МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
ХАРКІВСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ

STRUCTURE AND PROPERTIES OF ALDEHYDES AND KETONES. STRUCTURE, PROPERTIES AND BIOLOGICAL SIGNIFICANCE OF CARBOXYLIC ACIDS AND AMINES

Methodical instructions for the 1st-year students' self-work
in biological and bioorganic chemistry

БУДОВА І ВЛАСТИВОСТІ АЛЬДЕГІДІВ І КЕТОНІВ. СТРУКТУРА, ВЛАСТИВОСТІ ТА БІОЛОГІЧНЕ ЗНАЧЕННЯ КАРБОНОВИХ КИСЛОТ ТА АМІНІВ

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

Затверджено
Вченою радою ХНМУ
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Будова і властивості альдегідів і кетонів. Структура, властивості та біологічне значення карбонових кислот та амінів: метод. вказ. для самостійної роботи студентів 1-го курсу з орг. та біоорг. хімії // уклад. Сирова Г.О., О.Л. Левашова, Н.М. Чаленко та ін. – 2-е вид., переробл., випр., доп. – Харків: ХНМУ, 2018. – 16 с.

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STRUCTURE AND PROPERTIES OF ALDEHYDES AND KETONES. STRUCTURE, PROPERTIES AND BIOLOGICAL SIGNIFICANCE OF CARBOXYLIC ACIDS AND AMINES.

1. **Number of hours 4**

2. **Material and methodological support.**

- tables: graphological structure of those; nomenclature of aldehydes, ketones, carboxylic acids; A_N reaction to carbonyl group; mutual transformations of carboxylic acids derivatives; metabolic reactions in the human body;
- models of molecules;
- educational and methodical literature:

1. Biologically important classes of bioorganic connections. Biopolymers and their structural components: Theoretical course of biological and bioorganic chemistry, Module 1 / A. O. Syrovaya, E. R. Grabovetskaya, N. M. Tkachuk, L. G. Shapoval, V. N. Petiunina, S. A. Nakonechnaya. – X.: «Цифровая типография № 1». – 2013. – 183 p.

2. Biological and Bioorganic Chemistry : in two books : Textbook. Textbook 1. Bioorganic Chemistry / B.S.Zimenkovsky, V.A.Muzychenko, I.V.Nizhenkovska, G.O.Syrova; edited by B.S.Zimenkovsky, I.V.Nizhenkovska. – K.: AUP «Medicina», 2017. – 288 p.

3. Lecture notes.

3. Motivational characteristic of the subject

Functional groups of aldehydes and ketones (oxo-group), carboxylic acids (carboxylic group), amines (amino group) are part of biologically active compounds of natural origin such as monosaccharides, amino acids, vitamins, prostaglandins, and many medicinal products. Participation of these compounds in biochemical transformations, metabolism of medicinal products in the organism is provided by the functional groups. Aldol condensation of oxo-compounds is the basis of biosynthesis of citric and N-acetylneuramic acid. Formation of Schiff's base after reaction between oxo-compounds and amines ensures biosynthesis of nonessential amino acids. Carboxylic acids transform in Krebs cycle – main energetical cycle of the organism.

4. Objectives

The study of this topic is necessary for understanding some of the biochemical reactions taking part in metabolic processes in the body (peroxide oxidation of lipids, formation of hydroxy acids from unsaturated acids in the Krebs cycle, etc.), as well as understanding the mechanism of such reactions during the synthesis of drugs and analogues of natural compounds. Competence in this subject is indispensable for the study of the following courses: hydroxo- and hydroxy acids, carbohydrates, lipids, nucleic acids, as well as disciplines: biological chemistry, normal and pathological physiology, pharmacology, and others.

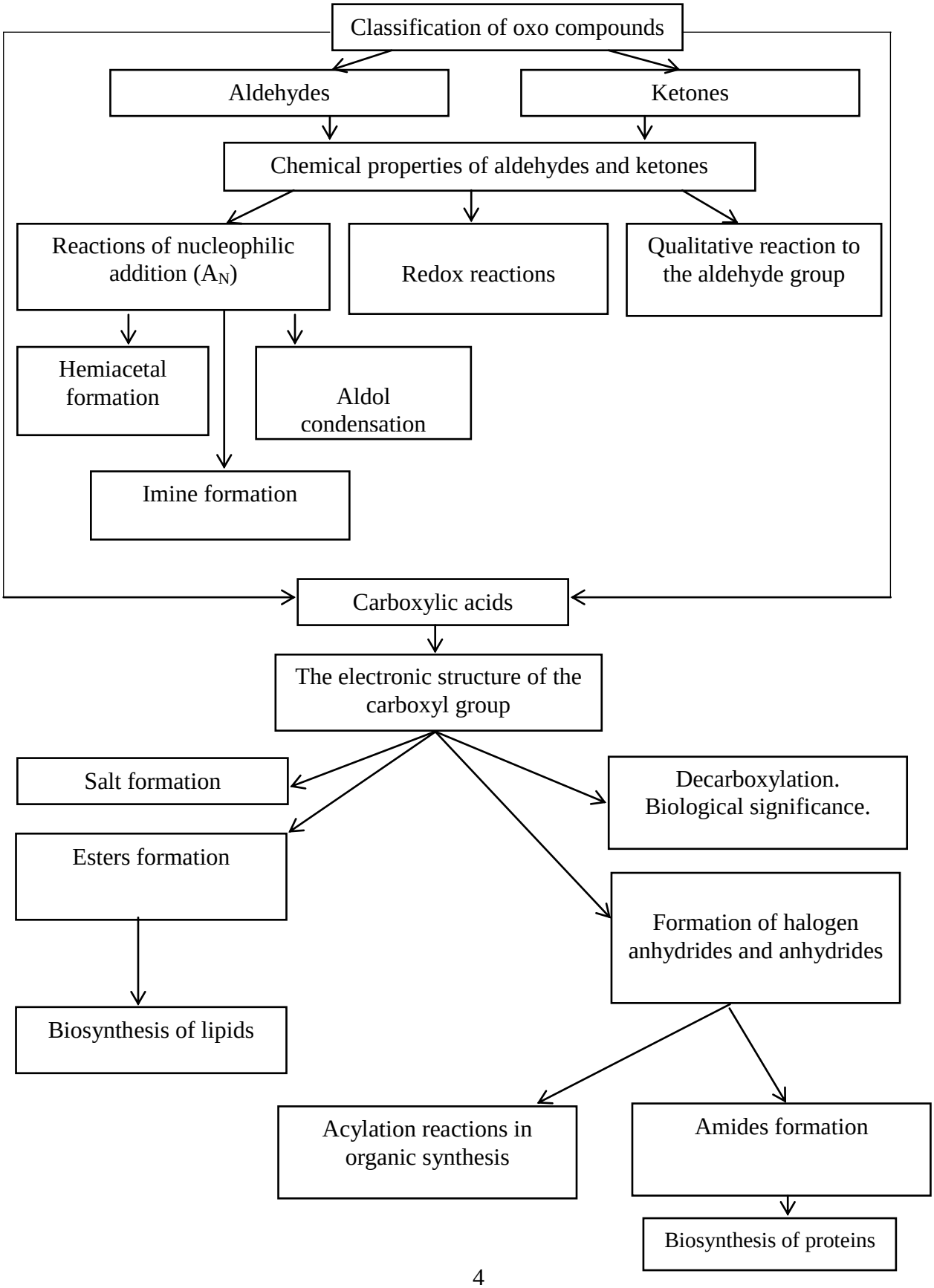
5. Practical skills

1. Apply the relationship of the electronic and spatial structure of functional groups for the chemical properties characteristic of the corresponding classes of organic compounds.

2. To write reactions and describe the mechanisms of reactions that are typical of oxo compounds, carboxylic acids and amines.

3. To master the methods of conducting reactions characteristic for oxo compounds and carboxylic acids.

6. Graph structure of the subject.



7. **Plan of students' work**

№	Stages	Time (min.)	Training and visual aids	Location
1.	Motivation description and plan of topics. Questions and answers	25	Manual	Class room
2.	Incoming control	20	Incoming control tests	
3.	Correction of knowledge and skills of students by solving situational learning tasks (independent work)	95	Methodical instructions for students, lecture notes manual for students' self-work, reference data, tables	
4.	Final control	25	Final control tests	
5.	Analysis and conclusions Home work	15		

Test questions

1. Give the mechanism of ethylene hydrogenation.

2. Describe mechanism of propenoic acid hydration reaction. Explain role of acid catalyst.

3. Write the equation of toluene (methylbezene) nitration. What is the mechanism of this reaction?

4. Explain deactivating and orienting effect of nitrogroup in the molecule of nitrobenzene by the example of bromination reaction.

1. Provide mechanisms of propanol bromination and dehydration. Justify a necessity of acid catalysis.

2. Obtain propionaldehyde ethyl hemiacetal, imine from methylamine and acetaldehyde; malonic acid mono- and diamide.

Teaching tasks

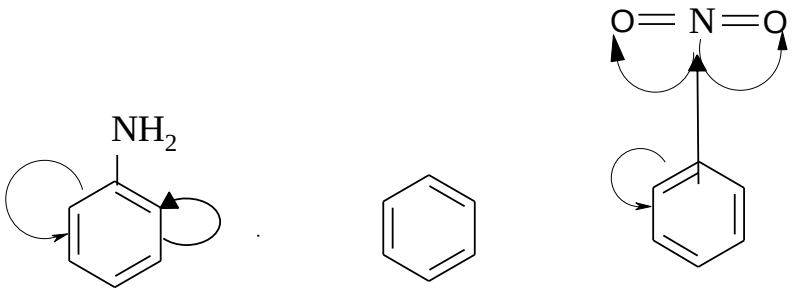
Task №1. Evaluate reactivity of benzene, aniline, nitrobenzene, pyrrol and pyridine electrophilic substitution reactions (S_E-reactions).

Solution. Activity of compounds in S_E-reactions depends on value of electron demcity in aromatic ring (direct dependence). Depending on this reactivity of compounds should be considered with reference with electronic effects of substituents and heteroatoms.

Amino group in aninline exhibits + M-effect, that results in increasing of dencity in benzene ring and its greatest concentration is in orto- and para-positions. Reaction behavior is facilitated.

Nitro group has -I and –M-effects in nitrobenzen, that's why it desctivates benzene ring notably in orto- and para-positions. Since interaction of electrophile occurs in the place of highest electron dencity then meta-isomers form. Thus, electron-donating substituents – these orto- and para-orientants (orientants of I type

and activators of S_E-reactions; electron withdrawing substituents – metha-orientants (orientants of II type) deactivators of S_E-reactions.



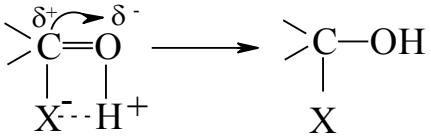
In five-membered heterocycles (pyrrole, furan, thiophen), which are π-excessive systems, S_E-reactions proceed easier then in benzene; in this case α-position is more reactive.

Heterocyclic systems with pyridine nitrogen are π –deficient, that's why they undergo electrophilic substitution reactions more difficult; in such a case electrophile occupies β-position in relation to nitrogen atom.

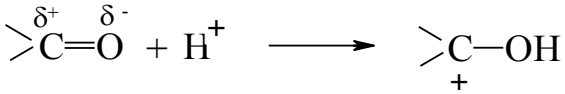
Task № 2. Give the mechanisms of acetic aldehyde and ethyl alcohol reaction in acidic medium.

Solution. Carbon atom in a carbonyl group $>C=O$ is sp^2-hybridyzed, which means it form three σ-bounds. The geometric arrangement of these three sp^2 hybrid orbitals is in a flat plane with 120-degree angles between them. Carbon and oxygen atoms are bonded by π-bond, which lies at 90^o angle to the hybrid σ-orbitals.

Since oxygen is more electronegative than carbon, the electron density attracted towards oxygen in a carbonyl group $>C=O$ (mostly π-electrons), so double bond is polarized in a way that there is high electron density on the oxygen atom and low on the carbon atom: $>C=O$. Therefore the π-bond must be broken easily under the attack of polar agents; hence the nucleophilic addition reactions (A_N) are typical for carbonyl compounds:

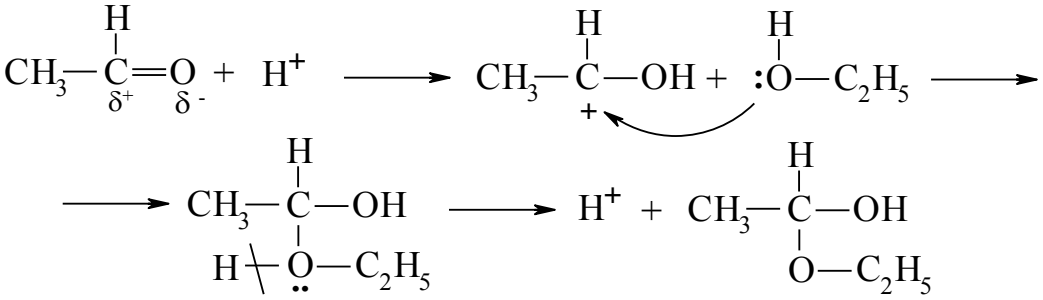


Usually the nucleophilic addition reactions catalyzed by acids, which convert a molecule into carbocation by addition of the proton:

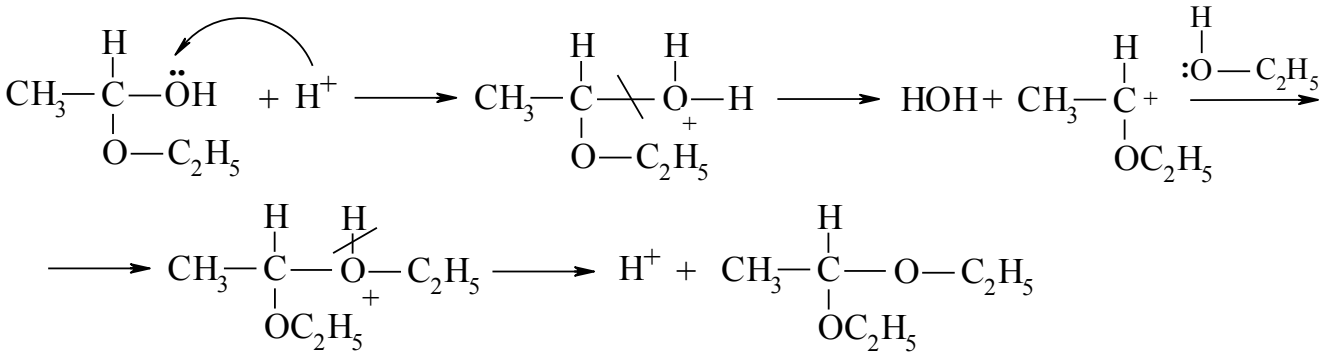


An addition of alcohols to aldehydes starts with initial protonation of the carbonyl group in acidic medium.

The carbocation forms a covalent bond with the alcohol molecule with a help of lone pair of electron from oxygen. The oxonium derivative that was formed is stabilised by deprotonation reaction:

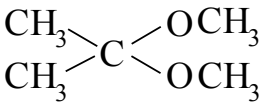


The product in this reaction is the hemiacetal in which an alcohol and ether attached to the same carbon. The acetal forms by the interaction of hemiacetal with a second alcohol molecule in acidic medium:



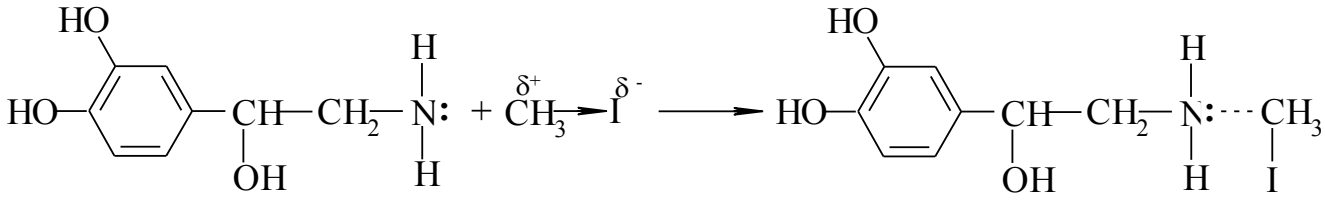
The presence of cyclic form of monosaccharaides can be explained by the formation of intramolecular hemiacetals.

The addition of alcohol to ketones is more difficult than with aldehydes. Ketone derivatives are ketals:

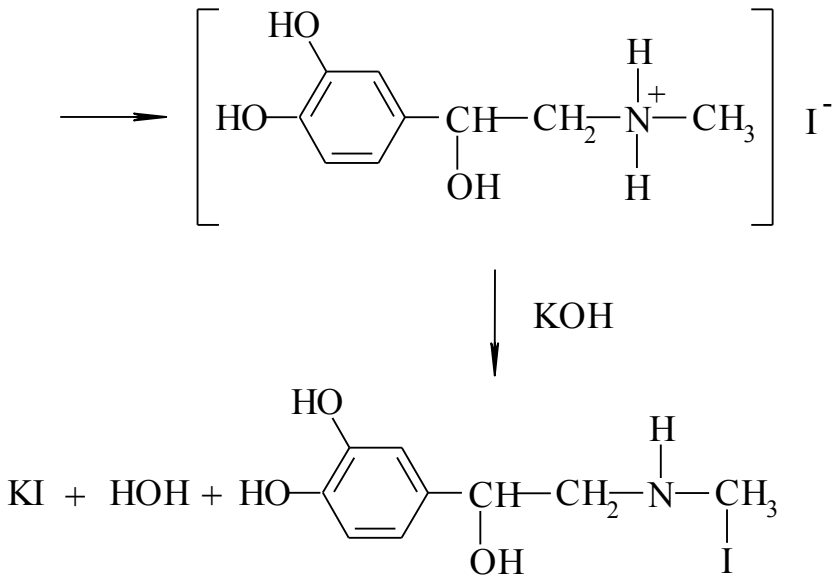


Task № 3. Obtain adrenaline from noradrenaline in vitro.

Solution. The alkylation reaction goes by S_N mechanism, where the product forms through a generation of an intermediate state. Alkylation means substituting an alkyl group into something – in this reaction into hydrogen. In other words, an alkylation is an addition of alkyl chain to another molecule. Alkyl halides are often used as alkylating agents. In our case the methyl iodide is used.



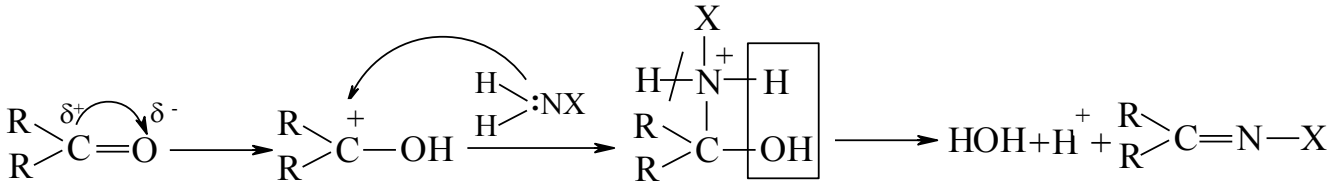
Noradrenaline

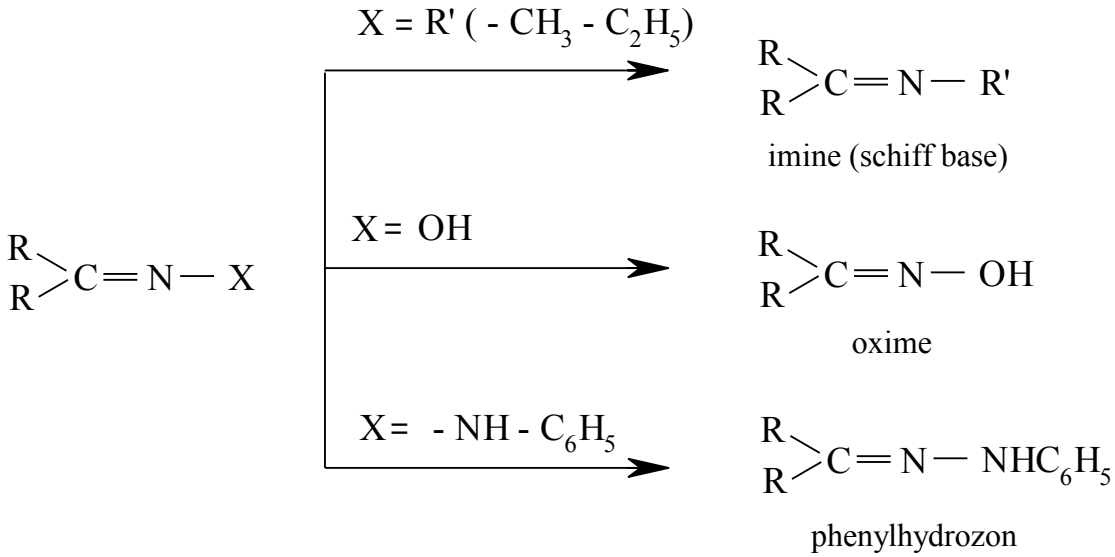


Adrenaline

Task № 4. Describe the mechanism of the carbonyl compounds reaction with amine and hydrazine.

Solution. Aldehydes and ketones react in substitution reactions, where oxygen of the carbonyl group can be substituted for another group. Reactions proceed by two steps: first it is an addition reaction based on a cleavage of the π-bond, second is elimination of a water molecule. Generally, the reactions are catalyzed by an acid:



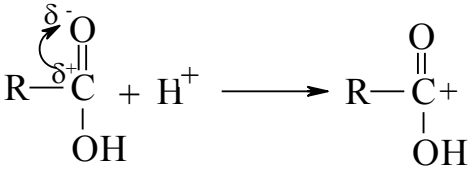


Imines (Schiff bases) formed in this reaction are intermediate products in enzymatic processes. Biosynthesis of amino acids in an organism goes through the formation of imine with pyridoxal-phosphate (vitamin B_6).

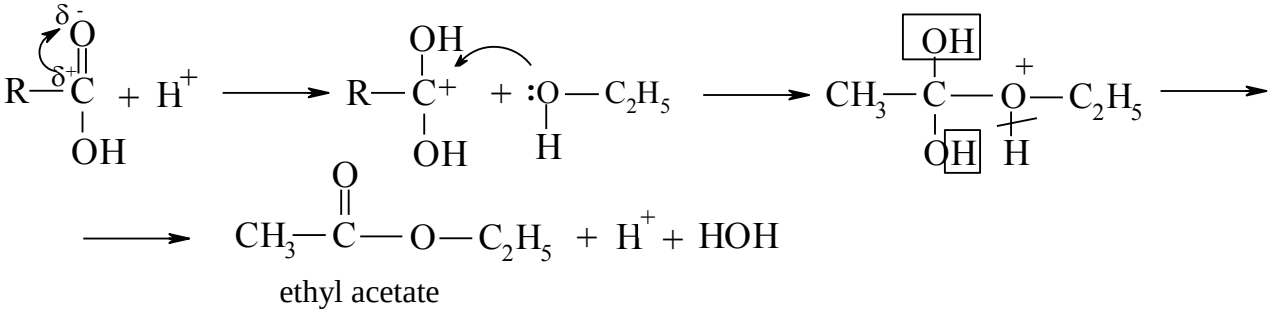
Oximes, phenylhydrazons are well crystallized and for this reason used for identification and isolation of aldehydes and ketones from a mixture with other substances.

Task № 5. Compare the properties of a carbonyl and hydroxyl of aldehydes, ketones, alcohols and carboxylic acids in nucleophilic reactions.

Solution. Carboxyl group conjugation complicates addition reactions by π-bond and a substitution of OH^- group. Nevertheless, carboxylic acids can be protonated and form carbocation in the presence of dehydrated mineral acids:

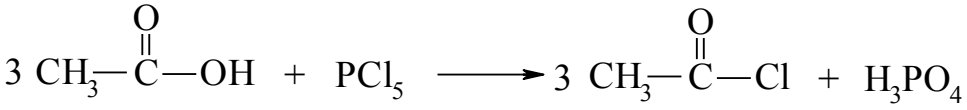


Carbocations are intermediates in different reactions such as ether formation:



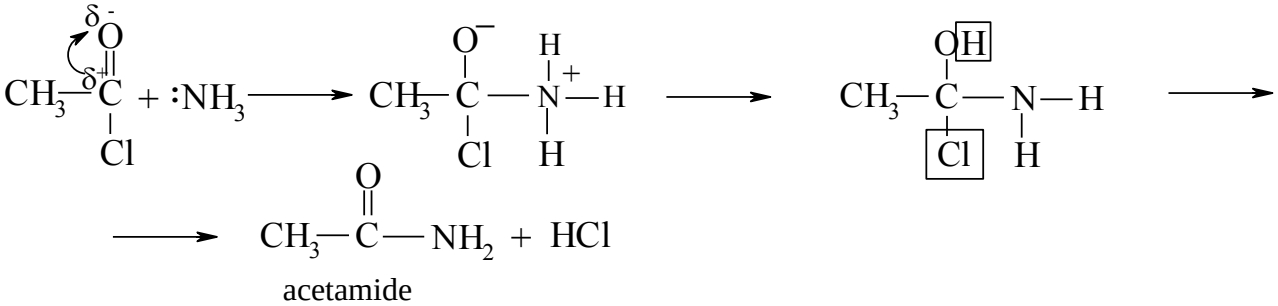
ethyl acetate

Phosphorous chloride (PCl_3, PCl_5) or thyonil chloride ($SOCl_2$) are strong chlorodehydrating agents which can be used to convert carboxylic acids to corresponding acid chlorides. The substitution of the hydroxyl group with a halogen takes place in this reaction:



acetyl chloride

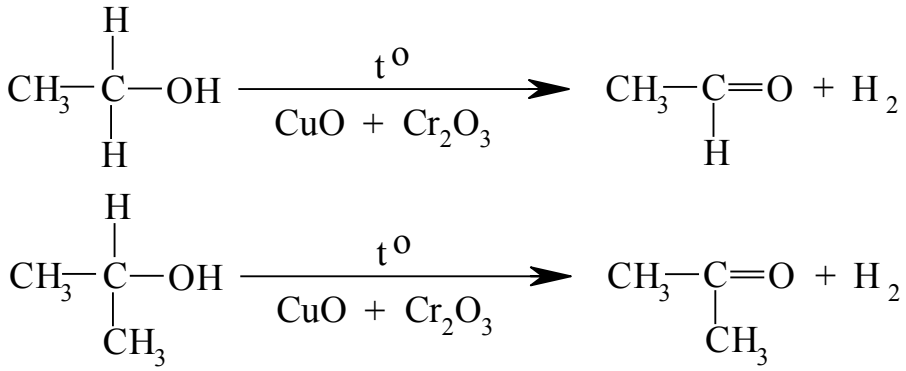
An acyl halide is a product in this reaction. These compounds are not stable and very reactive. They are widely used acylating agents to incorporate an acyl radical into organic compounds. Acylation applies for protection of amino group during the peptide synthesis. Amine acylation yields an amide formation:



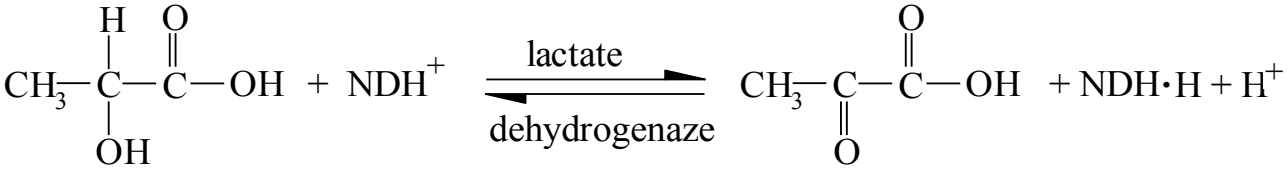
acetamide

Task№ 6. Give the scheme of the lactic acid oxidation *in vivo*.

Solution. Primary and secondary alcohols are oxidized much easier to the corresponding alkanes. Oxidation of alcohols can be done under the high temperature and in the presence of catalyst:

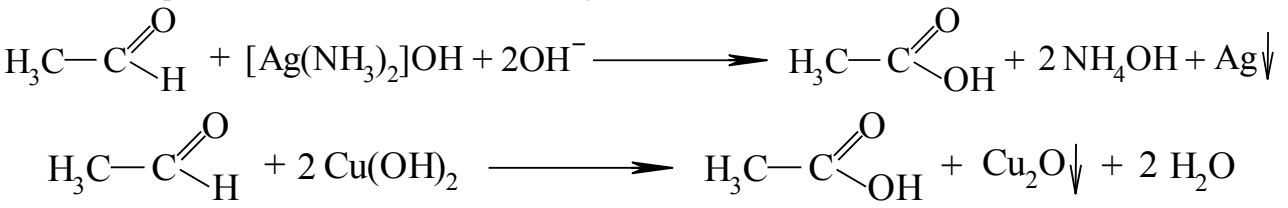


This is the dehydration reaction, which takes place in the organism upon the biological oxidation. This process is catalyzed by enzymes dehydrogenase, whose cofactor is NAD^+ (nicotinamide adenine dinucleotide). In the dehydration reaction the substrate looses 2 electrons and 2 protons or 1 proton and 1 hydride ion which is accepted by NAD^+:



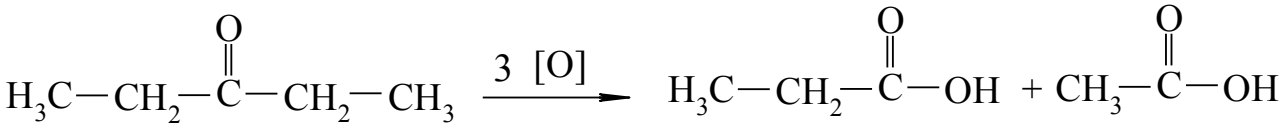
Task № 7. Compare aldehydes and ketones ability to oxidize.

Solution. Aldehydes can be easily oxidized to carboxylic acids by air oxygen or by mild oxidizing agents as ammonia solution of silver oxide or cupper hydroxide. These are qualitative reactions of aldehydes:



Carboxylic acids are products of aldehyde oxidation. The functional group of carboxylic acids represents a conjugated system with delocalization of electrons. Thus, oxidation of aldehydes leads to the more stable compound.

Ketones oxidize only by strong oxidant such as potassium permanganate. The carbon chain splits next to the carbonyl group with a formation of two molecules of acids:



The difference in aldehydes and ketones oxidation explains by different bond oxidation. C-H bond oxidizes in aldehydes whereas C-C bond oxidizes in ketones. The structure of ketones can be determined by product of oxidation.

Revision exercises

№ 1

1. Give the mechanism of the pyrrole bromination reaction. What is easier to brominate: pyrrole or pyridine and why?

2. Write the mechanism of the methyl-phenyl ketone nitration reaction at the synthesis of mesatonum (adrenoceptor agonist).

3. Write the reaction equation of nicotinic acid (β-pyridine carboxylic acid) nitration with account of electronic effect of heteroatom. Which compound is easier to brominate: pyridine or benzene? Why?

№ 2

1. Give the mechanism of the tetamon synthesis, used in therapy of cerebral angiospasm. It can be obtain by the reaction of triethanolamine with ethyl iodide.

2. Write the reaction equation for pyridine bromination taking into account orienting influence of heteroatom. What is easier to brominate: benzene or pyridine? Why?

3. Provide the scheme of the malic acid enzymatic oxidation to oxaloacetic acid.

№ 3

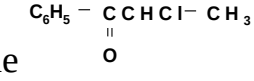
1. Write the reaction equation for benzaldehyde bromination. Compare this reaction with benzene bromination reaction.

2. Give the mechanism of the acetaldehyde reaction with methylamine.

3. Give the mechanism of the malic acid (2-hydroxybitandioic acid) dehydration in acidic medium.

№ 4

1. Describe the mechanism of the aniline bromination reaction with account of electronic effect of the amino group. Does presence amino-group in the benzene ring facilitate or trouble reaction?

2. Give the mechanism of the ephedrine formation in the reaction of 1-chloroethyl phenyl ketone  with methylamine.

3. Give the mechanism of the vitamin PP (nicotinic acid amide) formation from ammonia and nicotinic acid acyl chloride (pyridine-3-carbonyl chloride). The product is the anti-allergic medication.

№ 5

1. Which of the following compounds has more basic properties: ammonia, methylamine or aniline? Justify your answer.

2. Write the reaction equation of furfural (furan-2-aldehyde) nitration, on the base of which bactericides: furacilin, nitrofurantoin, furasolidone and others are synthesized.

3. Provide the mechanism of α-alanine (α-aminopropanoic acid) formation in the reaction of α-chloropropanoic acid with ammonia).

№ 6

1. Give the mechanism of ethanolamine (2-aminoethanol-1) alkylation by methyl iodide, where the quaternary ammonium base is formed.

2. Give the scheme of the reaction of propanal with ethylamine. Does this reaction take place in the organism? What is the significance of this reaction?

3. Give the mechanism of the malic (2-hydroxybutanedioic) acid dehydration under heating. How can you explain the easiness of this reaction?

№ 7

1. Which of the following compounds is the weakest base: ammonia, methylamine or aniline? Justify your answer.

2. Give the scheme of the chloral hydrate (2,2,2-trichloroethane-1,1-diol, sedative and hypnotic drug) formation by trichloroacetaldehyde hydration. Explain the stability of the obtained compound.

3. Synthesize lactic acid (2-hydroxypropanoic acid) by the reaction of α-halogen carboxylic acid with alkali (aqueous solution). Provide the mechanism of this reaction.

№ 8

1. Write the reaction equation of propanoyl chloride with methylamine. Name the product.

2. Describe the mechanism of the reaction of acrolein or acrylic aldehyde (prop-2-enal) with ethanol as one stage of the glyceraldehyde synthesis.

3. Give the scheme of the pyruvic (2-oxopropanoic) acid transformation into lactic acid.

№ 9

1. Write the alkylation reaction of ethylamine with methylchloride. Name the product.

2. Provide the mechanism of the acetone reduction with the aid of metal hydrides in acidic medium.

3. Obtain glycine (aminoacetic acid) from chloroacetic acid. Explain the mechanism of the reaction.

№ 10

1. Write the reaction characterizing acidic properties of amines.

2. Provide the scheme of the intramolecular reaction of 5-hydroxypentanal in acidic medium.

3. Obtain acetic acid methylamide from acetyl chloride and methylamine. Provide the mechanism of this reaction.

№ 11

1. Write the reaction characterizing basic properties of amines.

2. Give the mechanism of the acetone reaction with hydroxylamine NH_2-OH.

3. Give the mechanism of the malic acid (2-hydroxybitandioic acid) dehydration in acidic medium.

№ 12

1. Write the reaction of primary amine with nitrous acid (diazonium salt formation).

2. Describe the mechanism of the acetal formation from acetaldehyde and propanol in the presence of catalyst.

3. Give the scheme of the acetylcholine formation from amino alcohol and acetic acid.

№ 13

1. Give the mechanism of the reaction of pyridine with methyl iodine. What is the significance of this reaction?

2. Write the reaction equation of the butanal reduction.

3. Write the reaction of acetic acid oxidation by cupper (II) hydroxide. What is observed? Provide the mechanism of this reaction.

№ 14

1. Write the reaction of secondary amine with nitrous acid (diazonium salt formation).

2. Describe the mechanism of 5-hydroxypentanal transformations in acidic medium.

3. Give the scheme of the malonic (propandioic) acid decarboxilation. What is the significance of this type of reactions?

№ 15

1. Which of the following compounds is the weakest base: secondary or tertiary amine? Explain your answer.

2. Give the scheme of acetone formation from corresponding alcohol.

3. Provide the scheme of m-benzoic acid nitration. Explain the mechanism of this reaction.

SUGGESTED READINGS

1. Biologically important classes of bioorganic connections. Biopolymers and their structural components: Theoretical course of biological and bioorganic chemistry, Module 1 / A. O. Syrovaya, E. R. Grabovetskaya, N. M. Tkachuk, L. G. Shapoval, V. N. Petiunina, S. A. Nakonechnaya. – X.: «Цифровая типография № 1». – 2013. – 183 p.

2. Zurabyn S. E. Fundamentals of Bioorganic Chemistry. – M.: GEOTAR-MED, 2003. – 320 p.

Навчальне видання

Будова і властивості альдегідів і кетонів. Структура, властивості та біологічне значення карбонових кислот та амінів.

Методичні вказівки для самостійної роботи студентів 1-го курсу з медичної хімії

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