MINISTRY OF HEALTH CARE REPUBLIC OF BELARUS
GOMEL STATE MEDICAL UNIVERSITY

Department of general and bioorganic chemistry

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CHEMISTRY OF HETEROFUNCTIONAL & HETEROCYCLIC COMPOUNDS

Laboratory manual

Gomel
GSMU
2009

УДК 541.49(075.8)=20
ББК 24.2
Ф 53

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Ф 53 Химия гетерофункциональных и гетероциклических соединений: учеб. пособие для лабораторно-практических занятий по курсу биоорганической химии для студентов лечебного факультета, обучающихся на английском языке = Chemistry of heterofunctional and heterocyclic compounds: Laboratory manual / авт.-сост.: В. А. Филиппова, А. В. Лысенкова, Л. В. Чернышева. — Гомель: УО «Гомельский государственный медицинский университет», 2009. — 36 с.

ISBN 978-985-506-236-4

Учебное пособие предназначено для организации лабораторного практикума и самостоятельной работы студентов, изучающих курс биоорганической химии на английском языке. Оно призвано помочь студентам в формировании представлений о строении и свойствах гетерофункциональных соединений алифатического, бензольного и гетероциклического ряда. Особое внимание уделено биологической роли указанных соединений и их применению в медицине.

Утверждено и рекомендовано к изданию Центральным учебно-научно-методическим советом Учреждения образования «Гомельский государственный медицинский университет» 15 апреля 2009 г., протокол № 4.

УДК 541.49(075.8)=20
ББК 24.2

ISBN 978-985-506-236-4

CHAPTER 1

SPECIFIC PROPERTIES OF ALIPHATIC HETEROFUNCTIONAL COMPOUNDS

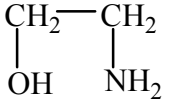
After reading this chapter, you should be able to:

- define heterofunctional compounds and give their examples;
- define chiral molecules and describe their specific properties;
- be able to write the Fisher's projections of enantiomers and diastereomers;
- discuss specific properties of hydroxo-, amino- and oxo acids;
- discuss the pathways of serine and phenylalanine metabolism.

1.1 General concepts

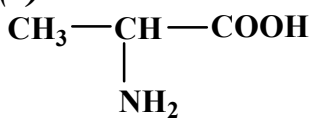
Heterofunctional compounds contain at least two different functional groups. The most important naturally occurred are:

(1) Amino alcohols



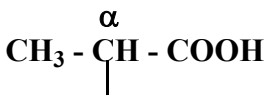
Ethanolamine or **Colamine**

***(2)** Amino acids*

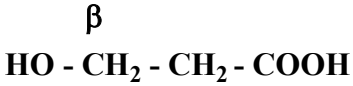


α-Alanine

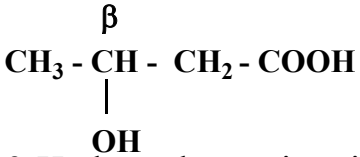
(3) *Hydroxy acids* that contain -OH and -COOH groups (α-, β- and γ-hydroxy acids are distinguished)



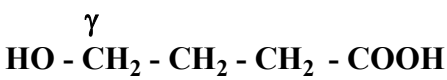
2-Hydroxy propanoic acid or **Lactic acid** (α-acid)



3-Hydroxypropanoic acid (β-acid)

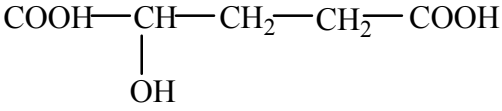


3-Hydroxy butanoic acid
β-hydroxy butyric acid

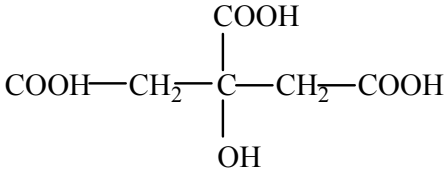


4-Hydroxy butanoic acid (γ-acid)
γ–hydroxy butyric acid

The vital *di* - and *tri-hydroxy carboxylic acids* that are involved in metabolic processes are:

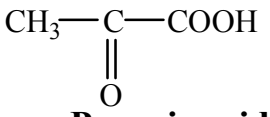


Malic acid

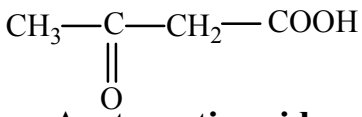


Citric acid

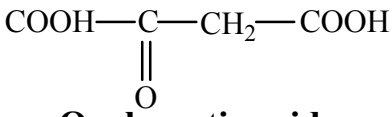
(4) *Oxo Acids* that are subdivided into aldehydo- and keto- acids.



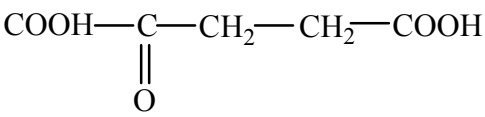
Pyruvic acid



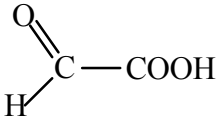
Acetoacetic acid



Oxaloacetic acid

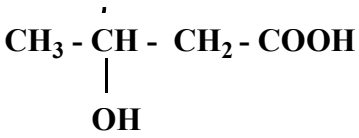


α-Ketoglutaric acid

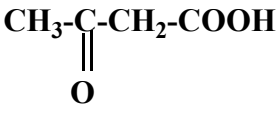


Glyoxalic acid

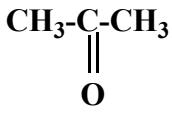
Acetoacetic acid is the product of fatty acids metabolism and β-hydroxy butyric acid oxidation *in vivo*. These two acids and acetone accumulate in bodies of people suffering from diabetes mellitus. They are called *Ketones Bodies*:



β-Hydroxy Butyric Acid



Acetoacetic Acid



Acetone

Their high content in biological fluids signals about diabetes mellitus.

1.2 Optical isomerism

Molecules are three dimension objects and as all objects they may be symmetric or asymmetric. Symmetric molecules contain a plane of symmetry, which bisects them into two equal halves. Such molecules are named *achiral*. Symmetric (achiral) molecules can be superimposed upon their mirror images (figure 1).

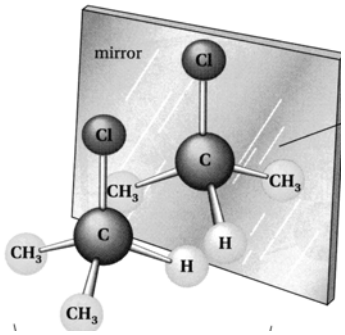
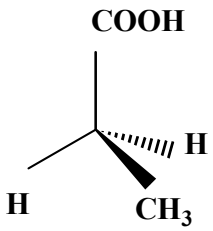
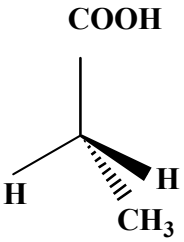


Figure 1 — Model of 2-chloropropane and its mirror image

Propanoic acid is another example of achiral molecule: CH_3-CH_2-COOH.





Molecules that lack a plane of symmetry are chiral (asymmetric); they and their mirror images cannot be superimposed on each other. The term «chiral» comes from Latin word «chiro» that means «hand».

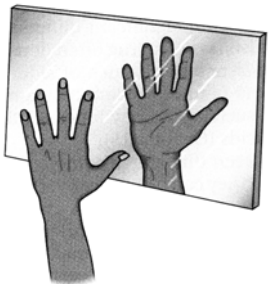


Figure 2 — The mirror image of a left hand is not a left hand, but a right hand

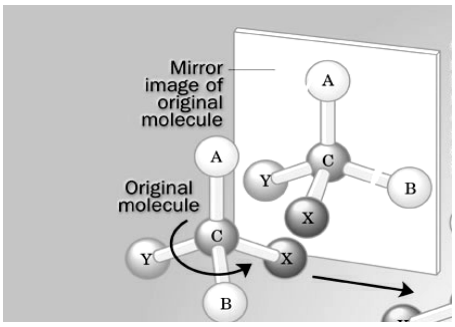
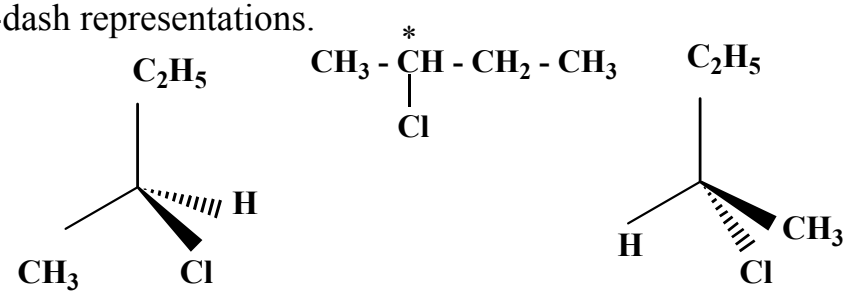


**Figure 3 — Model of a chiral molecule and its mirror image.
The mirror image is not superimposable on the original molecule**

All chiral molecules contain one or several stereogenic centers. *Stereogenic center* is sp^3-hybridized carbon atom with four different substituents attached to it.

Let's consider a chiral molecule of 2-chlorobutane. Its molecule contains one stereogenic center and forms two stereo isomers. Here you can see their wedge-and-dash representations.



Chiral compounds exhibit the following properties:

(1) they are optically active (figure 4). It means that they rotate a plane of polarized light in some number of degrees.

(2) they form configurational (optical) stereoisomers, which differ in a configuration of a stereogenic center. A number of optical isomers is equal to 2^n, where n is a number of stereogenic centers in a molecule of a chiral compound.

Optical isomers fall into two categories:

- enantiomers;
- diastereomers.

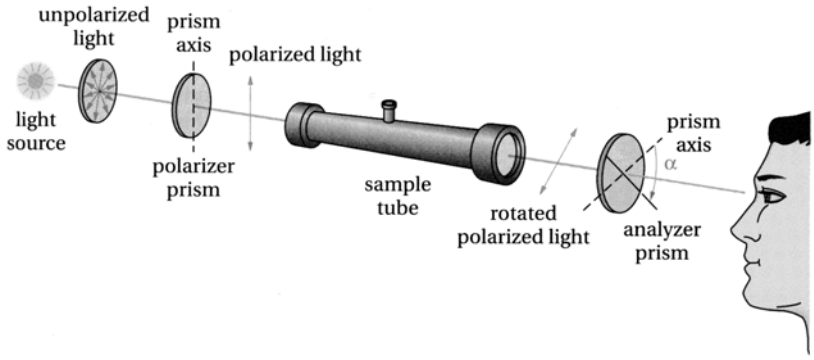


Figure 4 — Diagram of a polarimeter

Enantiomers are optical isomers that relate as nonsupreimposable mirror images. They exhibit identical physical and chemical properties, but differ in two significant ways:

(a) both enantiomers of a pair rotate a plane of polarized light by the same number of degrees but in opposite direction (one clockwise and another counter clockwise).

(b) each enantiomer of a pair reacts chemically in an individual way in an asymmetric environment to form another asymmetric compound. For example, they interact differently with enzymes or biological receptors (figure 5).

As a rule only one enantiomer from a pair is involved into metabolism.

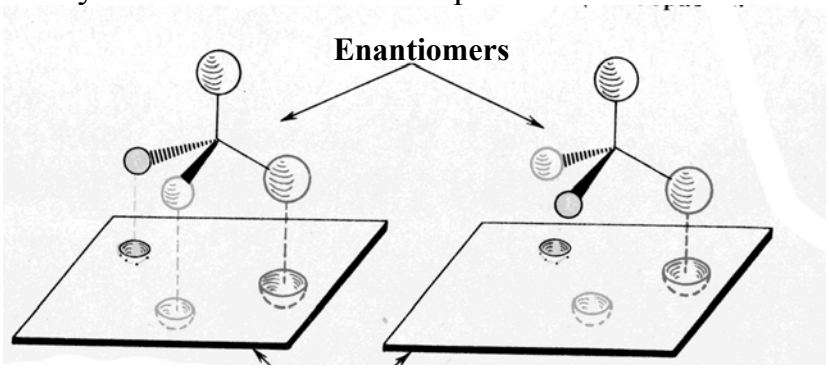


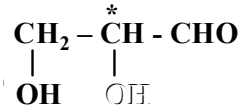
Figure 5 — The schematic representation for an interaction between a chiral substrate and an enzyme

Equimolar mixture of enantiomers is named a *racemic mixture*; it is optically inactive.

Diastereomers are stereoisomers that are not mirror images of one another. They exhibit different physical and chemical properties.

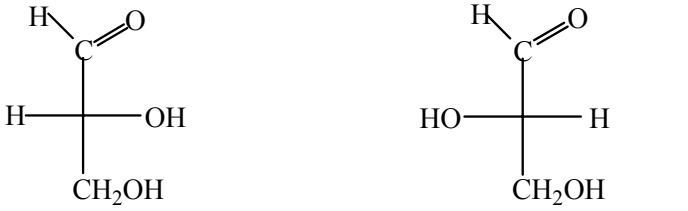
Structure of stereoisomers is usually represented as *Fisher projections*. In these formulas the stereogenic center is omitted and is represented as a crossing point of the horizontal and vertical lines. For example, glyceraldehyde contains one stereogenic center and forms a pair of enantiomers (figure 6). *Glyceraldehyde is applied as a configurational standard.* The types of all other stereoisomers are

determined in comparison with its stereogenic centers. Letter D means that an isomer belongs to D-stereo chemical series; letter L - it's a member of L-stereo chemical series. Mainly L-amino- and hydroxy acids are biologically active.



Glyceraldehyde

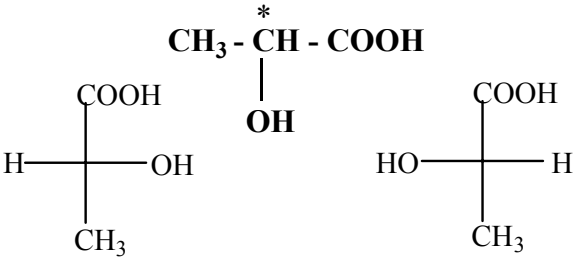
Fisher Projections for Glyceraldehyde



D-Glyceraldehyde **L-Glyceraldehyde**

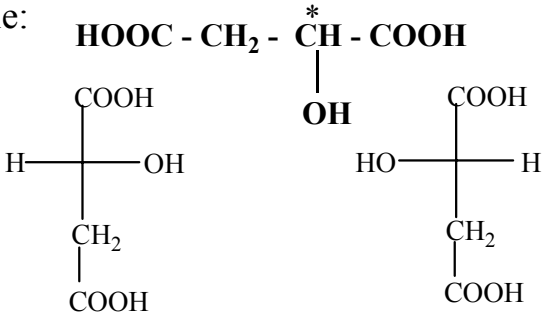
Figure 6 — Glyceraldehyde and its enantiomers

Let us consider lactic acid that is a product of glucose metabolic pathway.



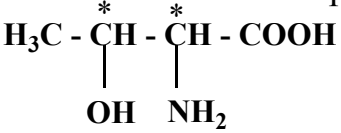
D-Lactic Acid **L-Lactic acid**

Consider the optical isomers of malic acid that is involved into tricarboxylic acid cycle:



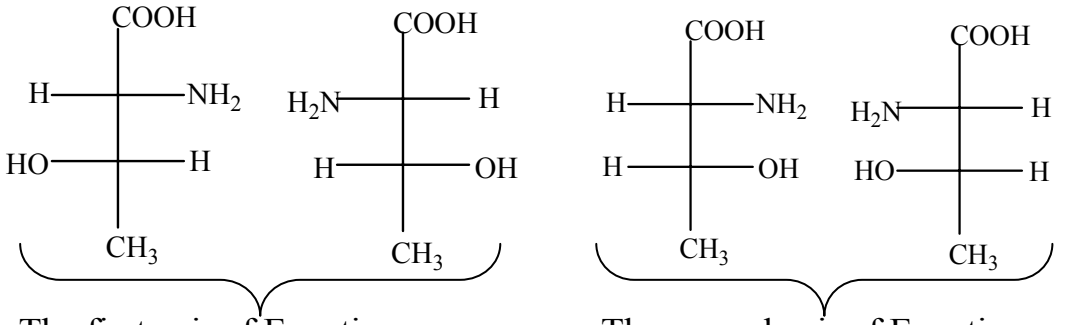
D-Malic Acid **L-Malic Acid**

Some hydroxy- and amino acids contain two stereogenic centers. For example, threonine (Thr) is α- amino acid involved in protein biosynthesis:



2-amino-3-hydroxy butanoic acid or **threonine (Thr)**

Threonine forms two pairs of enantiomers:



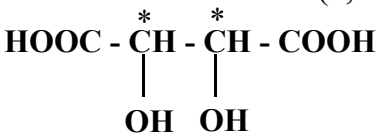
The first pair of Enantiomers — The second pair of Enantiomers

D-allo Thr **L-allo Thr** **D-Thr** **L-Thr**

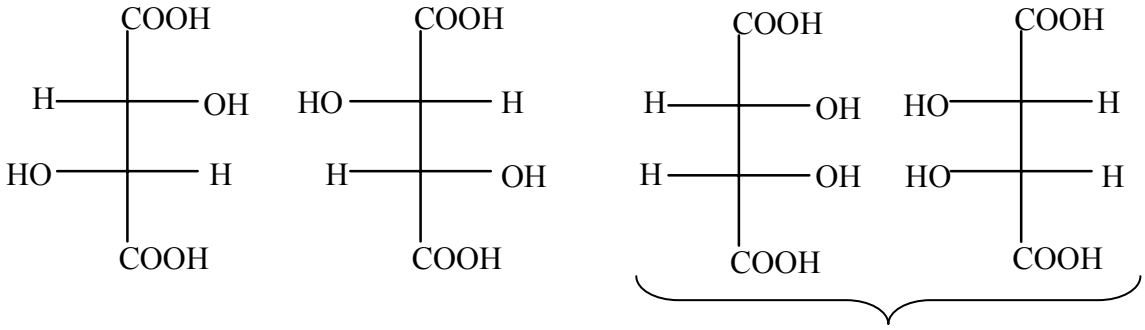
I **II** **III** **IV**

Enantiomers — I и II; III и IY. Diastereomers — I и III; I и IV; II и III; II и IV. Prefix *allo* is used to name stereoisomers, which are not involved in proteins' biosynthesis.

Let us consider stereoisomerism of tartaric acid (2, 3-dihydroxy butanedioic acid):



Its molecule contains two stereogenic centers and theoretically ought to form two pairs of enantiomers. But in fact there are only three stereoisomers: D-tartaric acid, L-tartaric acid and meso-tartaric acid.

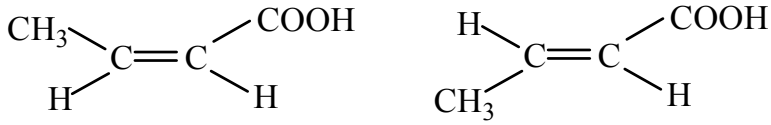


D-Tartaric Acid **L-Tartaric Acid** **meso-Tartaric Acid**

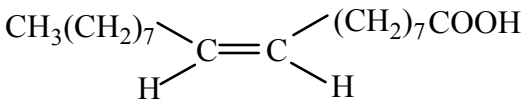
I **II** **III**

Meso-tartaric acid is achiral because contains a plane of symmetry, which bisects a molecule into two halves that are mirror images of each other. It is not optically active.

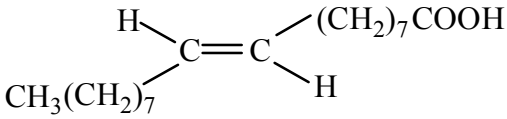
π-Diastereomers (cis-trans isomers) are achiral molecules with double bonds as a stereogenic centers. They differ from one another only in the way the atoms are positioned in space.



Isocrotonic acid **Crotonic acid**



Oleic acid



Elaidic acid

About 40 % of medicines are chiral; they are composed of several stereoisomers but only one isomer is therapeutically effective. Other isomers are ineffective and even dangerous for the health. In 1956 sedative thalidomide was introduced to the European market place. Immediately it became popular with pregnant women to control morning sickness. About the same time a number of congenitally deformed babies increased. The most seriously deformed babies were born with seal limbs (figure 7). Thalidomide had been carefully tested. It was proved that it is a molecule that exists as two optical isomers (figure 8).

Figure 7 — A babies with seal limbs

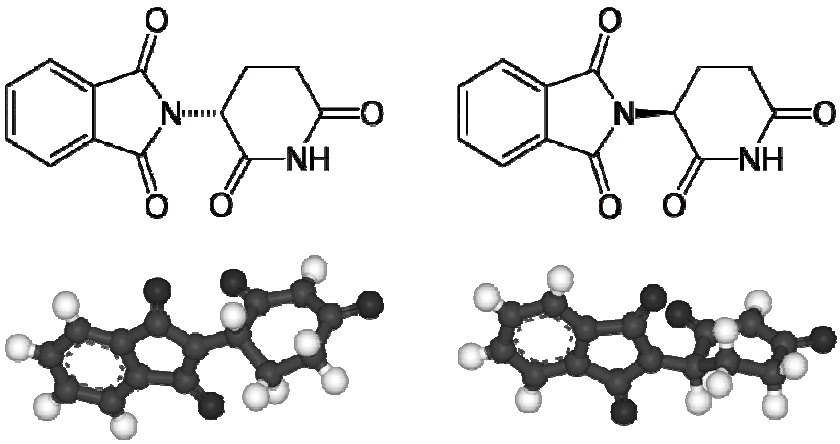


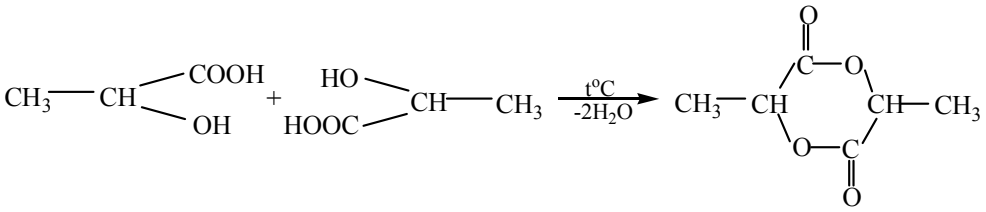
Figure 8 — Optical isomers of thalidomide

It was determined that one of its enantiomer was medically effective, but another was a teratogen and gave such a striking negative side effects. In 1998 the Food and Drug Administration (FDA) approved thalidomide for use in treating leprosy symptoms. Studies are also being conducted to determine the effectiveness of thalidomide in treating symptoms associated with AIDS, Behchet disease, lupus, Sjogren syndrome, rheumatoid arthritis, inflammatory bowel disease, macular degeneration, and some cancers.

1.3 Specific properties of hetero- functional compounds

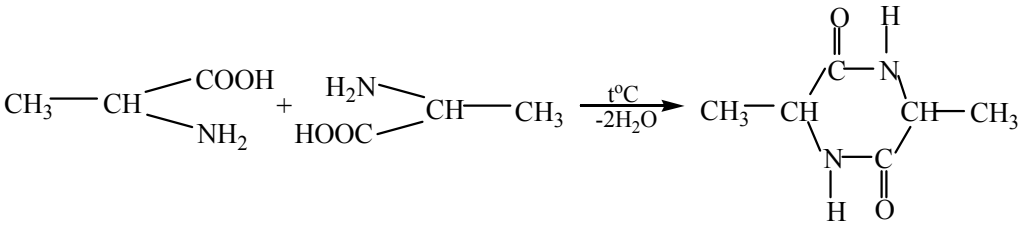
Specific chemical properties of hetero functional compounds are the result of different functional groups mutual affection. The groups effect each other by minus inductive effect (– I-effect) thus they all are electron withdrawing groups. Inductive effect falls rapidly with distance therefore only α, β and γ-location of substituents is responsible for specific properties of heterofunctional compounds.

α-Location of substituents is responsible for intermolecular cyclization in α-amino- and α -hydroxy acids. For example, heating of lactic acid results in formation of cyclic diester named *lactide*:



Lactic acid **Lactide of lactic acid**

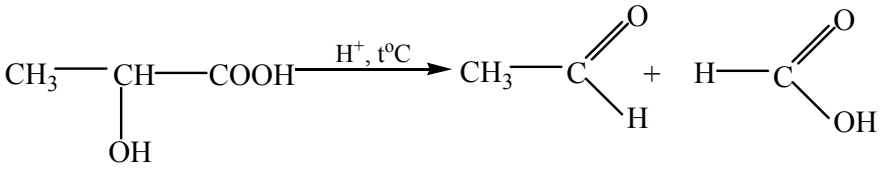
Heating of α-amino propanoic acid (for example, α-alanine) results in formation of cyclic diamide named *diketopiperozine:*



α-Alanine **Diketopiperozine**

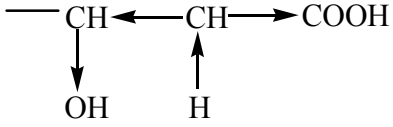
The formation of lactides and diketopiperozines is energetically favored due to high stability of six membered cycles.

Under heating in a strong acid medium α-hydroxy acids undergo decomposition into formic acid and an aldehyde:

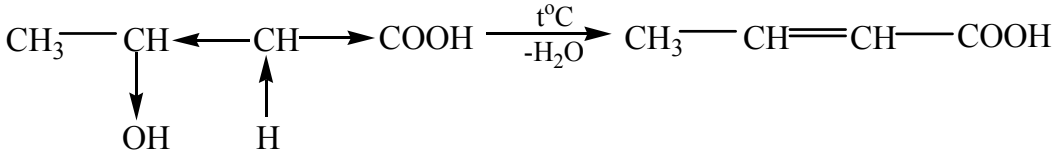


Lactic Acid **Acetaldehyde** **Formic Acid**

β-Location of functional groups in hydroxy acids is responsible for high acidity of CH-center which is situated between carboxyl and hydroxyl groups. These functional groups are electron-withdrawing substituents hence they enhance acidity of CH-acidity center:

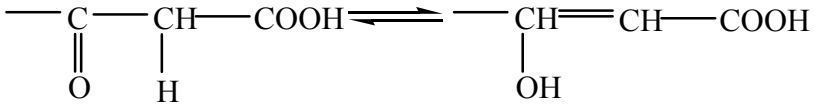


As the result β-location is responsible for H_2O and NH_3 elimination in amino- and hydroxy acids. The process runs under heating:



β-Hydroxy Butyric Acid **Crotonic Acid**

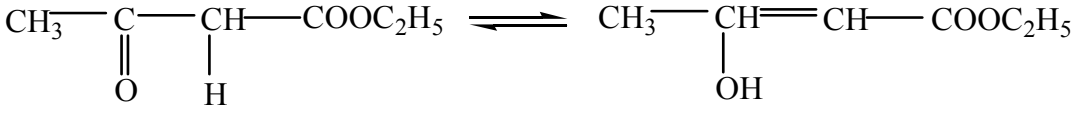
β-Location of functional groups is responsible for keto-enol tautomerism in oxo acids. They may exist as an equilibrium mixture of two forms, called *the keto form* and *the enol form.* The two forms differ in location of a proton and a double bond:



Keto form **Enol form**

This type of structural isomerism is called tautomerism (from Greek *tauto*, the same and *meros*, part). The two forms of oxo acids are called *tautomers*.

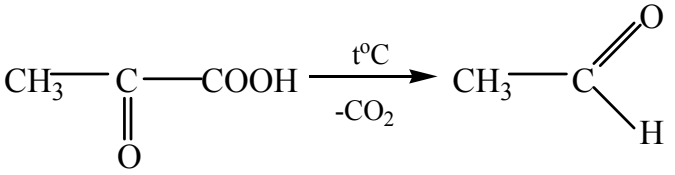
Most carbonyl compounds exist mainly in the keto form. Acetone, for example, is 99.9997 % on the keto form, with only 0.0003 % of the enol present. The main reason for the greater stability of the keto form is that the C=O plus C-H bond energy present in the keto form is greater than the C=C plus O-H bond energy of the enol form. However there are some carbonyl compounds that exhibit the greater portion of enol form. For example, the acetoacetic ester (ethyl ester of acetoacetic acid) is a mixture that contains 92.5 % of keto form and 7.5 % of enol form at equilibrium:



Keto form (92.5%) **Enol form (7.5%)**

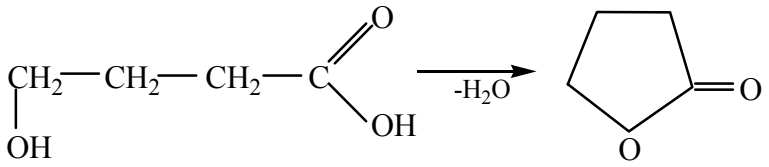
The enol form in acetoacetic ester is stabilized by π,π-conjugation of carbon, carbon double bond with carbonyl group. The acetoacetic ester gives reaction typical both for carbonyl compound and unsaturated hydrocarbons.

α- and β-Location of substituents promotes *decarboxylation* of carboxylic acids:

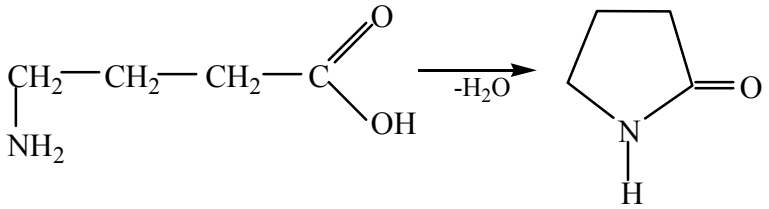


Pyruvic acid **Acetaldehyde**

γ- Location of functional groups in hydroxy and amino acids is responsible for intramolecular cyclization which results in formation of cyclic esters lactones and cyclic amides lactimes:



γ-Hydroxy Butyric Acid **γ – Butyro lactone**



γ-Amino Butyric acid **γ – Butyro lactam**

These reactions are favored energetically due to high stability of five membered cycles.

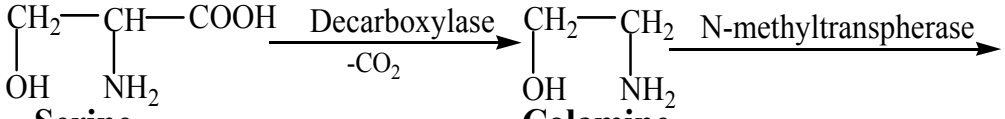
1.4 Amino alcohols and their biological functions

Amino Alcohols involved in metabolic processes in vivo are:

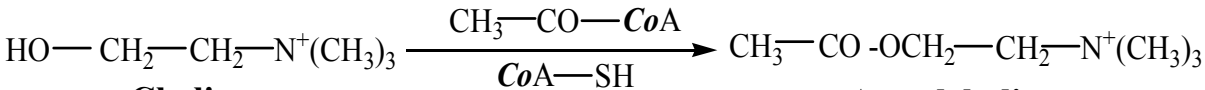
- colamine;
- choline;
- catecholamines (dioxyphenylamine, adrenaline, noradrenaline).

Colamine and choline are contained in complex phospholipids; they are compartments of cell membranes. In vivo they are synthesized from α-amino acid serine.

Pathway of Serine Metabolism

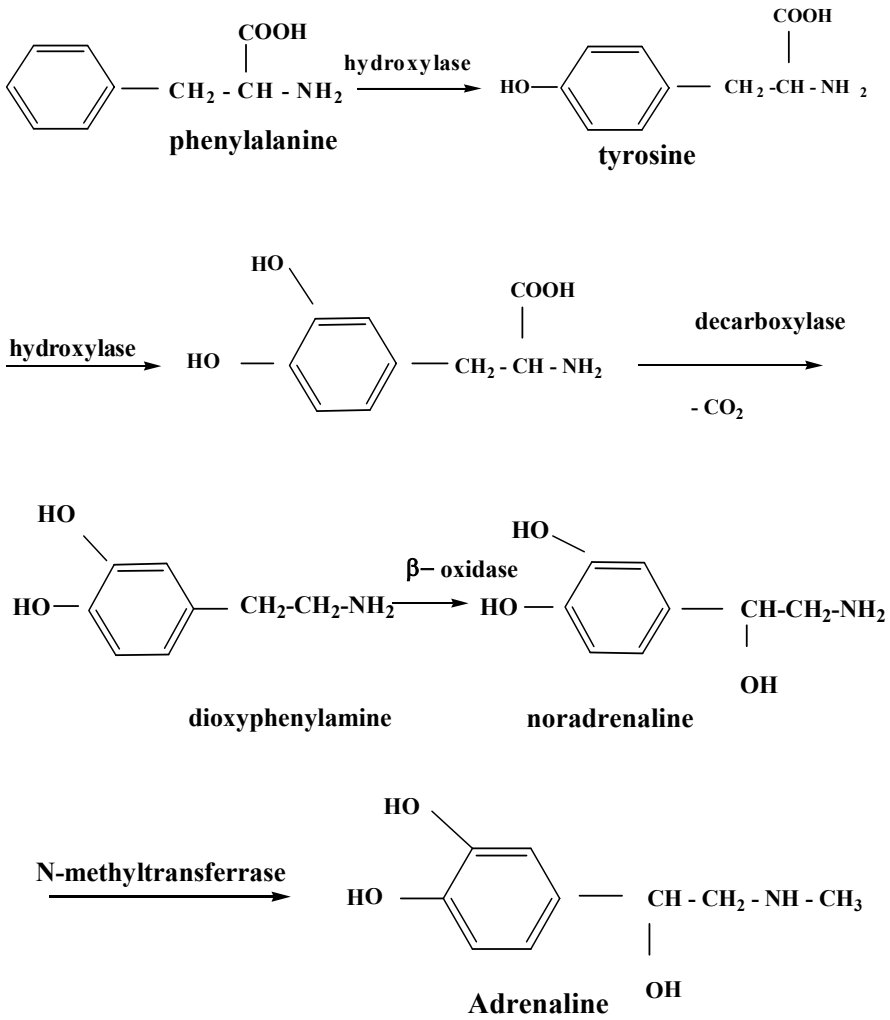


Serine **Colamine**



Choline **Acetylcholine**

Catecholamines are the products of phenylalanine metabolic pathway:



Adrenaline and noradrenaline are hormones which are secreted by adrenal gland. If you experience a sudden fright, a trace of adrenaline immediately flows and the result include a strengthen heartbeat, a rise in blood pressure, and a release of glucose into circulation from storage – all of which get the body ready to respond to the threat. Some people need to get their adrenaline flowing. Usually they go into extreme kinds of sport (alpinism, jumping with parachutes and so on).

1.5. Laboratory Work

Aliphatic heterofunctional compounds

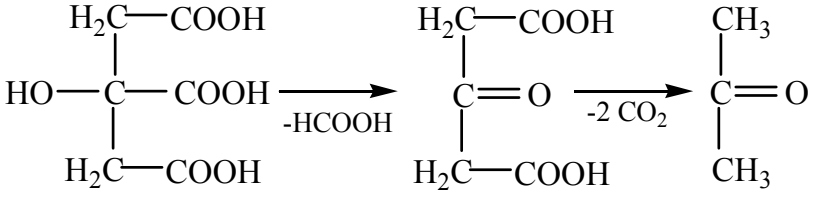
Test 1. Lactic acid decomposition catalyzed by concentrated sulfuric acid.

Pour 1 mL of lactic acid into a test tube and add 1 mL of concentrated sulfuric acid into it. Heat a mixture up to the boiling point. Try to ignite a liberated carbon monoxide. Write the equation for a fulfilled reaction.

Test 2. Citric acid decomposition.

Put some citric acid crystals into a dry test tube and treat them with 10 drops of concentrated sulfuric acid. Heat the prepared mixture with the help of spirit-lamp and use a gas-removing tube to pass the eliminated gas through barium hydroxide solution. After a solution turns turbid that proves CO_2 elimination, insert the gas-removing tube into a basic iodine solution. When you prepare iodine solution treat it with some drops of NaOH solution. Pay attention that iodine turns colorless in basic medium. Precipitation of pale yellow crystals gives evidence that acetone is the final product of citric acid thermal decomposition.

Citric acid is α-hydroxy acid, which undergoes decomposition under heating catalyzed by concentrated sulfuric acid according to the equation:



Citric acid **Acetone**

Test 3. Test reaction for α –hydroxy acids with iron (III) chloride reagent.

Pour 0.5 mL of 5 % phenol solution into a test tube and treat it with 1-2 drops of 1 %-$FeCl_3$ solution. After a solution turns violet, treat it with 1-2 drops of lactic acid. What can you see? A solution changes its color when α-hydroxy acid displaces phenol in a complex compound according to the scheme:

$$\textbf{Phenol} \xrightarrow{FeCl_3} \textbf{Fe}^{3+}_{\text{(phenol)}} \xrightarrow{\text{Lactic acid}} \textbf{Fe}^{3+}_{\text{(lactic acid)}},$$

where $\textbf{Fe}^{3+}_{\text{(phenol)}}$ and $\textbf{Fe}^{3+}_{\text{(lactic acid)}}$ are complexes of iron (III) with phenol and lactic acid respectively.

Test 4. Preparing of Pheling's reagent.

Mix 0.5 mL of 2 M copper (II) sulfate solution with 0.5 mL of 2 M sodium hydroxide solution. Treat the prepared precipitate with 3 % sodium potassium tart- rate solution. Heat the mixture up to the boiling point. What can you see?

Test 5. Preparing of barium citrate salt.

Put several crystals of citric acid into a dry test tube and dissolve them in distilled water. Neutralize a prepared solution by 10% ammonia solution and treat it with 0.5 mL 5 %-$BaCl_2$ solution. Heat the prepared mixture up to the boiling point. What can you see? Write an equation for the reaction occurred. Pay attention that the prepared precipitate is soluble in cold water.

Test 6. The evidence of two carboxyl groups in tartaric acid molecule.

Pour 2-3 drops of 15% tartaric acid solution into a test tube and treat it with 2 drops of 5 %-KOH solution. Stir a mixture. Cool a test tube with cold tap water and rub a test tube with a glass stick. After white crystals of acidic tartrate

precipitate from the solution dissolve them in 5-7 drops of KOH solution. Dissolving process occurs because neutral salt of the tartaric acid is readily dissolved in water. Write the equations of the reactions occurred.

1.6 Exercises for the self-control

1. Define and describe the following terms:
(a) stereogenic center;
(b) chiral molecule;
(c) enantiomers;
(d) diastereomers;
(e) plane of symmetry;
(f) racemic mixture.

2. Which of the following substances can exist in optically active forms?
(a) 2,2-dichloropropane;
(b) 1,2-dichloropropane;
(c) oxaloacetic acid;
(d) lactic acid;
(e) choline;
(f) malic acid.

3. Draw the Fisher projections for optical isomers of the following compounds:
(a) α-Alanine;
(b)(b) Lactic acid;
(c) Tartari acid;
(d) Threonine.

Mark the stereogenic centers with asterisks.

4. Write the formulas for the keto and enol forms of α-ketoglutaric acid. Explain a high content of enol form in a substance.

5. Write an equation for the decarboxilation for α-amino-β-hydroxypropionic acid.

6. Write an equation for the γ-aminohexanoic acid lactime preparing.

7. Write an equation for the γ-hydroxypentoic acid lactone preparing.

CHAPTER 2

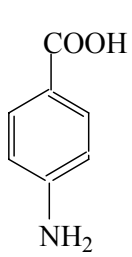
HETEROFUNCTIONAL AROMATIC AND HETEROAROMATIC COMPOUNDS

After reading this chapter, you should be able to:

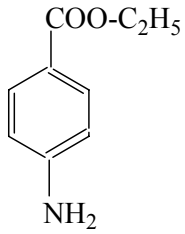
- discuss heterofunctional aromatic compounds that are derivatives of p-amino benzoic, sulfanilic and salicylic acids; give the examples of their application in medicine;
- review aromatic heterocycles with one nitrogen atom, such as pyrrole, indole, pyridine and quinline; give the examples of their bioactive compounds that are involved into metabolic processes or applied as drugs;
- review aromatic heterocycles with two nitrogen atoms, such as imidazole, pyrazole, pyrimidine and purine; give the examples of their bioactive compounds that are involved into metabolic processes or applied as drugs;
- define tautomerism and its types (keto-enol, prototropic and lactim-laktam);
- be able to describe tryptophan metabolic pathways;
- define purine alkaloids (theobromine, caffeine, theophilline) and their application in medicine as drugs.

2.1 Heterofunctional aromatic compounds

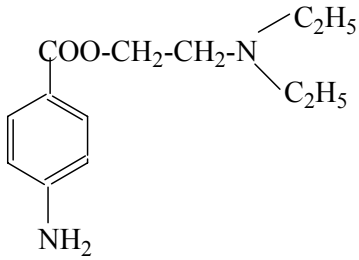
The recent years are characterized by the rapid development of new technologies and assays for new drugs production. The discovery of new classes of chemical compounds for fighting numerous diseases is predominated by studying their chemical structure and physiochemical properties. Never the less the groups of medicines, that are traditionally applied for treating people, are of a big practical use. Among them are medicines that contain benzene ring. Let us start to review the benzene ring containing drugs beginning from the derivatives of *para-amino benzoic acid (PABA):*



PABA



Anesthesine

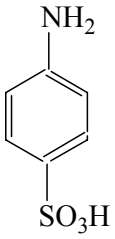


Novocain

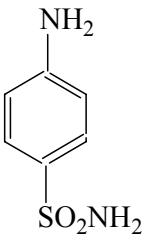
Anesthesine and *novocain* are used as local anesthetics, applied to desensitize a particular region of the body to pain.

The introduction of the *sulfa drugs* in the 1930s hailed the beginning of modern drug therapy. Before their introduction, even a minor bacterial infection could become potentially life threatening. Because no one understood how they

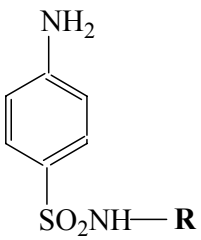
worked, at first, people, even physicians, considered sulfa drugs as almost magical. Sulfa drugs are the derivatives of *sulfanilic acid*, and they are named *sulfanilamides.* Sulfanilamide was the first drug of this group. It was synthesized in 1906 and used as a dye. Only in 1935 antibacterial activity of sulfanilamide was discovered. Nowadays more than 100 sulfanilamides are produced.



Sulfanilic acid

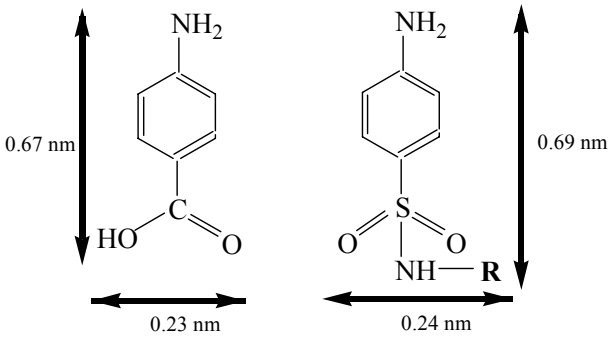


Sulfanilamide



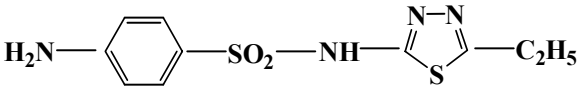
General formula of sulfanilamides

Mechanism of antibacterial activity. Sulfanilamides are drugs that exhibit high antibacterial activity. Bacteria require PABA to biosynthesize folic acid, necessary for their living. Sulfanilamides and PABA are so similar that bacteria mistake them for PABA.

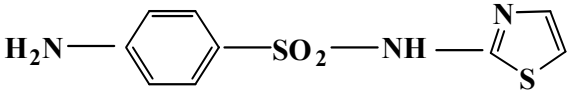


In the body sulfanilamides retard biosynthesis of folic acid, thus decreasing bacterial growth and allowing the body's natural defenses to effect a cure.

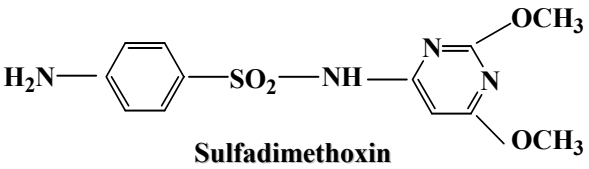
Here is the list of sulfanilamides with prolongated activity:



Aethasol

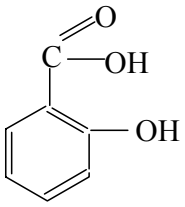


Norsulfasol

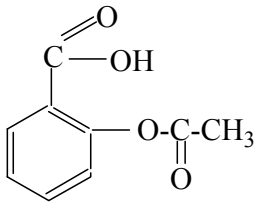


Sulfadimethoxin

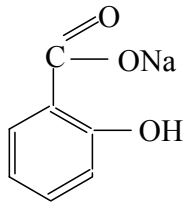
The derivatives of *salicylic acid* are applied in different branches of medicine. The most popular drug of this group is *aspirin or acetylsalicylic acid*. Salicylic acid and its derivatives are mild non-addictive analgesics. Aspirin is also used to improve reological properties of blood.



Salicylic acid

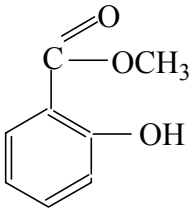


Aspirin

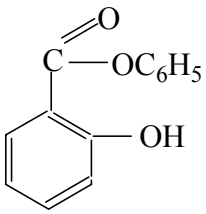


Sodium salysilate

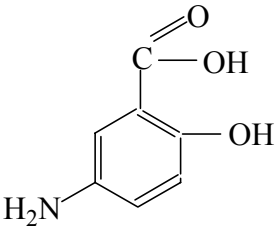
Other derivatives of salicylic acid that are applied in modern medicine are:



Methyl salysilate



Phenyl salysilate



p-Amino salicylic acid

Phenyl salysilate is applied for disinfection of intestinal tract; *p-amino salicylic acid* is used as anti-TB drug.

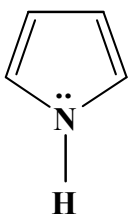
2.2 Aromatic heterocycles with one nitrogen atom

From an organic chemist's point of viewpoint, heteroatoms are atoms other than carbon or hydrogen that may be present in organic compounds. The most common heteroatoms are oxygen, nitrogen, and sulfur. In heterocyclic compounds, one or more of these heteroatoms replaces carbon in a ring.

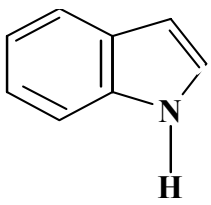
Heterocycles form the largest class of organic compounds. In fact, most natural products and drugs contain heterocyclic rings; indeed, well over half of all organic chemical publications deal in one way or another with heterocycles. Much more important are the aromatic heterocycles that are N-containing heteroaromatic compounds.

Five-membered Cycles with one Nitrogen Atom

Now let us examine five-membered heteroaromatic compounds *pyrrole* and *indole*.

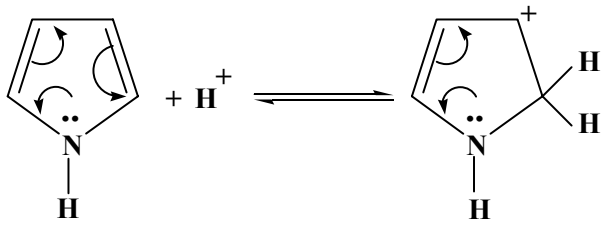


Pyrrole

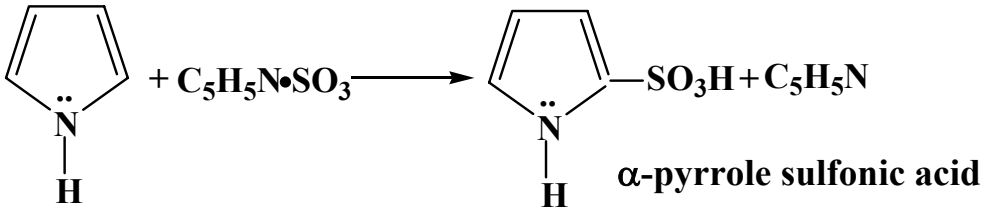


Indole

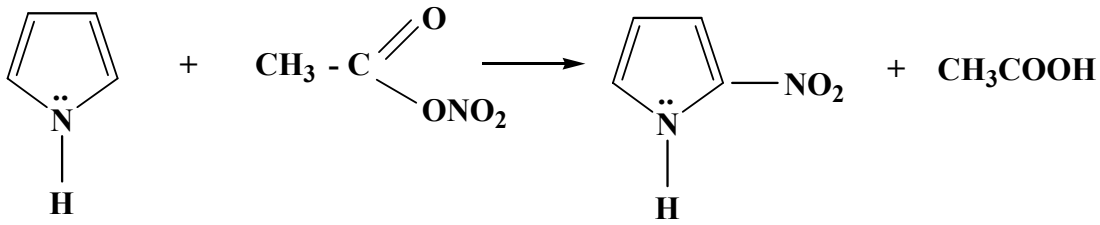
In pyrrole, the unshared electron pair of nitrogen is part of the aromatic 6 π electron system. Its protonation would destroy the aromatic system, thus losing aromaticity (*acidophobic compound*). Hence pyrrole is a very weak base, in very strong acids it is protonated on carbon:



Pyrrole is much more reactive than benzene toward electrophilic substitution. Here are typical examples:

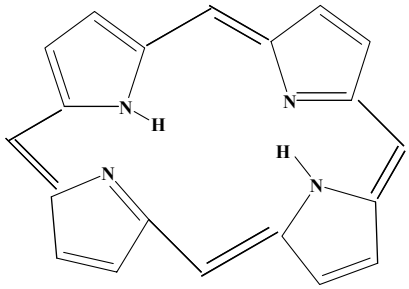


α-pyrrole sulfonic acid

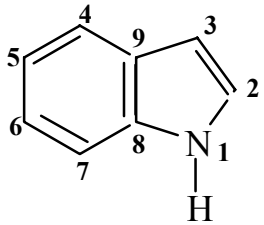


α-nitro pyrrole

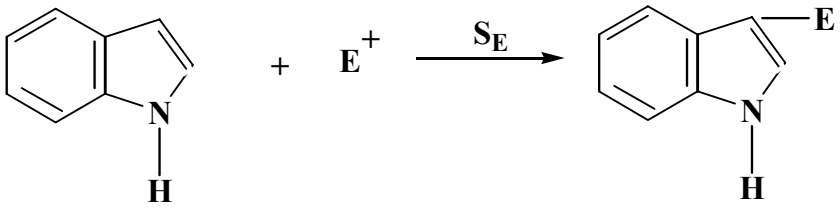
Porphine is a compartment of hemoglobin, cytochromes and chlorophyll. Porphine contains four pyrrole rings in conjugation; stabilization energy is 840 kJ/mol.



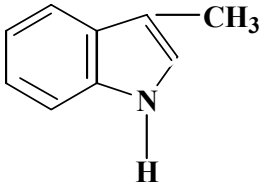
In indole molecule a benzene ring is fused to pyrrole. Electrophilic reagents are directed toC-3 (β-position):



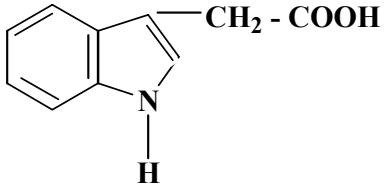
The scheme of electrophilic substitution can be represented as follows:



The indole ring occurs in several important natural products. Here are the examples:

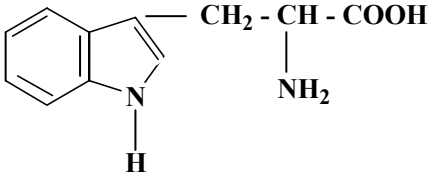


Skatole is a final product of decay

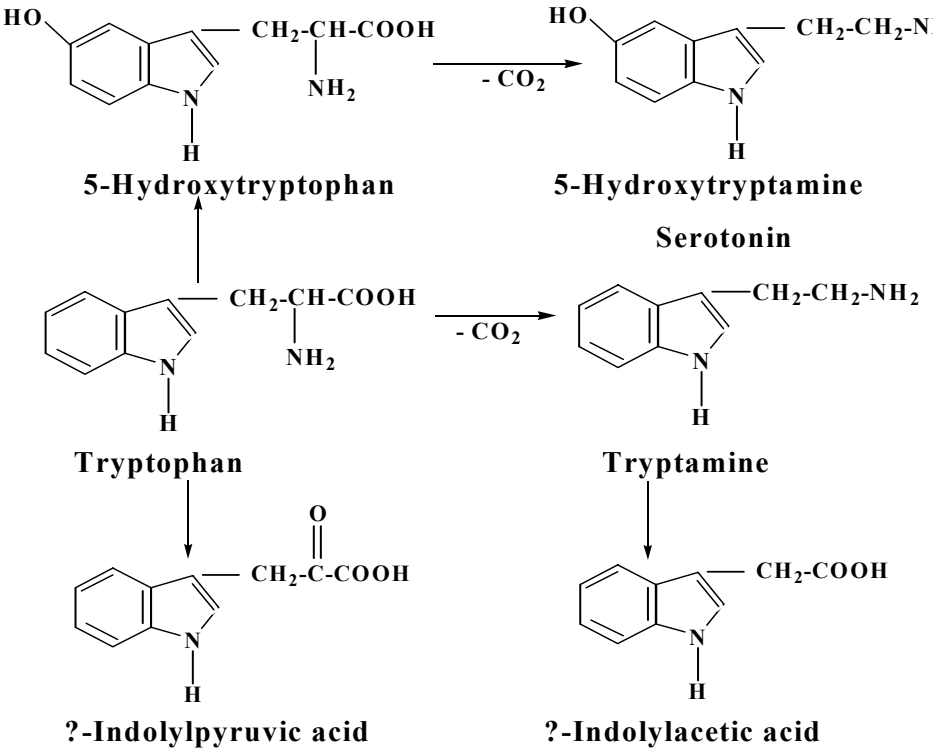


3-Indolyl acetic acid is a plants growing hormone

Tryptophan is the essential amino acid involved in proteins biosynthesis:

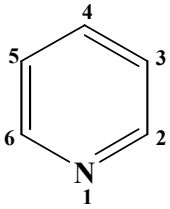


Tryptophan metabolic pathways

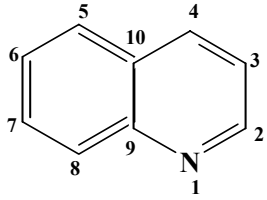


Serotonin is a neurotransmitter and vasoconstrictor active in the central nervous system. The disturbance of its metabolism may course schizophrenia.

Among six-membered cycles with one nitrogen atom the most important are pyridine and quinoline:



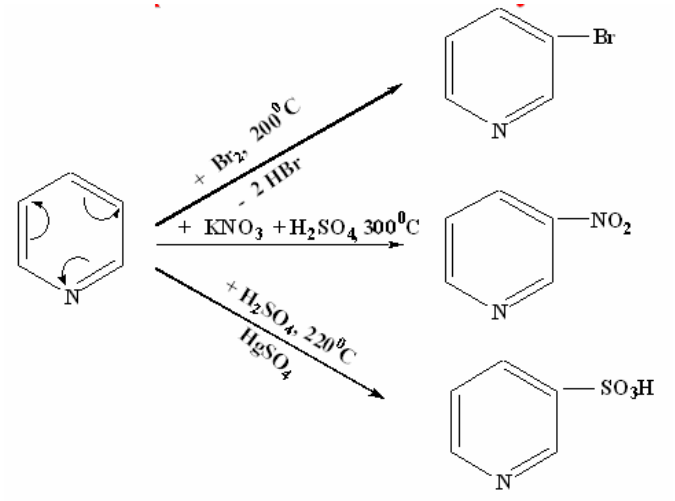
Pyridine



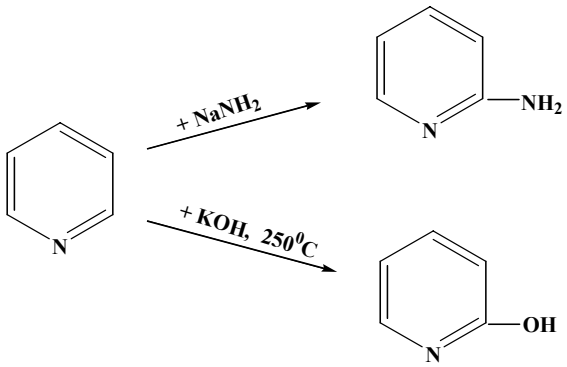
Quinoline

Pyridine has a structure similar to that of benzene, except that one CH unit is replaced by a nitrogen atom. Because of the similarities in bonding, pyridine resembles benzene in shape. It is aromatic, and tends to undergo substitution rather than addition reactions. Nitrogen atom attracts aromatic 6 π electron system toward.

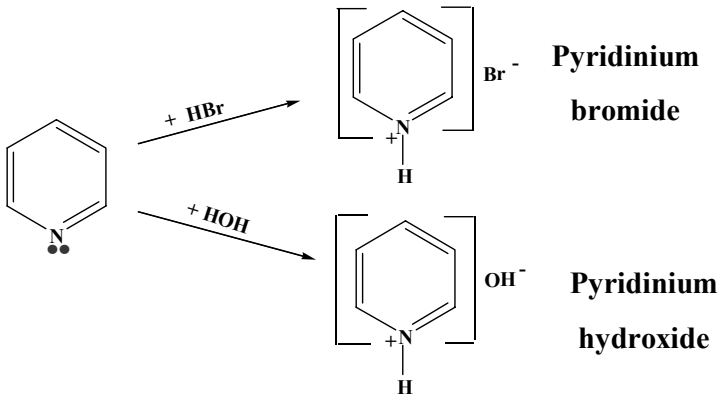
Itself. thus deactivating pyridine cycle to electrophilic substitution reactions. They can run under drastic conditions:



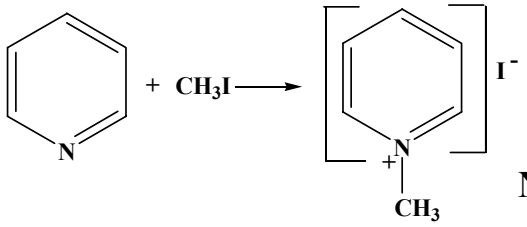
Although resistant to electrophilic substitution, pyridine undergoes nucleophilic substitution. The pyridine ring is partially positive (due to electron withdrawal by the nitrogen) and is therefore susceptible to attack by nucleophiles. Here are two examples:



Pyridine is a weakly basic tertiary amine, with $pK_a = 5.29$. It is much weaker base than aliphatic amines ($pK_a \approx 10$). Pyridine reacts with strong acids to form pyridinium salts and hydroxides:

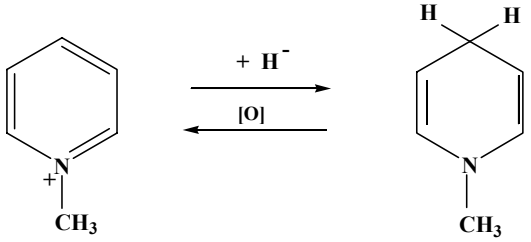


Nitrogen atom in pyridine exhibits nucleophilic properties and undergoes alkylation that results in the formation of alkylpyridinium salts:



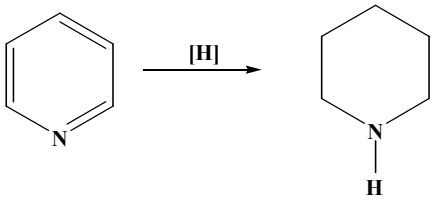
N-methylpyridinium iodide

Due to positively charged nitrogen atom these cycles are able to add nucleophilic reagents (for example hydride-ion H^-):



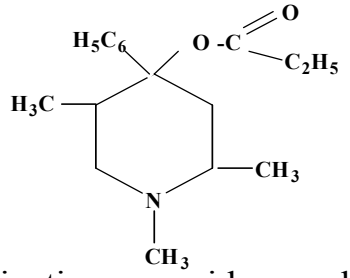
1,4-dihydro-N-methyl pyridine

Pyridine is readily reduced to piperidine:

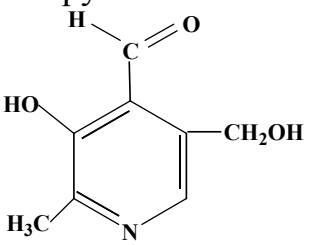


Piperidine

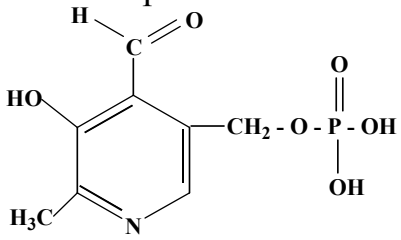
Promedole (narcotic analgesic) is a derivative of piperidine:



Bioactive pyridine derivatives are widespread in nature:

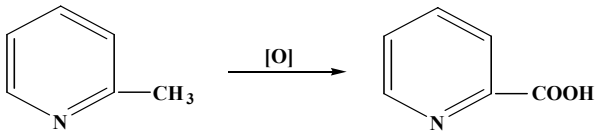


Pyridoxine (vitaminB_6)

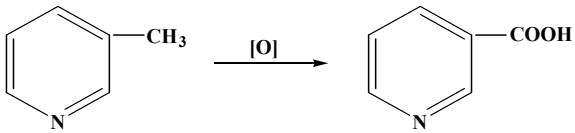


Pyridoxine phosphate (a coenzyme)

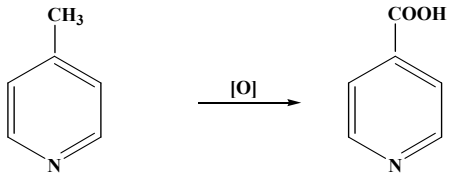
Pyridine ring is contained in three carboxylic acids, which are the products of picolines side-chain oxidation:



α-Picoline **Picolinic acid**

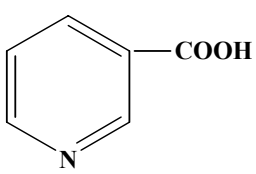


β-Picoline **Nicotinic acid**

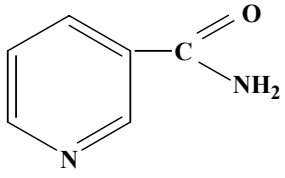


γ-Picoline **Isonicotinic acid**

Nicotinic acid and nicotinamide are the components of vitamin PP essential in the human diet to prevent the disease *pellagra*:

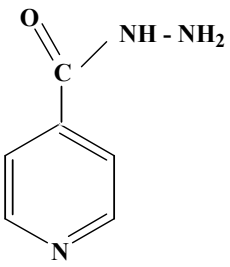


Nicotinic acid

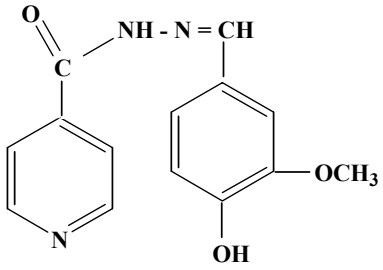


Nicotinamide
(main component
of coenzymes NAD and NADP)

The derivatives of isonicotinic acid are applied as drugs for the treatment of tuberculosis (TB):



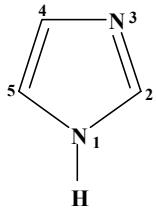
Izoniaside
Hydrozide of isonicotinic acid



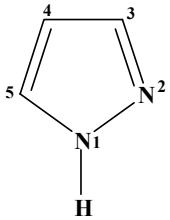
Phthivaside
(a product of izoniaside condensation with vanillin**)**

2.3 Aromatic heterocycles with two nitrogen atoms

Five-membered cycles with two nitrogen atoms are named azoles:

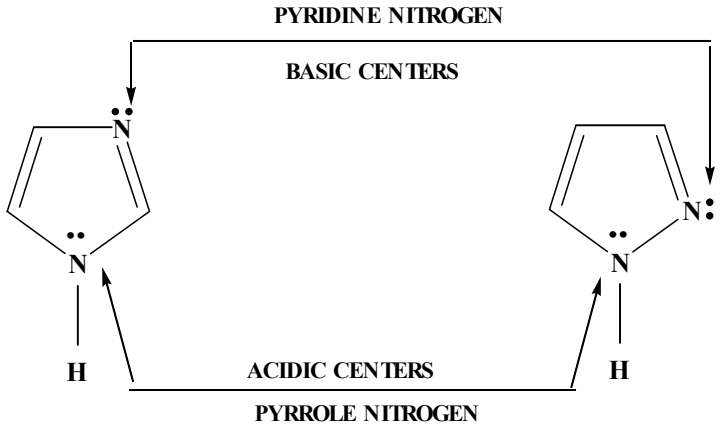


Imidazole



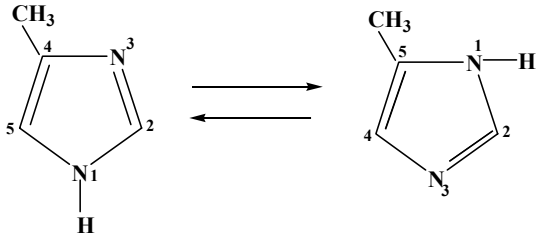
Pyrazole

Azoles exhibit acid-base duality because contain both NH-acid center and ammonium basic center (N-3):

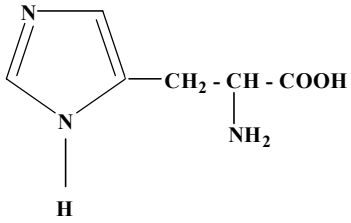


According to Brønsted theory amphoteric properties of organic compounds are responsible for hydrogen bond formation. Protons can easily migrate among associated molecules, which give rise to *protortopic tautomerism:*

Protortopic tautomers are structural isomers that differ in location of proton and a double bond:



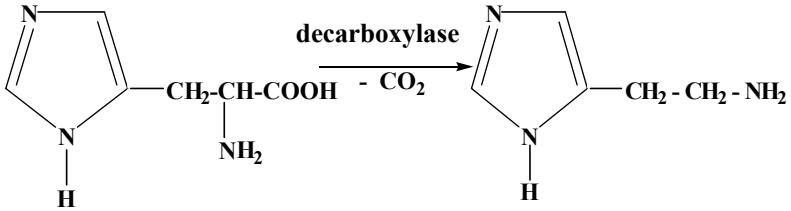
Imidazole ring systems occur in nature. For example, its skeleton is present in the amino acid histidine:



Histidine

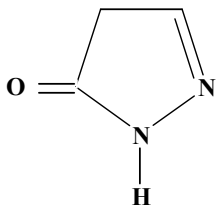
Histidine is found abundantly in hemoglobin; it has been used in the treatment of rheumatoid arthritis, allergic diseases, ulcers & anemia. A deficiency can cause poor hearing.

Decarboxylation of histidine gives biological amine histamine, which is a hormone controlling digestion. It is also responsible for allergic reactions:

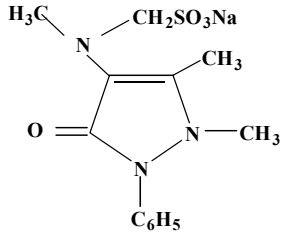


Histamine

Pyrazole and its derivatives do not occur in nature; they are applied to produce non-narcotic analgesics:

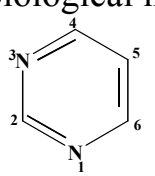


Pyrazalone-5

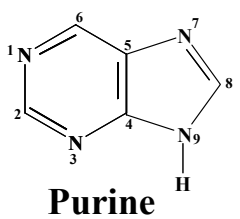


Analgine

Among *six-membered cycles* with two nitrogen atoms pyrimidine and purine are of most biological importance:

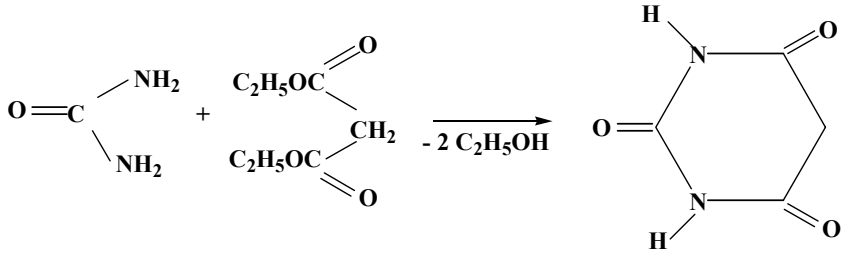


Pyrimidine



Purine

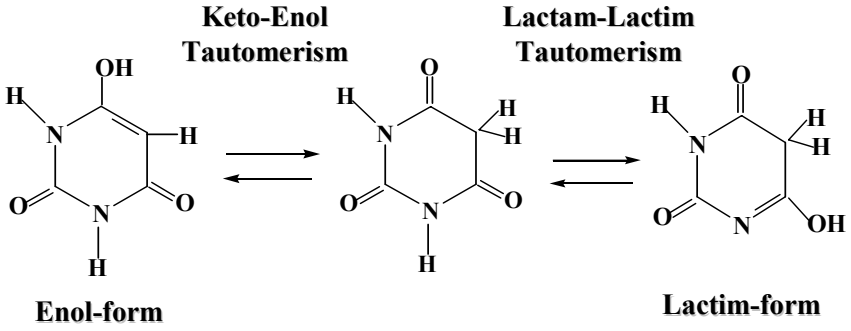
Their hydroxyl derivatives exhibit rather strong acidic properties. For example, 2,4,6-trihydroxy pyrimidine (barbituric acid) is stronger acid than CH_3COOH. Barbituric acid was first synthesized in 1863 by Adolf von Baeyer by condensation of malonic ester with urea:



Formamide **Malonic Ester** **Barbituric acid**

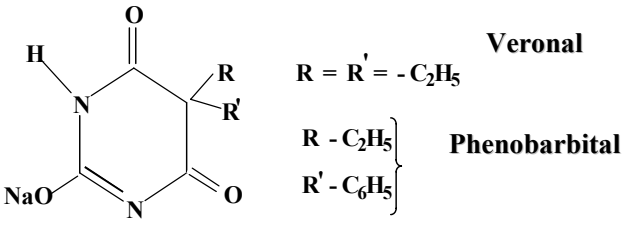
Barbituric acid is a nonsystematic name, and this fact gave rise to different hypothesis that are popular among chemists. Some admitted romantics theorize that von Baeyer was courting a woman named Barbaraand named the compound in her honor. Less romantic chemists came to belief that the acid was named barbituric because he synthesized it on Saint Barbara day (December 4).

Barbituric acid exhibits keto-enol and lactim-laktam of tautomerism. It was proved that enol tautomer is most acidic. Here you can see three tautomers of barbituric acid at equilibrium state:



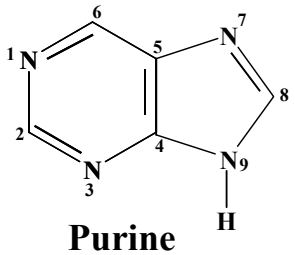
Enol-form **Lactim-form**

Barbiturates are the derivatives of barbituric acid that are wide applied in modern medicine. They exhibit sedative and anticonvulsant effects:



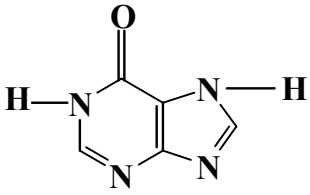
All barbiturates are addictive. Anyone taking them regularly will suffer withdrawal when they discontinue using them. Typically barbiturate addiction takes about six month of regular use.

The purines are another biologically important class of fused-ring heterocycles. They contain a pyrimidine ring fused to an imidazole ring:

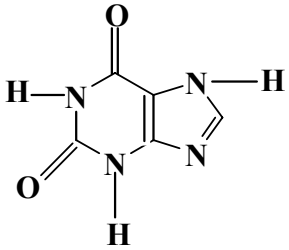


Purine

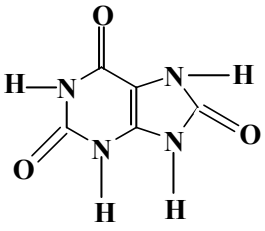
Here the purine hydroxyl derivatives are represented:



Hypoxanthine (6-oxopurine)

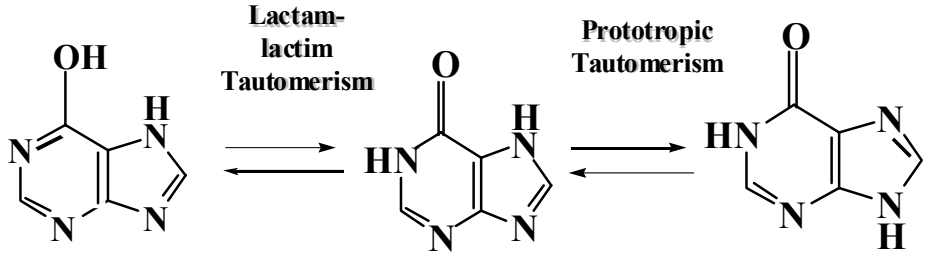


Xanthine (2, 6-dioxopurine)



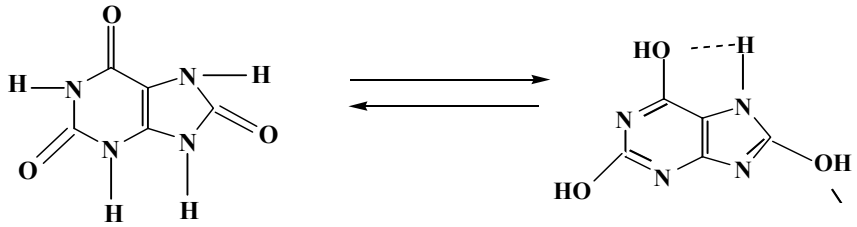
Uric acid (2, 6, 8-trioxopurine)

The purine hydroxyl derivatives exist in several forms due to lactim-laktam and prototropic tautomerism. In this case, Prototropic tautomerism is a migration of proton between N-7 and N-9 (ten shifts per second). Hypoxanthine tautomerism is represented in the following scheme:



Lactim-form **Lactam-form**

Uric acid is present in the urine of all carnivores and is the main product of nitrogen metabolism in the excrement of birds and reptiles. Its lactam and lactim forms exist at equilibrium:

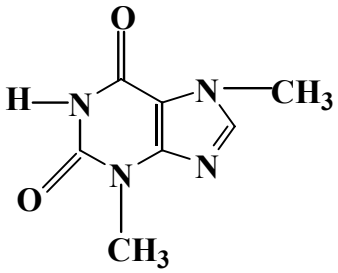


Lactam form **Lactim form**

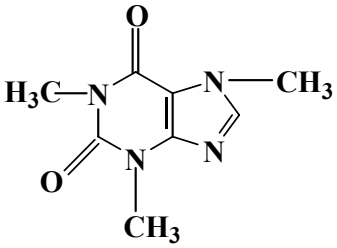
Lactim-form contains two OH-acidic centers. It's a diprotic acid. Urates are salts of uric acid. Such a disease as the gout is the result of sodium urates in joints and tendons.

Alkaloids. Alkaloids are basic N-containing compounds of plant and animal origin, which are extremely physiologically active. Purine alkaloids are xanthene derivatives. They are wide applied in medicine as drugs.

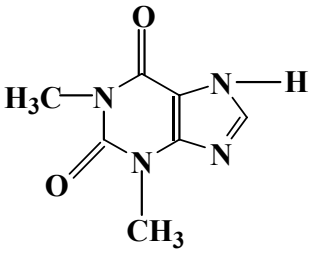
Purine alkaloids



Theobromine
(contained in cocao)



Caffeine
(contained in coffee, tea and cola beverages)



Theophilline
(contained in tea)

Caffeine is applied in medicine to increase blood pressure and stimulate heart activity. Theobromine and theophilline are diuretics.

2.4 Laboratory work

Hetero functional aromatic and heterocyclic compounds

Test 1. Nicotinic acid interaction with Cu (II) acetate.

Interaction of nicotinic acid with Cu (II) acetate in acetic acid medium results in Cu (II) nicotinate precipitation. Put 5-10 mg of nicotinic acid crystals into a test tube and dissolve them in 15-20 drops of 10 % acetic acid solution under heating. Heat a prepared solution up to the boiling point and treat it with 15-20 drops of 5 % Cu (II) acetate solution. Pay attention that a solution becomes turbid. Blue precipitate of nicotinic acid salt appears in several minutes.

Test 2. Solubility of salicylic acid and its salts.

Put some crystals of salicylic acid into a test tube and dissolve them in 2-3 ml of distilled water. Is salicylic acid soluble in water or not? Treat a prepared mixture with sodium hydroxide solution. What can you see? Is sodium salicylate soluble in water or not? Add some drops of mineral acid to the solution. What can you see? Explain the result. Write the equations for fulfilled reactions.

Test 3. Aspirin hydrolysis.

Put some aspirin crystals into a test tube and try to dissolve them in 5-6 drops of distilled water. What can you say about aspirin solubility in water? Separate a prepared solution into two test tubes and boil a mixture in the first test tube during 1-2 min. Cool the solution by tap water. Treat the solutions in both test tubes with 2-3 drops of iron (III) chloride. What can you see? Explain the result. Write the equation for aspirin hydrolysis.

2.5 Exercises for the self-control

1. Write the equations of chemical reactions for pyridine sulfonation and hydroxylation. Name the mechanism of the given reactions.

2. Write the equation for tryphtophan decarboxylation. What enzyme is involved into this process? Name a prepared bioactive amine.

3. Why imidazole and pyrazole molecules are associated under physiological conditions? Write formulas for imidazole's cluster.

4. Describe hypoxanthine lactam-lactime and prototropic tautomerism.

5. Write the equation for aspirin acid-catalyzed hydrolysis. Name the products. How to check up its quality?

6. Write structural formulas for nicotinic acid and its amide. What vitamin is composed of these substances?

7. Write a structural formula for uric acids. Describe its lactam-lactim tautomerism. What disease is initiated by disturbance of urates metabolism?

8. Write structural formulas for xanthene and purine alkaloids (caffeine, and thiobromine).

CONTENT

LITERATURE

1. Morrison and Boyd. Organic chemistry. Fourth edition. 1987. — P. 1267–1286.

2. Harild Hart and other. Organic chemistry (A Short Course). — Tenth edition.

3. Schuets Hart. Organic chemistry – Fifth edition. — P. 105–129, 206–208, 229–230, 330, 373.

CLOSSARY

A

Achiral A molecule with a mirror plane of symmetry. Achiral molecules are superimposable on their mirror images.

Alkaloid A physiologically active, heterocyclic amine isolated from plants. Purine alkaloids are xanthene derivatives. They are theobromine (contained in cocao), caffeine (contained in coffee) and theophilline (contained in tea).

Analgesics Drugs that are applied as pain killers. There are two classes of analgesics: (a) those that act at the site of the pain, (b) those that act on the central nervous system to modify the brain's processing of the pain signals.

Analgine A non-narcotic analgesic that is a derivative of five-membered heterocyclic compound named pyrazole.

Anesthesine A local anesthetics, applied to desensitize a particular region of the body to pain. Anesthesine is an ethyl ester of p-amino benzoic acid.

Aspirin (acetylsalicylic acid) A mild non-addictive analgesics that is also used to improve reological properties of blood.

B

Barbiturates Sedative and anticonvulsant drugs that are derivatives of barbituric acid. All barbiturates are addictive. Anyone taking them regularly will suffer withdrawal when they discontinue using them. Typically barbiturate addiction takes about six month of regular use.

C

Chiral The property of a substance that means it is not superimposable on its mirror image. The term *chiral* is used synonymously with optically active in describing a compound.

E

Enantiomers Stereoisomers that are nonsupreimposable mirror images of each other. Also called optical isomers.

D

Diastereomers Stereoisomers that are not mirror images of each other.

D-family, L-family The names of the two optically active families to which substances can belong when they are considered solely according to one kind of molecular Chirality or the other.

H

Heteroatoms Atoms other than carbon or hydrogen.

Heterocyclic compounds Cyclic organic compound in which one or more carbon atoms are replaced with heteroatoms.

K

Ketone Bodies β-Hydroxy butyric acid, acetoacetic acid and acetone.

L

Lactams Cyclic amides.

Lactones Cyclic esters.

M

Meso compound Compounds that are achiral but contain stereogenic centers; such compounds always have a mirror plane of symmetry.

Neurotransmitter A substance released by one nerve cell to carry a signal to the next nerve cell.

Novocain A local anesthetics, applied to desensitize a particular region of the body to pain. Novocain is the β-diethyl amino ethyl ester of p-amino benzoic acid.

O

Optical activity The property of rotating plane-polarized light.

Optically active A substance that rotates plain-polarized light.

P

Plane of symmetry A plane that passes through a molecule in such a way that what is on one side is the exact reflection of what is on the other side.

Plane-polarized light Light composed of waves that vibrate in parallel planes.

Purines Biologically important heterocyclic compounds containing a pyrimidine ring fused to an imidazole ring.

Pyridines Six-membered ring aromatic heterocycles containing one nitrogen atom.

Pyrimidines Six-membered ring aromatic heterocycles containing two nitrogen atoms at ring position 1 and 3.

R

Racemic mixture A 50:50 mixture of enantiomers which is optically inactive.

S

Serotonin Biologically active amine (5-hydroxytryptamine), which is a neurotransmitter in the central nervous system. The disturbance of its metabolism may course schizophrenia.

Stereogenic center (chiral center) A carbon atom to which four different groups is attached.

Sulfanilamides Sulfa drugs with high antibacterial activity that are derivatives of sulfanilic acid.

T

Tautomerism The process of interconversion of tautomers, such as keto and enol forms of a carbonyl compound.

Tautomers Structural isomers that differ in the location of a proton and a double bond.

U

Uric acid An organic acid that is tri oxo purine; it is present in the urine of all carnivores and is the main product of nitrogen metabolism in the excrement of birds and reptiles.

Urates The salts of uric acid. Such a disease as the gout is the result of sodium urate in joints and tendons.

V

Vitamin PP Nicotinic acid and nicotinamide are the components of vitamin PP essential in the human diet to prevent the disease *pellagra*.

Учебное издание

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ХИМИЯ ГЕТЕРОФУНКЦИОНАЛЬНЫХ И ГЕТЕРОЦИКЛИЧЕСКИХ СОЕДИНЕНИЙ
(на английском языке)

Учебное пособие для лабораторно-практических занятий
по курсу биоорганической химии для студентов лечебного факультета,
обучающихся на английском языке

Компьютерная верстка ***А. М. Елисеева***

Подписано в печать 21. 04. 2009
Формат $60\times84^{1}/_{16}$. Бумага офсетная 65 г/м^2. Гарнитура «Таймс»
Усл. печ. л. 2,09. Уч.-изд. л. 2,3. Тираж 100 экз. Заказ № 102

Издатель и полиграфическое исполнение
Учреждение образования
«Гомельский государственный медицинский университет»
246000, г. Гомель, ул. Ланге, 5
Ли № 02330/0133072 от 30. 04. 2004