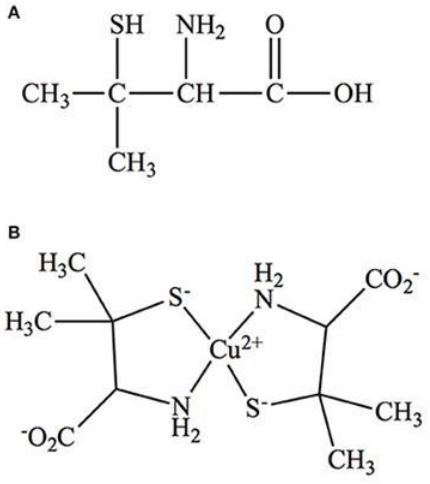
EDTA



Deferoxamine



Unitiol



Penicillamine

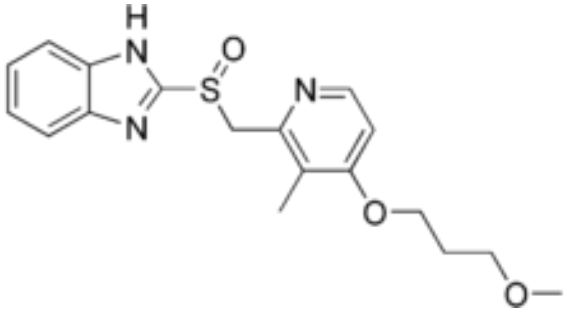
The effectiveness of the chelating compound is determined by the number of ligands in its base capable of binding to the metal. The more of them, the more stable the metal-chelate complex. But complexons have low selectivity. Along with toxic agents, they can bind

endogenous ions necessary for the body, for example, calcium and zinc. The final result of such an interaction is determined by the affinity of toxic exogenous and essential (endogenous) metals to chelating drugs.

Anti-ulcer drugs

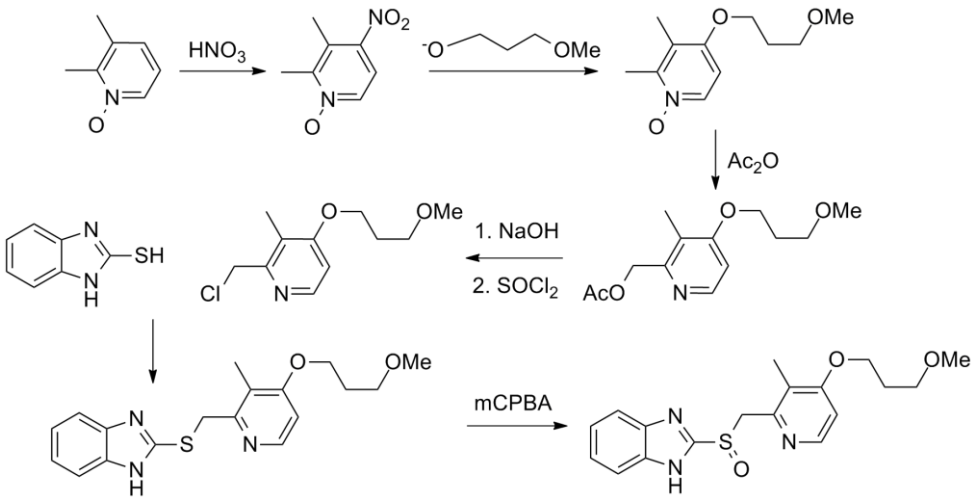
Anti-ulcer drugs- a group of drugs used in the treatment of gastric and duodenal ulcers, gastroesophageal reflux, hyperacid gastritis and other diseases of the gastrointestinal tract caused by hypersecretion.

Rabeprazole (Rabeprazole)



Mechanism of action. The drug's mechanism of action consists in inhibiting the H^+/K^+ ATPase enzyme of the parietal cells of the stomach (which is also called the proton pump, which leads to the blocking of the transfer of hydrogen ions from the parietal cells to the stomach cavity and inhibition of the final stage of hydrochloric acid secretion.

Synthesis.

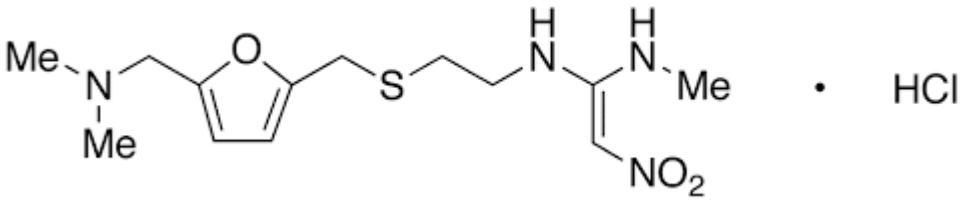


Properties. White or yellowish-white crystalline powder. Very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate, insoluble in ether and n-hexane.

Storage. Store in the original packaging at a temperature not higher than 25 °C.

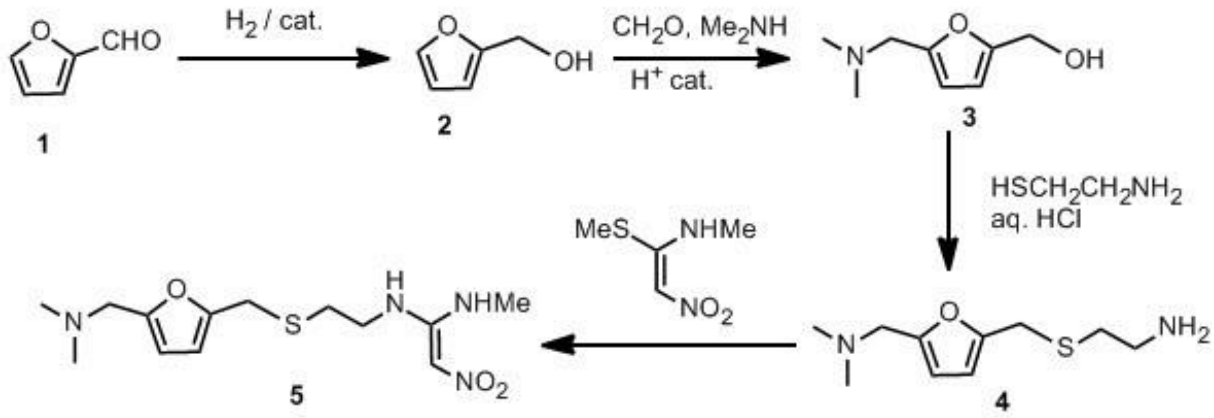
Application. Active peptic ulcer of the duodenum, active benign gastric ulcer. It is also used for the prevention and treatment of drug-induced lesions of the stomach and duodenum caused by non-steroidal anti-inflammatory drugs and thienopyridines.

Ranitidine hydrochloride (Ranitidine hydrochloride)



Mechanism of action. The mechanism of action is due to the competitive inhibition of H^2-histamine receptors of the membranes of the parietal cells of the gastric mucosa. Reduces basal and stimulated secretion of hydrochloric acid, reducing the volume of gastric juice.

Synthesis.



Properties. White or pale yellow crystalline powder. Easily soluble in water, sparingly soluble in dehydrated alcohol and very slightly soluble in dichloromethane.

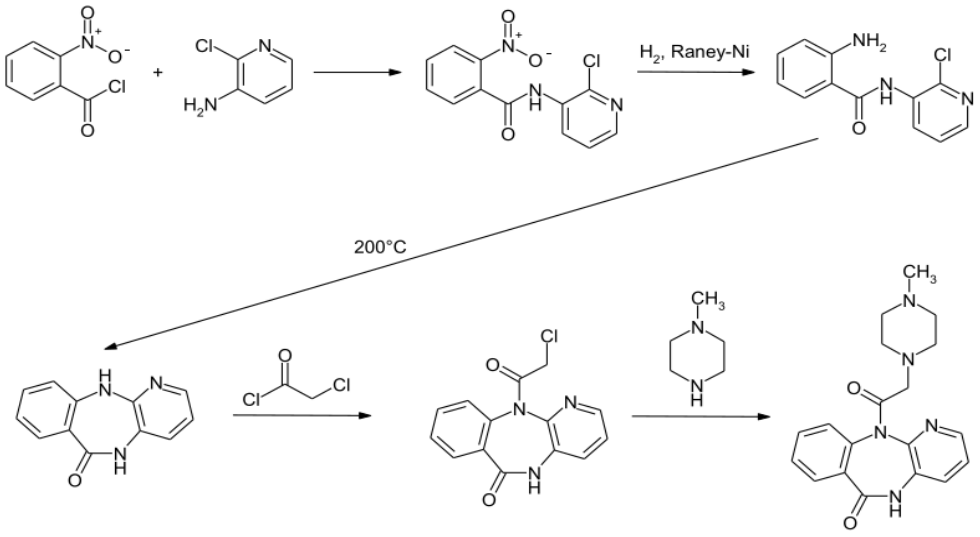
Storage. Store in the original packaging at a temperature not higher than 25 °C.

Application. Peptic ulcer of the stomach and duodenum, not associated with Helicobacter pylori (in the acute phase), including ulcer associated with the use of nonsteroidal anti-inflammatory drugs; functional dyspepsia; chronic gastritis with increased acid-forming function of the stomach in the acute stage.

Pirenzepin (Pirenzepinum)

Mechanism of action.A selective blocker of M1-cholinergic receptors of lining and main cells of the mucous membrane of the stomach. Reduces basal and stimulated secretion of hydrochloric acid, peptic activity of gastric juice, slightly reduces the tone of smooth muscles of the stomach.

Synthesis.



Properties. White powder, sparingly soluble in water, practically insoluble in ether, easily soluble in methanol.

Identification:

- identify by the IR absorption spectrum of the substance;
- HPLC method, spectrophotometric method.

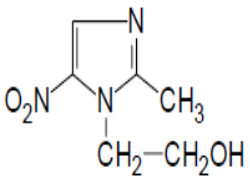
Quantitative definition. Quantitatively determined by alkalimetric titration with potentiometric fixation of the end point of the titration.

Storage. Store in a place protected from light.

Application. With peptic ulcer disease of the stomach and duodenum; erosive and ulcerative lesions of the gastrointestinal tract; stress ulcers; chronic hyperacid gastritis, duodenitis; erosive gastritis, esophagitis; reflux esophagitis; Zollinger-Ellison syndrome;

bleeding from erosions and ulcerative lesions in the upper parts of the gastrointestinal tract; peptic ulcers of the intestines.

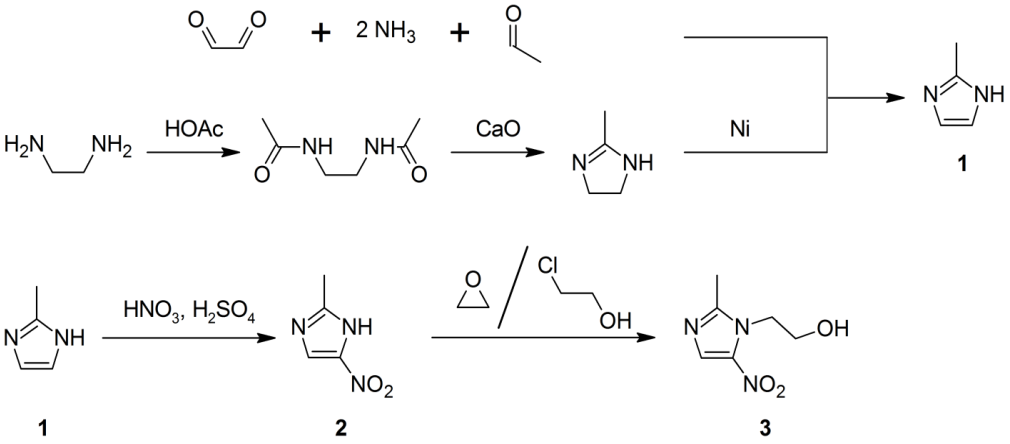
Metronidazole (Metronidazolum)



2-(2-Метил-5-нітро-1*H*-імідазол-1-іл)етанол

Mechanism of action. It consists in the biochemical reduction of the 5-nitro group of metronidazole by intracellular transport proteins of anaerobic microorganisms and protozoa. The restored 5-nitro group of metronidazole interacts with the DNA of microorganisms, inhibiting its synthesis, which leads to the death of microorganisms.

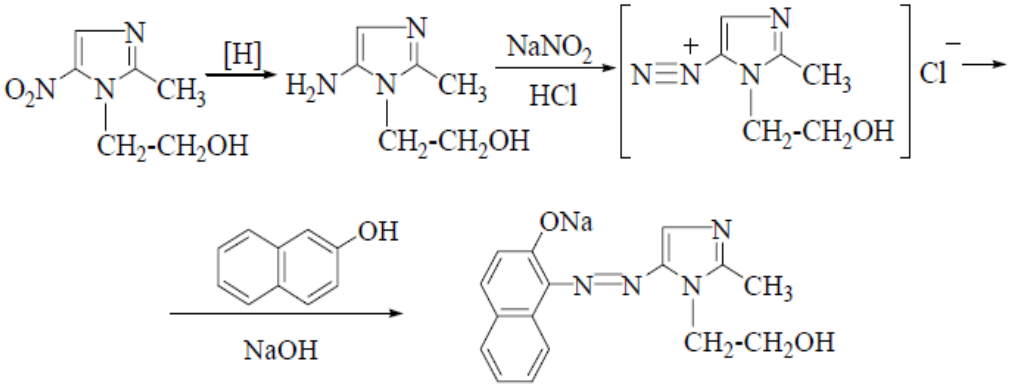
Synthesis.



Properties. White or slightly greenish-yellow crystalline odorless powder. Sparingly soluble in water, sparingly soluble in ethanol.

Identification:

- physicochemical methods: determination of melting points, IR and UV spectroscopy;
- when heated with a 4% NaOH solution, a red-violet color appears, which changes to yellow when hydrochloric acid is added, and appears again when alkalinized;
- for t. pl. picrate (148–153 °C);
- the reaction of the formation of an azo dye after the preliminary reduction of the nitro group to the amino group:



Quantitative definition.

1. Acidimetry in a non-aqueous medium, the indicator is crystal violet, s=1.
2. UV spectrophotometry.
3. Photocolorimetry.

Storage. In a closed container, in a place protected from light.

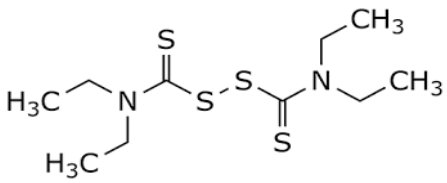
Application.A broad-spectrum antiprotozoal agent. Antibacterial agent for the treatment of anaerobic infections. It is also used for the treatment of stomach ulcers and for sensitization to alcoholic beverages in case of alcoholism.

Means for the treatment of alcoholism

Classification. Medical treatment of alcoholism involves the use of drugs, which can be conditionally divided into two groups:

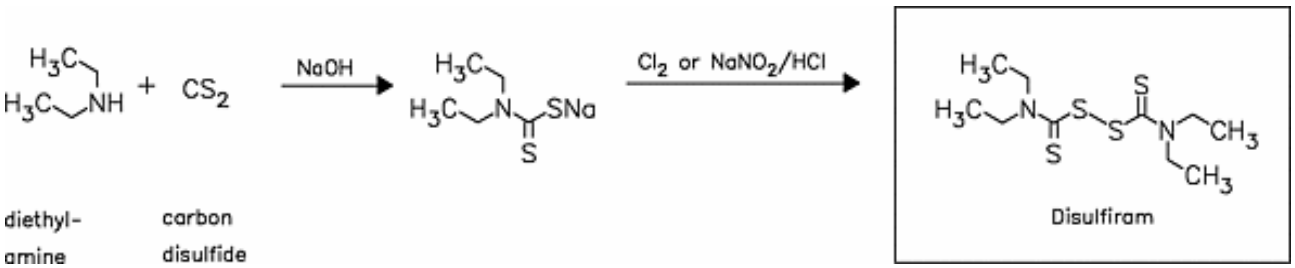
- *aversive drugs*(from Latin aversio – disgust) cause negative effects in combination with alcohol;
- *anticraving drugs*- do not cause negative effects together with alcohol, designed exclusively for the treatment of addiction, reduce the pathological addiction to alcohol, increase the duration of remission, reduce the volume of alcohol consumption and the severity of alcoholic excesses.

Disulfiram (Disulfiramum)



Mechanism of action. It works by inhibiting the enzyme acetaldehyde dehydrogenase (ALDH2), which leads to unpleasant hangover sensations immediately after drinking alcohol.

Synthesis.



Properties. White or almost white crystalline powder, practically insoluble in water, easily soluble in methylene chloride, soluble in ether, moderately soluble in 96% alcohol.

Identification:

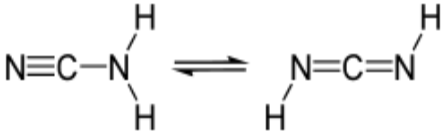
- identify by T pl, by the IR absorption spectrum of the substance;
- by TLC method;
- according to the reaction of a methanol solution of the substance with a solution of copper (II) chloride - a yellow color appears, changing to greenish-yellow.

Quantitative definition. Quantitatively determined by the argentometric method in an acetone environment in the presence of potassium nitrate potentiometrically.

Storage. Store at a temperature not higher than 25 ºC.

Application. Treatment of chronic alcoholism in cases where it is not possible to obtain a therapeutic effect by other methods (psychotherapy, use of apomorphine, etc.).

Cyanamide (Cyanamide)



Mechanism of action. The action of cyanamide is based on the blockade of enzymatic biotransformation of ethyl alcohol, leads to an increase in the concentration of the metabolite of ethyl alcohol - acetaldehyde, which causes negative sensations (flushing, nausea, tachycardia, shortness of breath), which make drinking alcohol extremely unpleasant after taking the drug.

Synthesis.

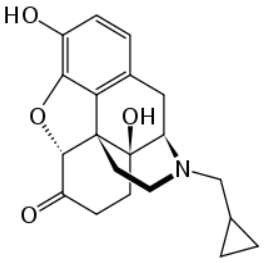
$CaCN2 + H2O + CO2 \rightarrow CaCO3 + H2NCN$

Properties. White crystalline powder.

Storage. Store in a place protected from light at a temperature not higher than 25 °C.

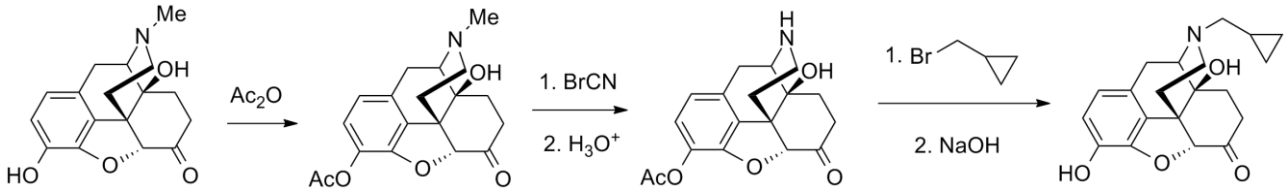
Application. Treatment of chronic alcoholism and prevention of relapses.

Naltrexone (Naltrexone)



Mechanism of action. Competitive antagonist of opiate receptors. Naltrexone blocks the pharmacological effect of exogenously administered opiates by competitive binding of opiate receptors. This blockade can be reversed by the administration of large doses of opiates. Due to the blockade of opiate receptors, alcohol addiction is eliminated. Does not cause addiction and drug dependence.

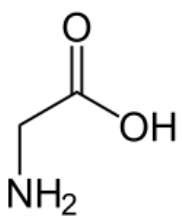
Synthesis.



Storage. Store in a dark, dry place at a temperature not higher than 25 ºC.

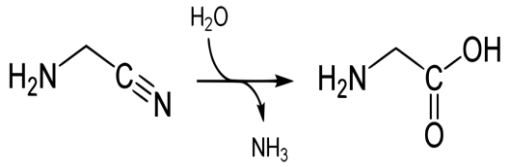
Application. It is prescribed in the complex therapy of alcoholism to curb the urge to drink alcohol, prevent excessive alcohol consumption, reduce the level of alcohol-induced euphoria, and also to reduce the frequency of relapses.

Glycine (Glycinum)



Mechanism of action. Improves metabolic processes in brain tissues; has a sedative, hypnotic, psychostimulant, nootropic and anxiolytic effect; reduces the craving for alcohol and manifestations of absinthe syndrome.

Synthesis.



Properties. White crystalline powder, easily soluble in water, sparingly soluble in 96% alcohol, practically insoluble in ether.

Identification:

- identify by the IR absorption spectrum of the substance;
- by TLC method;
- carry out the reaction of oxidative decarboxylation of the drug under the action of concentrated sodium hypochlorite during boiling with the addition of hydrochloric acid and resorcinol in an alkaline medium (the solution turns purple with greenish-yellow fluorescence, after a few minutes the color of the solution changes to orange, then to yellow, and intense fluorescence remains).

Quantitative definition. It is quantitatively determined by titration with a 0.1 M solution of perchloric acid in a mixture of anhydrous formic acid and glacial acetic acid (1:10) with potentiometric indication of the equivalence point.

Storage. Store in the original packaging at a temperature not higher than 25 °C.

Application. During the period of remission in depressive states, increased irritability, sleep disturbances, memory impairment, mental retardation in children, senile dementia. Additionally - with chronic alcoholism, an acute period of abstinence, vegetative-vascular dystonia with asthenic syndrome, muscle dystrophy

General material and bulk-methodological support of the lecture:

- ✓ computer presentation;
- ✓ illustrative materials;
- ✓ examples of solving typical tasks or performing typical tasks;
- ✓ multimedia projector.

Questions for self-control:

1. Pharmaceutical analysis of anorexic agents

2.Pharmaceutical analysis of sorbents, antidotes and complexes

3.Pharmaceutical analysis of antiulcer drugs

4.Pharmaceutical analysis of means for the treatment of alcoholism

References:

Main:

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11. Pharmaceutical chemistry. General and special pharmaceutical chemistry. Medicines of an inorganic nature: laboratory-practical classes. Study guide / L.G. Mishina - Vinnytsia: PP "TD "Edelweiss and K"", 2010. - 384 p.

12. Analytical chemistry and instrumental methods of analysis / A.I. Gab, D.B. Shakhnin, V.V. Malyshev -Ukraine University, 2018- 396 p.

Electronic information resources:

1. Specialized medical online publication for doctors, pharmacists, pharmacists, students of medical and pharmaceutical universities. - [Electronic resource]. - Access mode:http://www.morion.ua.

2. World Health Organization. - [Electronic resource]. - Access mode:http://www.who.int.

3. Pharmaceutical encyclopedia. - [Electronic resource]. – Access mode: http://www.pharmencyclopedia.com.ua.

4. Official website of the International Organization for Standardizationhttp://www.iso.org/iso/home.html

5. Compendium online. [Electronic resource]. - Access mode:https://compendium.com.ua/bad/

6. Medline search database [Electronic resource]. – Access mode: National Library of Medicinehttps://www.nlm.nih.gov/bsd/medline.html