

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
ХАРКІВСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ

**HYDROXY- AND OXOACIDS.
HETEROFUNCTIONAL COMPOUNDS
OF BENZENE SERIES -
METABOLITES AND PARENT STRUCTURES OF
MEDICINES**

Methodical instructions for 1st year students' self-work
in Biological and Bioorganic Chemistry
(module 1)

**ГІДРОКСИ- ТА ОКСОКИСЛОТИ.
ГЕТЕРОФУНКЦІОНАЛЬНІ СПОЛУКИ БЕНЗОЛЬНОГО
РЯДУ – МЕТАБОЛІТИ ТА РОДОНАЧАЛЬНИКИ
ЛІКАРСЬКИХ ЗАСОБІВ**

Методичні вказівки для самостійної роботи студентів 1-го курсу
з біологічної та біоорганічної хімії
(модуль 1)

Затверджено
Вченою радою ХНМУ.
Протокол № 10 від 21. 11. 2013

Харків
2014

Hydroxy- and oxoacids. Heterofunctional compounds of benzene series. Metabolites and parent structures of medicines: methodical instructions for 1st year students' self-work in Biological and Bioorganic Chemistry (module 1) / compiled by A.O. Syrovaya, L.G. Shapoval, V.N. Petiunina et al. – Kharkiv: KhNMU, 2014. – 25 p.

Compiled by:

A.O. Syrovaya,
L.G. Shapoval,
V.N. Petiunina,
E.R. Grabovetskaya,
S.A. Nakonechnaya,
S.N. Kozub

Гідрокси- та оксокислоти. Гетерофункціональні сполуки бензольного ряду. Метаболіти та родоначальники лікарських засобів: метод. вказ. для самостійної роботи студентів 1-го курсу з біол. та біоорг. хімії / уклад. Г.О. Сирова, Л.Г. Шаповал, В.М. Петюніна та ін. – Харків: ХНМУ, 2014. – 25с.

Укладачі:

Г.О. Сирова,
Л.Г. Шаповал,
В.М. Петюніна,
Є.Р. Грабовецька,
С.А. Наконечна,
С.М. Козуб

Subject I. HETEROFUNCTIONAL COMPOUNDS
PARTICIPATING IN THE PROCESSES OF THE METABOLISM.
HYDROXY- AND OXOACIDS

Motivational characteristic of the subject

Studying of the structure and chemical properties of the heterofunctional compounds (hydroxy- and oxoacids) is a basis for understanding metabolic process in the living organism. Numerous redox processes in the organism are associated with formation and participation of hydroxy- and oxoacids (oxidation of carbohydrates and fatty acids in the organism, formation of citric acid in Krebs cycle, etc.).

Some of these compounds or their derivatives are medical products. For example, salts of a lactic acid (lactates) are used in anemia treatment, citric acid is used in blood preservation.

Objective

To study the structure, chemical properties of aliphatic heterofunctional compounds (hydroxy- and oxoacids), as the basis for understanding their metabolic conversions in the organism.

Training questions

1. To know the structure of the most important hydroxy- and oxoacids.
2. To be able to explain the properties of hydroxy- and oxoacids as bifunctional compounds, as well as specific reactions of α , β and γ hydroxy-acids.
3. To know transformation of hydroxy- and oxoacids in Krebs cycle.
4. To be able to explain keto-enol tautomerism on the example of acetoacetic acid.
5. To be able to draw the L and D enantiomers. To understand the difference in their properties and biological activity.
6. To know the peculiarities of isomerism for molecules with two chiral centers.

Initial level

1. Electronic effects of substituents.
2. Acidity and basicity of organic compounds, C-H acidity.
3. Nucleophilic reactions of carbonyl compounds.
4. Reactions of nucleophilic substitution and elimination at unsaturated carbon atom in hydroxy- and oxoacids.

Practical skills

To be able to make qualitative reactions for hydroxy- and oxoacids. Defining the oxoacids in the physiological fluids.

Test questions

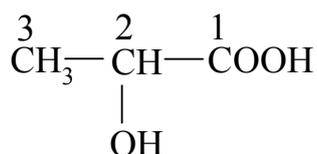
1. Give examples of reactions for β -hydroxybutyric acid involving carboxyl and hydroxyl groups. Write a specific reaction, taking place when heated.
2. Write projection formulas of α -oxybutyric acid enantiomers, mark the asymmetrical carbon atom and define their affiliation to stereochemical series.
3. Write tautomeric forms of acetoacetic ester and prove the existence of these forms with chemical reactions.

Teaching tasks

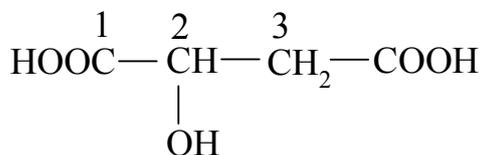
Task 1. What functional groups enter the content of oxoacids? Explain rules of the nomenclature of hydroxyacids.

Solution. Hydroxyacids are organic substances, which consist of carboxyl and hydroxyl groups. The quantity of carboxyl groups defines basicity of acids: monobasic acids, dibasic acids, tribasic acids, etc.

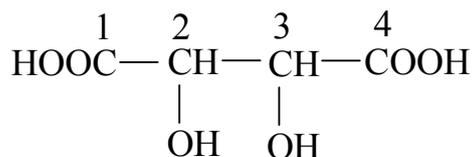
The rational and IUPAC nomenclatures are used for making the names of hydroxyacids. However trivial names of hydroxy- (oxo-) acids are more often used:



α -oxypropionic acid (rational)
2-oxypropanoic acid (IUPAC)
lactic acid (trivial)



α -oxysuccinic acid (rational)
2-oxybutanedioic acid (IUPAC)
malic acid (trivial)



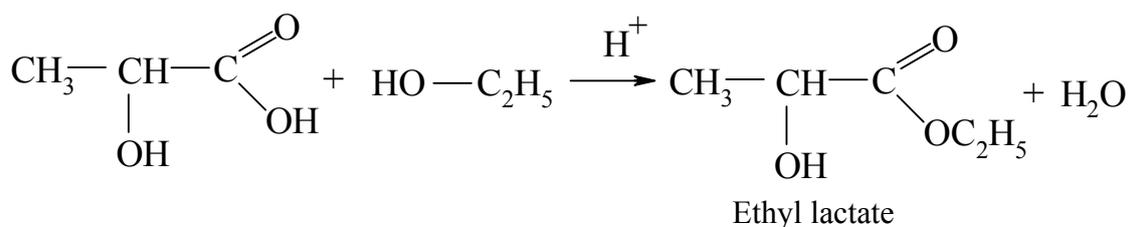
α, β -dioxysuccinic acid (rational)
2,3-dioxybutanedioic acid (IUPAC)
tartaric acid (trivial)

Task 2. What chemical properties of hydroxyacids confirm their affiliation to the heterofunctional compounds?

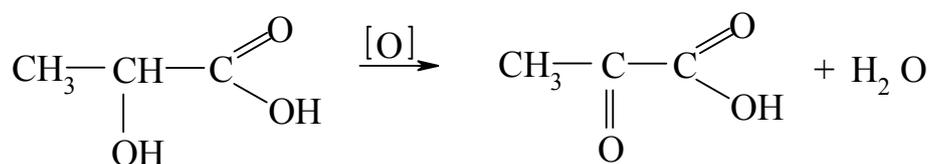
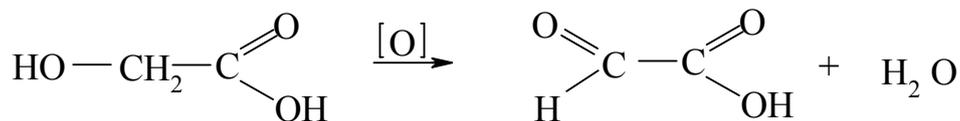
Solution. The hydroxyacids show all characteristic properties of alcohol and carboxylic acids. They have stronger acid properties than the one-basic acids with the same quantity of atoms of carbon that is caused by influence of the hydroxy groups.

The closer the hydroxyl is to the carboxyl group, the stronger acid.

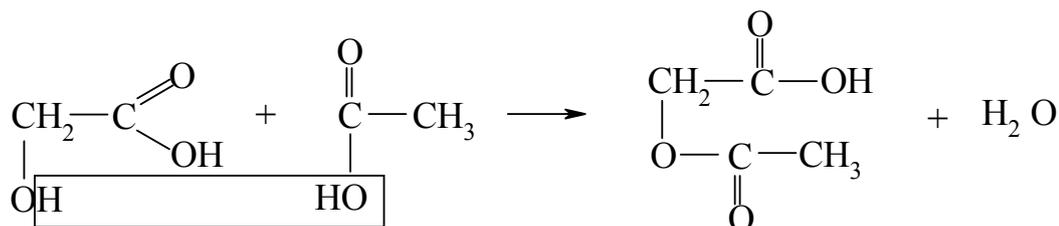
The carboxyl group of hydroxy- and oxoacids reacts with alcohols forming salts and/or esters.



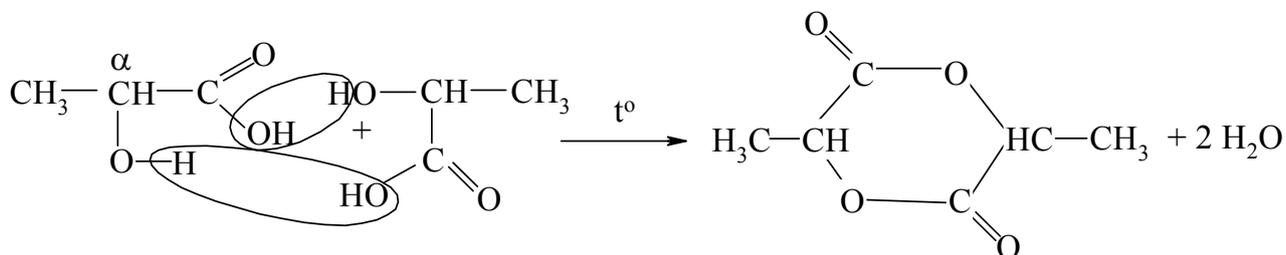
The alcohol's hydroxyl of the oxoacids can be oxidized forming aldo- or ketoacids.



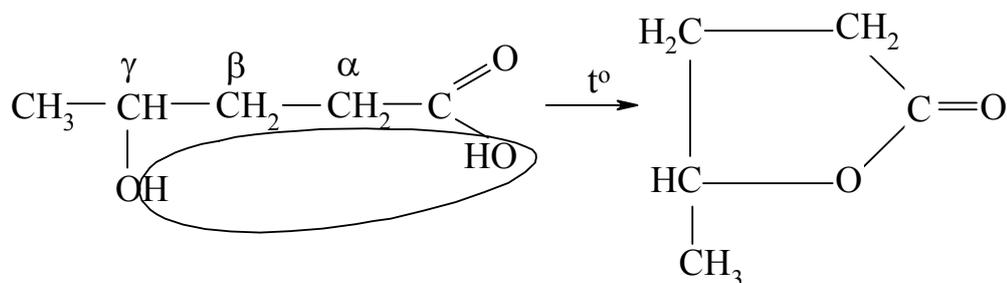
The interaction of the hydroxyl group of the hydroxyacid with carboxylic acid yields the formation of esters:



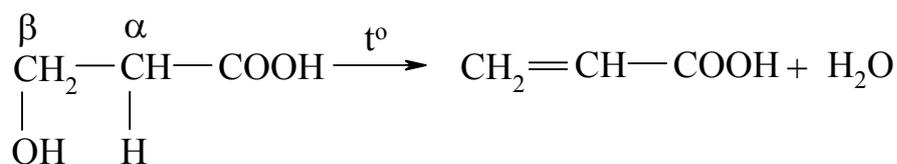
In addition, hydroxyacids can show properties, which are characteristic for alcohols and acids because of the presence of these functional groups in their structure. Heating of α -hydroxyacids is accompanied by the release of water and the formation of cyclic esters – lactides:



Elimination of water from one molecule of an acid and formation of cyclic esters – lactones is observed at the heating of γ -hydroxyacids:



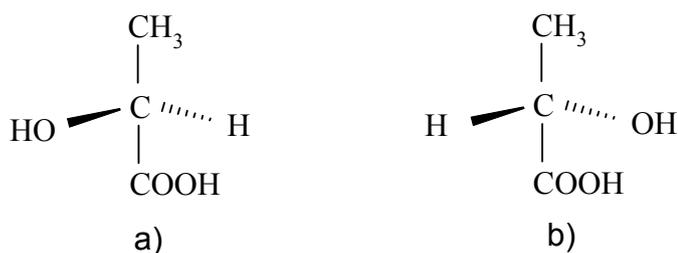
When heated, β -hydroxyacids form unsaturated acids by the intramolecular release of the water molecule:



These reactions are caused by high C-H acidity of hydrogen atoms of the methylene group in α - position.

Task 3. How can be explained optical activity of hydroxyacids? How do you define their affiliation to L- and to D-series?

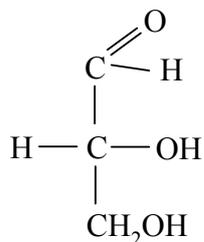
Solution. Many hydroxyacids have optical activity, i.e. ability to rotate a plane polarized light. Polarization of a ray of light takes place under the passage through the crystals of tourmaline and the fluctuations of such ray of light are in one surface. Under the passage through a solution of such optically active substance, the surface of polarization deviates by certain angle. It has established, that in some cases the substances which rotate a plane of polarization to the right and to the left on the same angle, are isomers.



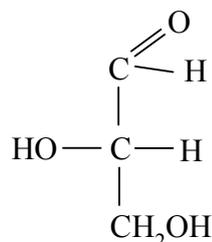
Optical activity of a substance arises if the molecule cannot be combined with its mirror image (chiral molecule). The molecule that can be combined with its mirror image is called achiral. The general attribute of chiral center is absence of symmetry surface or symmetry center in the molecule. Molecules, which have the carbon atom connected with four different substituents correspond to this condition. Such atom is called as dissymmetric atom or chiral center. For example, if lactic acid molecule is placed upward methyl groups, other substituents can be placed irregularly: a) hydrogen atom, carboxyl and hydroxyl – clockwise, b) hydrogen atom, carboxyl and hydroxyl – counter-clockwise.

Both molecules differ one from another, as an object and its image in a mirror. Chiral molecule and its mirror image are different substances, which are isomers. They are called mirror or optical isomers while they rotate a surface of a beam of polarized light by the same angle in the opposite directions.

To identify configurations of optical isomers D-, L-system is applied especially in the chemistry of carbohydrates and amino acids. Glyceraldehyde is used as the standard. Thus D-isomer was called a substance, which had group OH to the right from asymmetric carbon atom.



D-glyceraldehyde

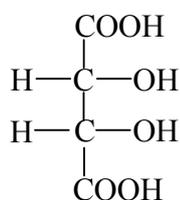


L-glyceraldehyde

Substances which formulas can be formed of D-glyceraldehyde by the adjustment of a hydrocarbon chain from the side of aldehyde group belong to a D-series, and from L-glyceraldehyde – to L-series. Not in all cases substances of D-series rotate a surface of plane polarized light to the right, and substances of L-series – to the left. Letters D and L are used before the name of substance designation of a configuration and a direction of rotation of a plane of polarization. Also before name of the substance must be written signs (+) and (-) corresponding to the rotation to the right or to the left.

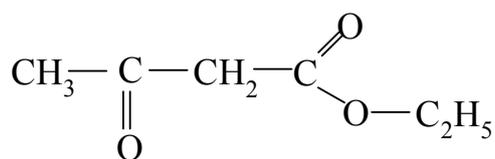
Mixture of identical quantity of optical isomers (racemic mixture) can appear under formation of chiral molecules. Such mixture is optically inactive.

Compounds with several dissymmetric carbon atoms, can be optically inactive because they consist of identical quantity of oppositely constructed dissymmetric centers. For example, in a molecule of mesotartaric acid, accommodation of substituents at the top asymmetric atom causes the right rotation of a plane polarized light, and at the bottom – left rotation. Such compounds are called meso-forms or meso-isomers. Meso-isomers are achiral, because they have a plane of symmetry.



mesotartaric acid

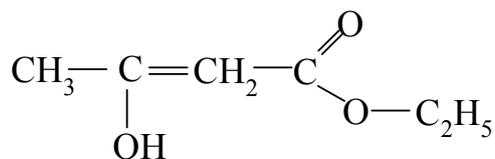
Optical activity of organic compounds is very important. Most of the natural compounds represent the one of the possible optical active forms and not racemic mixture. Optically active enzymes, which selectively interact with only one of optical isomers in the living organisms, that's why enzymes are highly specific.



acetoacetic ester

(1)

The ethyl ester shows the basic properties of ketones, and at the same time it interacts with sodium as alcohol, and attaches bromine as unsaturated compounds. These properties can be explained if ester is considered as ester of hydroxycrotonic acids:



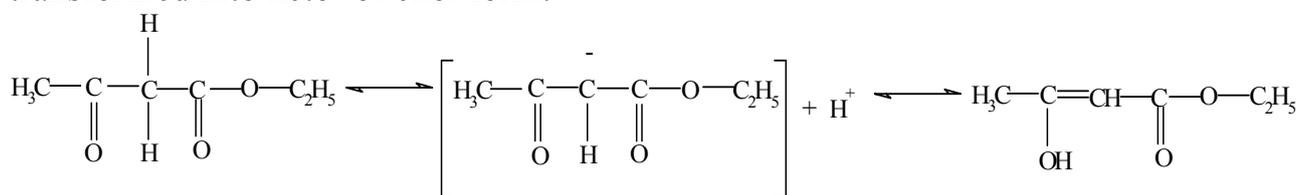
(2)

Researches show that acetoacetic ester is a mixture of isomers, with corresponding formulas (1) and (2). These isomers are called ketonic form or enol form respectively at the presence the ketonic or enol groups. At a room temperature acetoacetic ether contains 92,3 % ketonic form and 7,7 % enol form. Both the keto and the enol forms are in equilibrium through a process of tautomerism, continuous interconversion between two forms This phenomenon is called tautomerism. Forms which turn one into another are tautomers and their mutual transition are tautomeric transformations.

If tautomers are substances with carbonyl and enol groups (for example, isomerism of acetoacetic ester), than tautomerism is called keto-enol.

Tautomerism of acetoacetic ester is caused by hydrogen atoms of methylene group being in between of two carbonyl groups which withdraws electron density from the adjacent C-H bonds and increase its C-H acidity. Hydrogen atoms possess high mobility and can be removed in the form of a proton (C – H acidity).

Depending on the place of proton attaching to the formed ion, the last is transformed into keto- or enol form:



Conjugation is a factor that stabilizes the enol form.

Revision exercises

№ 1

1. Give the definition of enantiomers. Draw projection formulas of β -hydroxybutyric acids enantiomers, determine dissymmetric carbon atom and establish whether it is a D or L isomer?
2. Write the reaction equations of the lactic acid with NaOH solution and H_2SO_4 at heating. Name the products of the reaction.
3. Give the schemes of the reactions characteristic for keto-enol forms of acetoacetic ester.

№ 2

1. Give the definition of diastereomers. Write the projection formula of tartaric acid and its diastereoisomers. What configuration of carbon atom defines an affiliation of hydroxyacid to stereochemical series?
2. Write the reactions equations of γ -hydroxyvaleric acid with NaOH solution at heating (specific reaction).
3. Give the scheme of acrylic acid hydration. Name the products of reaction.

№ 3

1. Give the characteristic of mesotartaric acid structure. Write a projection formula, define an asymmetric carbon atom. Specify the reason of the absence of optical activity of mesotartaric acids.
2. Show the tautomeric forms of oxaloacetic acid. What is the name of this tautomerism? Explain the increased content of enol form.
3. Give the scheme of glyoxalic acid oxidation with ammoniac solution silver hydroxide.

№ 4

1. Give the definition for racemate. Write projection formulas of tartaric acid stereoisomers which form racemate - a racemic tartaric acid.
2. Write the reaction equations of pyruvic acid and ethyl ester.
3. Give the schemes of reactions, characteristic for enol form of acetoacetic ester.

№ 5

1. Write projection formulas of the lactic acid and key substance on which the affiliation to a stereochemical series is defined.
2. Write the equations for reaction of α -ketoglutaric acids (2-oxopentandioic acid) with excess of ethyl alcohol.
3. Give the scheme of obtaining of lactic acid lactide.

№ 6

1. Give the definition of diastereomers. Write projection formulas of a tartaric acid and its diastereomers. Which carbon atom configuration in hydroxyacids determines belonging to stereochemical series?
2. Write the reaction equation of acidic hydrolysis of α -hydroxyvaleric acid lactone.
3. Give the scheme of the citric acid decomposition proceeding at heating.

№ 7

1. Write projection formulas of malic acid enantiomers. Define the dissymmetric carbon atoms and specify an affiliation to series.
2. Write the reduction and decarboxylation reaction of α -ketobutyric acid which lead to the formation of ketone bodies.
3. What hydroxyacids form lactones at heating? Give examples.

№ 8

1. Write the reaction equations of acidic hydrolysis for lactone α -hydroxyvaleric acid.
2. Prove the existence of acetoacetic ester in two tautomeric forms by means of chemical reactions.
3. Write the schemes of reactions that prove presence of aldehyde group in glyoxalic acid.

№ 9

1. Give the definition of enantiomers. Write projection formulas of enantiomers of glyceraldehyde, define dissymmetric carbon atoms and specify their affiliation to the stereochemical series.
2. Write the reaction equations of acetoacetic acid decarboxylation. In what diseases the presence of decarboxylation products in urine and blood is observed?
3. Obtain lactic acid from propionic acid. Write the reaction equation of lactic acid with acetic anhydride, hydrochloric acid, and ethanol.

№ 10

1. Write projection formulas of β -oxybutyric acid enantiomers. Point out asymmetric carbon atom and specify its affiliation to series.
2. Write the reaction equation of interaction for lactic acid with ethanol, and write the specific reaction taking place at heating.
3. Define structure and name of the compound $C_2H_2O_3$ if it is known, that it interacts with ethanol (at the presence of H_2SO_4), forms acyl chloride, amide, reduces Ag_2O and $Cu(OH)_2$, gives positive reactions on carbonyl group.

№ 11

1. Show how to separate the racemic mixture by the example of hydrotartrate.
2. Give the definition of tautomerism. Write all tautomeric forms for oxaloacetic acid and compare their stability.

3. Give the scheme of interaction for Seignette salts with copper (II) hydroxide. Name the obtained products.

№ 12

1. Write the reaction equation for γ -oxybutyric acids with acyl chloride, and write the specific reaction taking place under heating.

2. Write the reaction equation for carboxylation of pyruvate anion.

3. Write the scheme of interaction between γ -oxybutyric acids and sodium (in excess).

№ 13

1. Write projection formulas of a D-lactic acid and key substance using which it is possible to determine its affiliation to stereochemical series (a relative configuration).

2. Write the reaction equation of malic acid dehydration and name the product.

3. Give the scheme of reaction that proceeds under the heating of β -oxycaproic acid (3-oxyhexanoic acid).

№ 14

1. Write projection formulas of dioxyvaleric acid stereoisomers. Show the chiral centers.

2. Give the hydrolysis reaction of α -, β - valerolactone (γ -lactone of oxyvaleric acid). What is the medium for this reaction?

3. Write the reaction equation of pyruvic acid with HCl. What is the mechanism of this reaction?

№ 15

1. What isomers are called antipodes (enantiomers)? Give examples.

2. Give the scheme of interaction between oxyacetic acid lactide and NaOH solution.

3. What is the difference between lactic acid and pyruvic acid?

Subject II. HETEROFUNCTIONAL COMPOUNDS OF BENZENE SERIES – METABOLITES AND PARENT STRUCTURES OF MEDICINES

Motivational characteristic of the subject

Heterofunctional compounds of benzene series are ancestors of the most significant groups of drugs and physiologically active substances: non-narcotic analgesics, local anesthetics, antiseptic and anti-parasitic medications, drugs for tuberculosis treatment.

Objective

To consolidate the knowledge about the structure and chemical properties of the most significant heterofunctional aromatic compounds used in medicine.

Training questions

1. p-Aminophenol, its structure and properties, drugs – derivatives of phenol: phenacetin, paracetamol.
2. Salicylic acid, its structure and properties as a heterofunctional compound. Salicylic acid derivatives, their pharmacological properties and implementation.
3. p-Aminobenzoic acid, its structure and properties. Drugs (anesthesine, novocain, dicain) and their use.
4. Sulfanilic acid, its structure and properties. Sulfanilamide, the ancestor of sulfanilamides with antibacterial properties.
5. p-Aminosalicylic acid, its structure and properties. Drugs (PASA, PAS-Na) and their pharmacological action.

Methodological questions

1. Heterofunctionality is one of the characteristic attributes of compounds, which take part in vital processes.
2. Amphoteric properties of amino acids.
3. Role of national scientists in the development of sulfanilic medicines.

Initial level

1. Amphoterism.
2. Basic and acid properties of organic substances.
3. Conjugation and aromaticity.
4. Chemical properties of hydroxy-, amino- and carboxyl groups.

Practical skills

To be able to perform qualitative reactions for some medicines of benzene series.

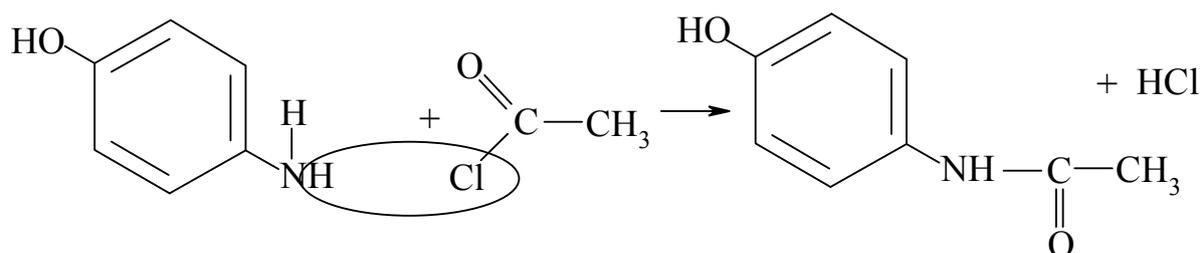
Test questions

1. Write a qualitative reaction for phenolic hydroxyl group. Why is this reaction used to define the purity of aspirin, which can decompose at storage?
2. Write the reactions equation causing the production of sulfanilic acid amide (streptocide) from aniline.
3. Write the reaction equation of p-aminophenol with ethanol. How are p-aminophenols used in medicine?
4. Write the reaction equation of salicylic acid with phenol. What is the name of the obtained substance? How is it used in medicine?
5. Draw the structure of sulfadimethoxine containing a substituted pyrimidine cycle as a radical in the sulfamide group.

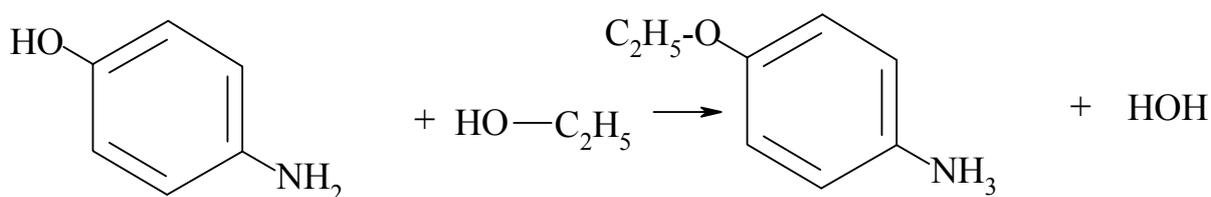
Teaching tasks

Task №1. Write a structure of p-aminophenol and its properties. What derivatives of p-aminophenol are used in medicine?

Solution. p-aminophenol contains hydroxyl group and amino group in para position, exhibiting properties of phenols and amines. Particularly possible reaction of acylation on aminogroup:

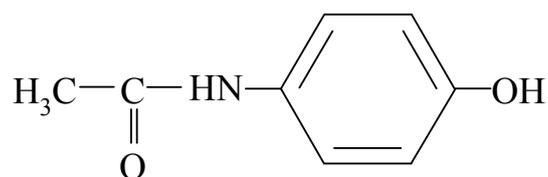


Formation of ethers with alcohol is possible on hydroxyl group:



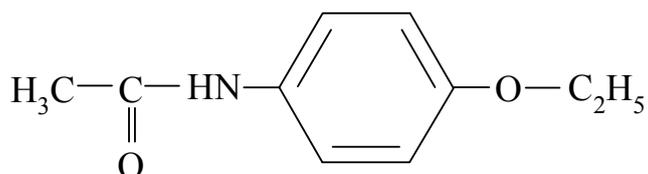
Main effects of aniline derivatives are anesthetizing and febrifugal. However p-aminophenol is poisoning and cannot be used for reception internally. That's why derivatives of p-aminophenol - paracetamol and phenacetin - are used in medicines as active substances.

Paracetamol is a product of acylation of p-aminophenol with acyl halides of acetic acid:



Paracetamol

Phenacetin is derivative of p-aminophenol, in which amino group is acetylated and hydroxygroup is esterificated with ethanol:



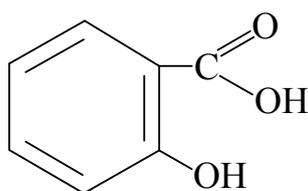
Phenacetin

Gradual hydrolysis of ester and amide bonds occurs at the entering of phenacetin in blood and therefore toxic substances do not collect in a significant amount.

Paracetamol and phenacetin are nonnarcotic analgetic which have anesthetizing and antipyretic actions.

Task №2. Describe chemical properties of a salicylic acid. Which derivatives of salicylic acid are used in medicine?

Solution. Salicylic acid (o-oxybenzoic acid) exhibits out the greatest physiological activity from three possible isomers of phenoloacids.

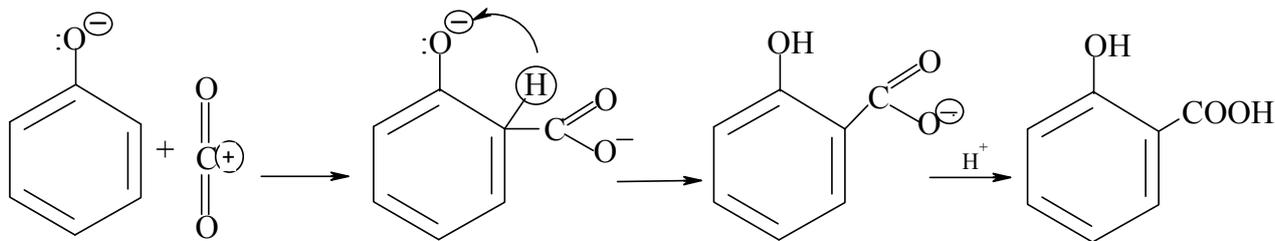


Salicylic acid

The salicylic acid is widely widespread in the nature: in free state is in a camomile, in the form of a methyl ester is in many essences.

The salicylic acid and its derivatives enter into the composition of many medicines. Phenol is used as initial compounds for their reception.

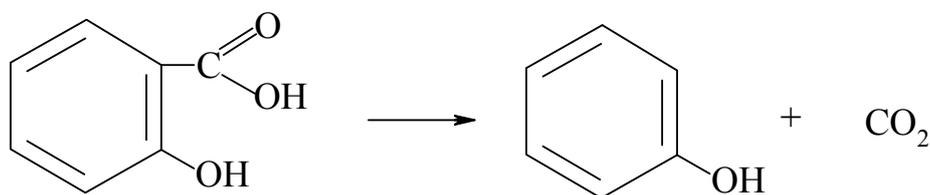
Hydroxyl group in phenol has strong +M effect with activating of benzene ring and directs following substituents in orto- and para-position. It allows the use of phenol direct carboxylation for salicylic acid obtaining. Carbon dioxide which is weak electrophile can be used as a reagent. Reactivity of benzene ring rises if to use not phenol, but its salt - sodium phenolate.



The main reaction proceeds in one stage and without separation of by-products.

Salicylic acid is stronger than benzoic acid. This is connected with the formation of an internally molecular hydrogen bond which assists in the stabilization of the carboxylate anion and, thus, raises acidity.

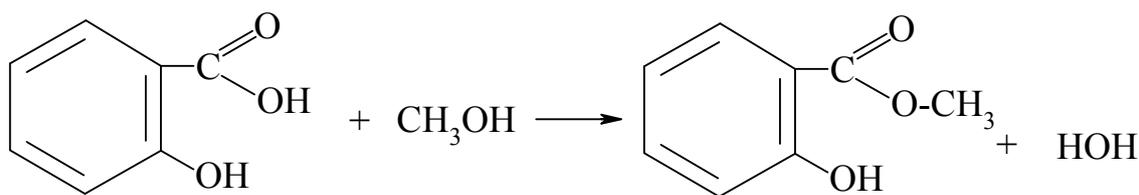
Salicylic acid, like other α -oxyacids, can be easily decarboxylated upon heating, forming phenol:



Salicylic acid has strong local irritating properties; therefore, it is not prescribed internally. Derivatives of salicylic acid have anesthetic, febrifugal, and anti-inflammatory effects. Anti-inflammatory activity is caused by the presence of the hydroxy group: all derivatives of phenol which contain a hydroxy group possess a bactericidal action.

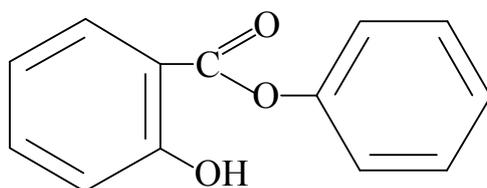
From a chemical point of view, derivatives of salicylic acid (salicylates) are generally esters which are obtained using both functional groups.

When heated, salicylic acid with methanol in the presence of H_2SO_4 , methylsalicylate is formed:

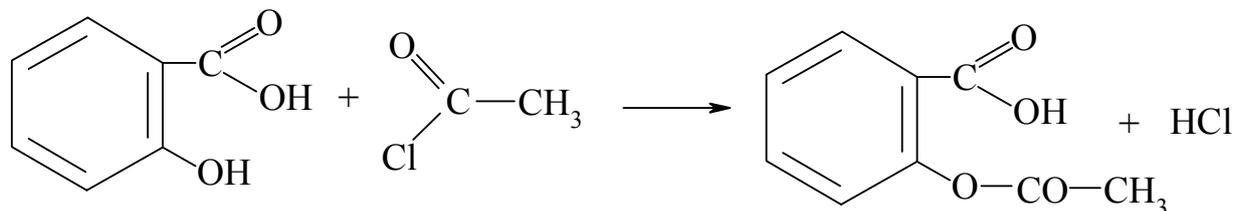


Methylsalicylate is a colorless liquid with a fragrant smell. It shows irritating, anesthetic, and anti-inflammatory action; it is used for massages and compresses (with vegetable oil in rheumatoid arthritis).

Phenyl salicylate (salol) is an ester of salicylic acid and phenol:



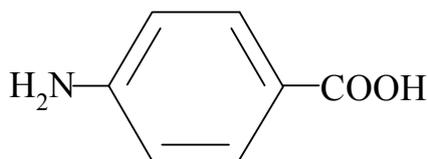
Salicylic acid forms esters with acids using phenolic hydroxyl. Ester of salicylic acid and acetic acid (aspirin) can be obtained in reaction of salicylic acid with acetic acid anhydride or acetic acid chloride:



Aspirine is a white crystalline powder with a slight smell and faintly acid taste; it is slightly soluble in water possessing antipyretic and analgesic properties. It is used in the form of powders and tablets. Aspirin is often combined with other analgesics (asophene, citramonum, etc.).

Task №3. What preparations of p-aminobenzoic acid are used in medicine? Give the chemical and pharmacological characteristics for these preparations.

Solution. p-aminobenzoic acid (PABA) is in the yeast, liver, eggs, milk, etc.

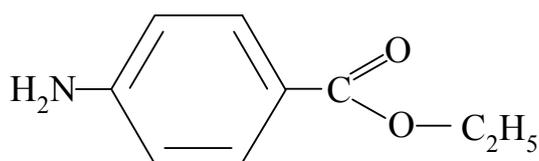


p-aminobenzoic acid (PABA)

This is an amphoteric organic compound, it does not form internal salts in water solution, owing to significant delocalization of electrons. It forms salts with acids and bases possessing high physiological activity. This compound is the factor of growth of microorganisms; takes part in many biochemical processes. Deficiency of p-aminobenzoic acid in food leads to graying and loss of hair.

Esters of p-aminobenzoic acid (PABA) (benzocaine, novocaine, tetracaine) are local anesthetics.

Anesthesin – ethyl ether of PABA – is a white crystal powder, it is a weak base (aromatic amine), basicity of which is weakened by a carbonyl group which shows -M and -I effects. Anesthesin does not form stable water-soluble salts with acids, therefore it is used in the form of powders, ointments, pastes at burns, ulcers on skin.

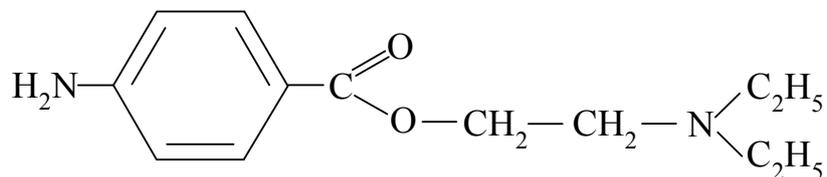


Anesthesin

One of the general local anesthetics is novocaine - hydrochloric salt of

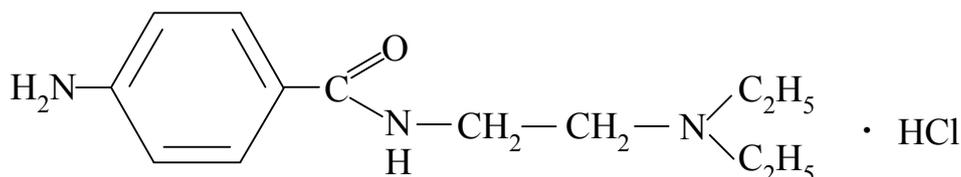
diethylaminoethyl ether of PABA. This salt can be obtained with acids due to tertiary nitrogen atom. It is a freely soluble in water, that's why novocaine is used in solutions for injections – from 0,5 to 5 %.

In the organism novocaine is hydrolyzed quickly with formation of aminobenzoic acid. Novocaine anaesthesia lasts near 30 minutes.



Novocaine

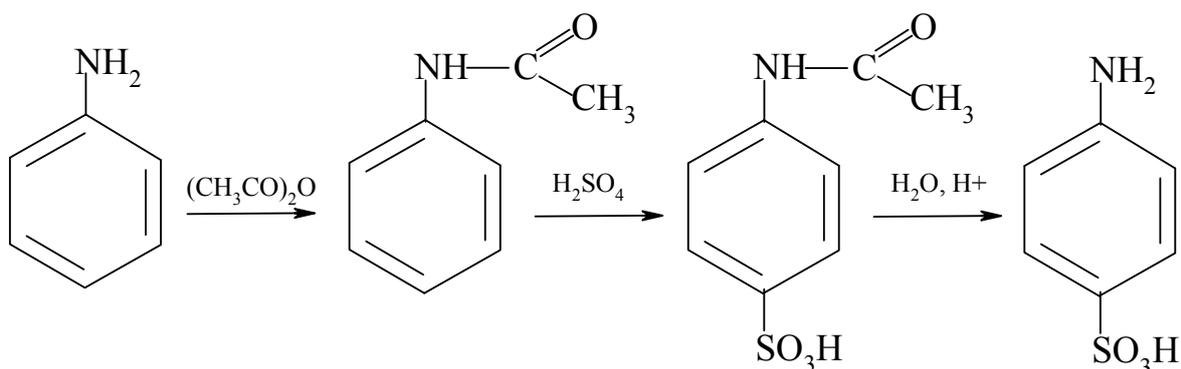
Introduction of amide group to the molecule of novocaine changes its physiological action. Procainamide hydrochloride is amide of p-aminobenzoic acid, it's an antidysrhythmic drug and used for treatment for heart rhythm disorders.



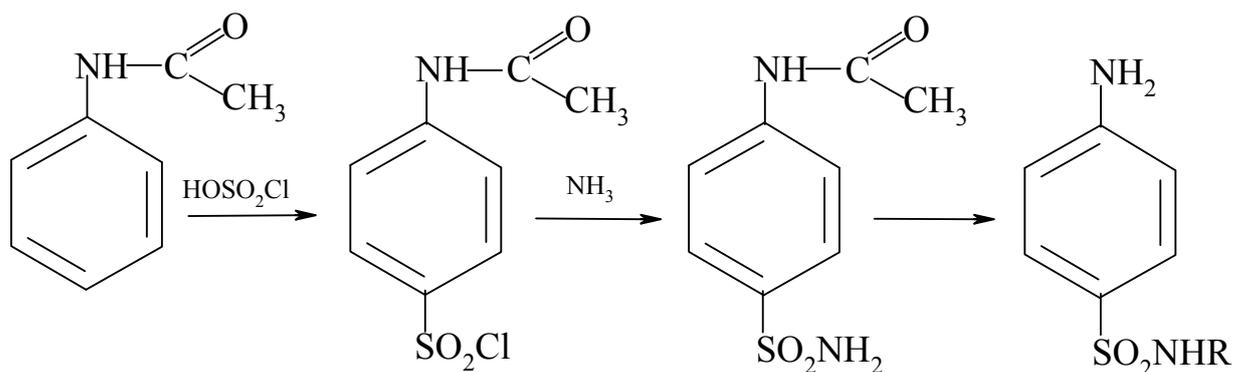
Procainamide hydrochloride

Task №4. Describe obtaining and properties of sulfanilic acid. What medical preparations are called sulphanilamides? What is their action?

Solution. p-Aniline sulfonic acid (sulfanilic acid) is obtained as a result of aniline sulfonation. In this case amino group should be protected preliminarily, for example, using acylation:

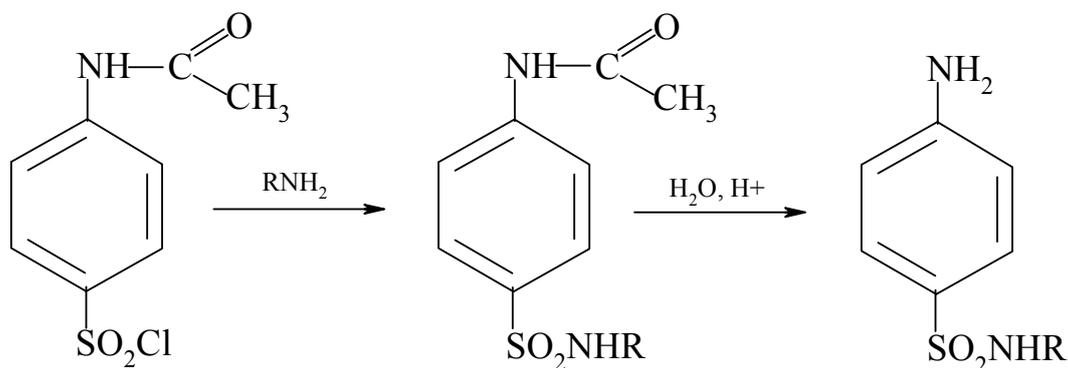


If sulfonation is performed without sulfuric acid but using its acyl chloride then acyl chloride of sulfanilic acid is obtained, which forms sulfanilamide after the interaction with ammonia:



Amide of sulfanilic acid (streptocide) has bactericidal action.

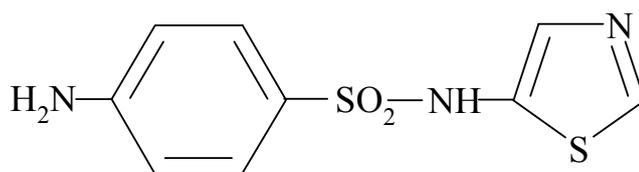
If amines are used instead of ammonia substituted sulfanilamides can be obtained:



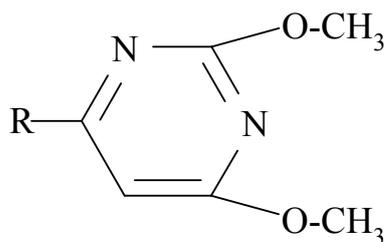
Antibacterial action and toxicity of sulfanilamides depend on the nature of radical, connected with amide nitrogen.

It is synthesized more than 5000 derivatives of sulfanilamide, however near 30 preparations have found practical use; almost all of them contain heterocyclic compounds in radical.

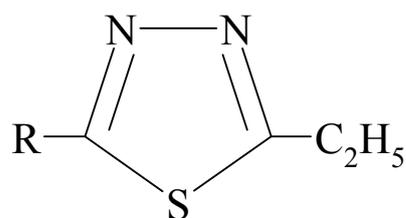
For example:



Norsulfazole (thiazol cycle)

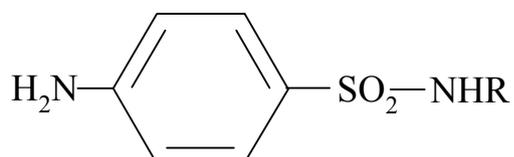


Sulfadimetoxine (pyrimidine cycle)



Ethazole (thiadiazole cycle)

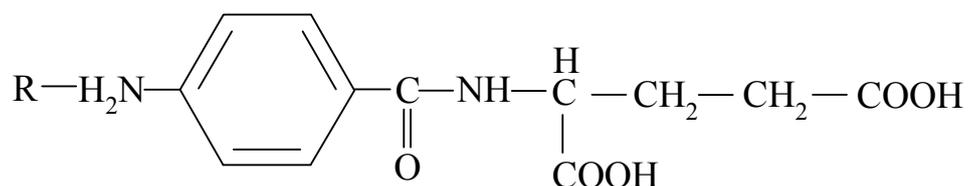
Sulfanilic radical is needed for antibacterial activity:



Shifting of amino group in other position and introduction of additional radicals in aromatic ring leads to loss of activity or to its significant weakening.

Contrary to bactericidal or antiseptic substances which kill microorganisms at the expense of protein denaturation, sulfanilamides exhibit bacteriostatic action. This action is due to disturbance of process of "growth factors" obtaining by microorganisms as a result of which generation of bacteria stops.

"Growth factors" for bacteria are the substances which contain in a molecule the residue of p-aminobenzoic acid, particularly, folic acid. p-Aminobenzoic acid has alkylated amino group and forms amide using carboxyl group:



R - pteridic ring- is a condensed system from two six-membered heterocycles – pyrimidine and pyrazine.

Folic acid is synthesized in the organism from the substituted pteridine glutamic acid and PABA.

Revision exercises

№ 1

1. What color reaction allows distinguishing of paracetamol from phenacetine?
2. Write the equation for the reaction of interaction between acetyl chloride of p-aminobenzoic acid with ethanolamine-1. Name a medical preparation. What is its medical application? Where does salt formation with HCl occur?
3. Characterize the acidic properties of sulfanilic acid.

№ 2

1. Write the equation for the reaction of paracetamol formation from p-aminophenol and acetic acid. How are derivatives of p-aminophenol applied in medicine?
2. Write the equation for the formation reaction of salicylic ester of an acetic acid. Name obtained medical preparation, what is its use in medicine?
3. Write the equation for the reaction of sulfanilic acid alkylation.

№ 3

1. Write the equation for the formation reaction of sulfanilic acid amide (streptocide) from aniline.
2. Obtain an ethyl ether of p-aminobenzoic acid. What is the name of medicinal preparation? What is its using in medicine?
3. Write the equation for the esterification reaction using both functional groups of a salicylic acid.

№ 4

1. Write the equation for the formation reaction of phenetidine as a result of interaction between p-aminophenol and ethanol. How p-aminophenol derivatives can be used in medicine?
2. Write the scheme for transformation of sulfanilic acid in streptocide. Describe application of sulfanylamide preparations in medicine.
3. Write the equation for the qualitative reaction on phenols by the example of salicylic acid.

№ 5

1. Write the reaction equation for hydrolysis of aspirin (acetylsalicylic acid), proceeding at its storage. How can you check purity of aspirin?
2. Write the equation for the reaction of p-aminophenol carboxylation. Name a medicinal preparation. At what diseases it can be applied?
3. Write the reaction equation for the formation of sulfanilic acid halide and amide.

№ 6

1. Write the structure of sulfonamide (streptocide). Name the medicinal preparation at which it can be used as active substance.
2. Write the reaction equation between p-aminobenzoic acid and diethylamino-

ethanolamine-1. Point nitrogen on which salt formation with HCl takes place. What is the name and application of this medicinal preparation?

3. Write the reaction equation of electrophilic substitution for salicylic acid.

№ 7

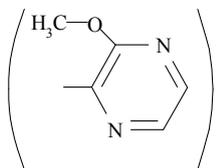
1. Write the reaction equation for ester formation of salicylic acid with phenol. Name the product obtained. What is the application of this compound in medicine?

2. Write the reaction equation of interaction between acyl chloride of p-aminobenzoic acid and ethanol-1. Write the alkylation reaction for obtained product and C₄H₉Br. Name obtained medicinal preparation. What is its application in medicine?

3. Write the reaction equation for Schiff's base formation from streptocide and acetaldehyde.

№ 8

1. Write the structure of sulfalene which contains replaced peridazine ring as a



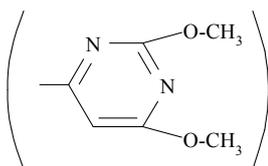
radical in sulfamide group

2. Write the reaction equation of interaction between salicylic acid and methanol. Name the product obtained. What is its application in medicine?

3. Write the reaction equation of salicylic acid decarboxylation.

№ 9

1. Write the structure of sulfadimetoxine which contains substituted pyrimidine



ring as a radical in sulfamide group

2. Write the reaction equation of interaction between p-aminophenol and acetic acid chloride. Name obtained medicinal preparation.

3. Write the reaction equation of salicylic acid decarboxylation.

№ 10

1. Write the reaction equation of ester formation for salicylic acid with acetic anhydride. Name obtained product. What is its application in medicine?

2. Obtain ethyl ester of p-aminobenzoic acid. Name obtained medicinal preparation. What is its application in medicine?

3. Write the reaction equations confirming acidic properties of sulfanilamides.

№ 11

1. Write the reaction equation of methyl salicylate hydrolysis.

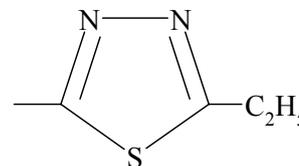
2. Write the reaction equation for p-aminophenol carboxylation. Name product

obtained. What is its application in medicine?

3. Write the reaction equation of interaction between amide of sulfanilic acid (streptocide) and bromine. What is the mechanism of this reaction?

№ 12

1. Write the structure of ethazole containing substituted thiadiazol ring as a radical in sulfamide group .



2. Write the reaction equations for the following transformations:

p-aminophenol + ethanol \rightarrow ? + acetic acid chloride \rightarrow ?

3. Write qualitative reaction for salicylic acid with FeCl_3 .

№ 13

1. Write the equation for formation reaction of anesthesin as a result of interaction between p-aminobenzoic acid and ethanol. What is anesthesin application in medicine?

2. Write the reaction equation for formation of salicylic ester of acetic acid. Name obtained product. What is its application in medicine?

3. Write the reaction equation for interaction amide sulfanilic acid (streptocide) with iodine. What is the mechanism of this reaction?

№ 14

1. Write the reaction equation for industrial producing of a salicylic acid using direct carboxylation method. Why is salicylic acid stronger than benzoic acid?

2. Write the transformation scheme for sulfanilic acid into streptocide. What is sulfanilamides' application in medicine?

3. Write esterification reaction mechanism for p-amino-benzoic acid.

№ 15

1. Write the reaction equation for novocain formation as a result of interaction between p-aminobenzoic acid and diethylaminoethanol. Write the structure of novocain hydrochloride used in medicine.

2. Write the reaction equation between salicylic acid and phenol. What is the name of the product? What is its application in medicine?

3. Write the reaction equation for Schiff's base formation as a result of interaction between streptocide and benzaldehyde.

SUGGESTED READINGS

1. Biologically important classes of bioorganic compounds. Biopolymers and their structural components: Theoretical course of biological and bioorganic chemistry, Module 1 / A.O. Syrovaya, E.R. Grabovetskaya, N.M. Tkachuk et al. – Kharkov: KhNMU. – 2013. – 183 p.
2. Zurabyan S.E. Fundamentals of bioorganic chemistry / S.E. Zurabyan – M.: Geotar-Med. – 2003. – 320 p.

Навчальне видання

**Гідрокси- та оксокислоти. Гетерофункціональні сполуки
бензольного ряду – метаболіти та родоначальники лікарських
засобів**

**Методичні вказівки для самостійної роботи студентів 1-го курсу з
біологічної та біоорганічної хімії (Модуль 1)**

Укладачі:

Сирова Ганна Олегівна,
Шаповал Людмила Григорівна,
Петюніна Валентина Миколаївна,
Грабовецька Євгенія Романівна,
Наконечна Світлана Анатолівна,
Козуб Світлана Миколаївна

Відповідальний за випуск Козуб С.М.

Комп'ютерний набір та верстка Козуб С.М.

Ризографія.

Умов. др. арк., тираж 200 прим.

ФЛП Томенко Ю.І.

м. Харків, пл. Руднева,4