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G. P. FANDO

ORGANIC CHEMISTRY

Laboratory handbook

In two parts

PART 1

Minsk BSMU 2017

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РЕСПУБЛИКИ БЕЛАРУСЬ
БЕЛОРУССКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ
КАФЕДРА БИООРГАНИЧЕСКОЙ ХИМИИ

Ф. Ф. Лахвич, О. Н. Ринейская, Г. П. Фандо

ОРГАНИЧЕСКАЯ ХИМИЯ

ORGANIC CHEMISTRY

Лабораторный практикум

В двух частях

Часть 1

Минск БГМУ 2017

УДК 547(076.5)(075.8)-054.6
ББК 24.2я73
Л29

Рекомендовано Научно-методическим советом университета в качестве лабораторного практикума 21.06.2017 г., протокол № 10

Р е ц е н з е н т ы: канд. биол. наук, доц. В. В. Хрусталёв; канд. фарм. наук Н. С. Голяк

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ISBN 978-985-567-772-8.

Содержит методические рекомендации для подготовки к лабораторным занятиям по органической химии на английском языке. К каждой теме даны цель занятия, вопросы для обсуждения, письменные задания, а также указана литература для подготовки. Приведены описания и протоколы лабораторных опытов.

Предназначен для студентов 2-го курса медицинского факультета иностранных учащихся, обучающихся на английском языке по специальности «Фармация».

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ISBN 978-985-567-773-5

REGISTRATION FORM

Student name _____ Group Number _____

PART 1

N	Theme	Date	Mark	Signature
1.	Classification and nomenclature of organic compounds			
2.	Chemical bonding and distribution of electrons in molecules			
3.	Stereoisomerism and stereochemistry			
4.	Chemical reactivity			
5.	Separation and purification of substances by means of solvent extraction			
6.	**Test № 1.** Structure and nomenclature of organic compounds			
7.	Instrumental methods of structure determination. Infrared spectroscopy			
8.	Nuclear magnetic resonance spectroscopy			
9.	Nonaromatic hydrocarbons I			
10.	Nonaromatic hydrocarbons II			
11.	Aromatic hydrocarbons			
12.	**Colloquium № 1.** Structure, reactivity and identification of hydrocarbons. **Academic research №1**			
13.	Organic halides			
14.	Alcohols, phenols, thiols, ethers, sulfides			
15.	**Test № 2.** Structure, reactivity and identification of halides, alcohols, phenols, thiols, ethers, sulfides. **Academic research № 2**			
16.	Amines; azo and diazo compounds			
17.	Oxo compounds			
18.	**Test № 3.** Structure, reactivity and identification of amines, aldehydes and ketones. **Academic research № 3**			
CREDIT				

LABORATORY SAFETY RULES

1. Dress appropriately for the lab. Wear white lab coat. Tie back long hair.
2. Know what safety equipment is available and how to use it. This includes eyewash place, fire blanket, fire extinguisher and sand.
3. Know the dangers of the chemicals in use, and read labels carefully. Do not taste or sniff chemicals.
4. Dispose of chemicals according to instruction. Use designated disposal sites, and follow the rules. Never return unneeded chemicals to the original containers.
5. Always add acids and bases to water slowly to avoid splattering. This is especially important when using strong acids and bases that can generate significant heat, form steam, and splash out of the container.
6. Never point test tubes at yourself or others. Be aware of reactions that are occurring so that you can remove them from the heat if necessary.
7. Do not eat or drink in the lab! It is too easy to take in some dangerous substance accidentally.
8. Follow all directions. Never occasionally mix chemicals. Pay attention to the order in which chemicals are to be added to each other, and do not deviate!
9. After the end of the experiment each student should submit an account of the work that have been done, then to wash up chemical crockery, clean a workplace and ask the student on duty to check it.

Responsibilities of the student on duty:

– to get all the necessary equipment from the laboratory assistant;

– to keep an order the laboratory room;

– student on duty should leave the laboratory the last, after receiving permition from the lab assistant.

I agree _____ 20___ year _____
(date) (signature)

PRECAUTIONS

Work with alcohol lamps

Careless work with an alcohol lamp can result in a fire, that is why it is necessary to follow the below requirements:

– the wick of an alcohol lamp should tightly enter the aperture of a metal bush; the topping should be put forward for 1 cm and fluffed up;

– the bush should close the aperture of a alcohol lamp tightly; the alcohol lamp should be filled with alcohol no more than 2/3 of the volume;

– the lighting of an alcohol lamp should be carried only by matches, it is strictly forbidden to light an alcohol lamp from another alcohol lamp, because the bush can stoop and coming out steams of alcohol can be fired;

– to blow out an alcohol lamp only by covering it with bell-glass;

– when heating up substances in chemical glassware it is necessary to heat them at the top or mid-range flame, not touching a wick, because a wick is always cool, and when hot glass contacts with it, glass may burst.

Work with chemical glassware

Heating substances in glassware should be performed gradually, slightly rotating it and cautiously shaking from time to time. When heating a test tube with a liquid on the open fire, splasing of a liquid is possible. Because of this fact, the aperture of a test tube should be directed aside from you and from your neighbors. Especially it is necessary to avoid injuring the eyes with hot splashes, that it is why it is forbidden to bend forward to the test tube and look inside. When heating the test tube, it should be kept at the angle of inclined position (45º), so that splashes will hit walls of a glassware and will not be thrown outside. If the liquid starts to rise in an exhaust tube, it is necessary to let down a test tube immediately, so that the fluid level in it will become lower than the end of an exhaust tube.

Work with inflammable liquids (IL)

IL (diethyl ether, alcohol, toluene, acetone, acetoacetic ether) are kept always in a fume hood. Experiments with these substances are carried out under draught, far from open fire and the turned on small stoves. If an ignition of the IL happened in a vessel, it is necessary to cover it quickly with a fire-prevention blanket. If the burning liquid has been spilt, it must be extinguished by sand. If the clothes begin to fire, it is necessary to wrap up quickly and densely in a fire-prevention blanket.

Work with acids and alkalis

Concentrated solutions of nitric, sulfuric, hydrochloric acids are kept in a fume hood. All experiments with concentrated acids and alkalis are carried out only in the fume hood. It is necessary to cover carelessly spilt on the floor acids and alkalis by sand and after that to clean up.

Work with toxicants

Toxic organic substances — aniline, methyl amine, toluene, picric acid are kept in a fume hood. It is necessary to be cautious with these substances, not to inhale their steams, to avoid injuring the hands as they can penetrate through the skin. In case of emergency when these substances got on hands, it is necessary to wash up quickly the hands with warm water and soap. If inhaled the steams — immediately to go out in the fresh air.

First-aid treatment in case of accidents:

– in case of hands are cut with glass first of all it is necessary to remove all the splinters out of the wound, then to treat the wound with an alcohol solution of iodine and to put a bandage;

– in case of thermal burns happen it is necessary to treat the burnt place with the 70 % solution of ethanol;

– in case of burns are caused by solutions of acids or alkalis it is necessary to wash up the burnt site with water quickly and to put an aseptic bandage;

– in case of acids or alkalis hit the eyes it is necessary wash them with water carefully and to refer the victim to the outpatient clinic;

– in case of skin burns caused by bromine it is necessary quickly to wash the injured place off with ethanol and to put anti-burn emulsion;

– in case of burns caused by hot organic liquids it is necessary to wash out the injured place with ethanol;

– in case of burns caused by liquid phenol it is necessary to massage the emerged sites of white skin with a glycerin until normal skin color is restored then to wash with water and to put the gauze bandage moistened with a glycerin solution;

– after providing the first-aid treatment it necessary to address to the health center of the university or to the outpatient clinic.

LABWORK № 1
CLASSIFICATION AND NOMENCLATURE OF ORGANIC COMPOUNDS

Objective: to promote safety awareness and encourage safe working practices in the chemical laboratory; to study structure, classification and nomenclature of organic compounds.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.

Problems for discussion:

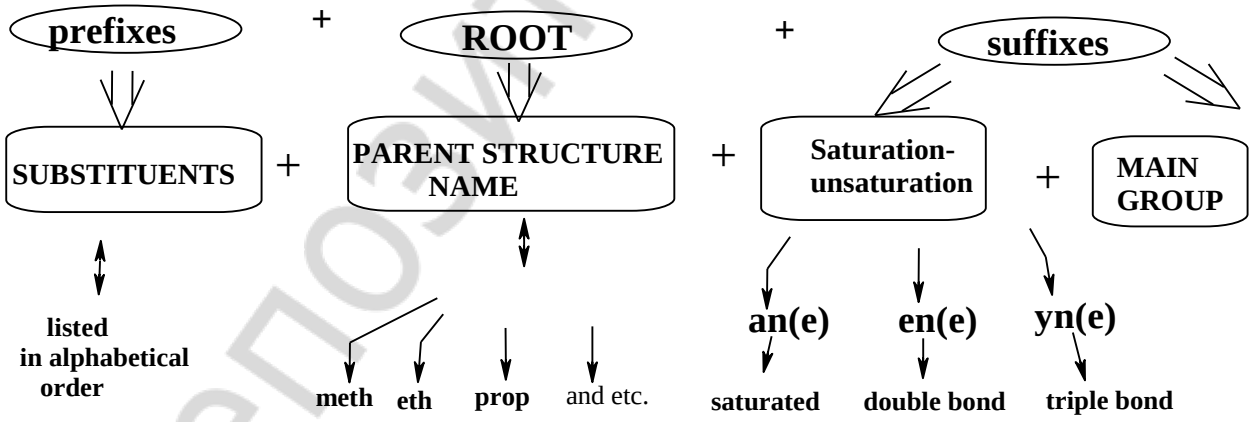
1. Organic chemistry laboratory: equipment, glassware and reagents.
2. Personal, equipment, glassware and reagents safety in the organic chemistry laboratory.
3. Constitution and isomerism of organic compounds.
4. Classification of organic compounds.
5. IUPAC nomenclature of organic chemistry.

NAMING OF ORGANIC COMPOUNDS

Names of organic compounds can be generated in different ways. Now it's known more than 50 million organic compounds. So the use of trivial (historic, common) names is limited and various types of systematic nomenclatures have been developed.

IUPAC (International Union of Pure and Applied Chemistry) has proposed the substitutive approach for naming of organic substances. To generate names according to this approach one should choose the **PARENT STRUCTURE**, followed by substitution of its hydrogen atoms by structural fragments (represented by suffixes and prefixes) as shown below:

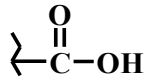
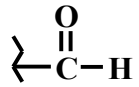
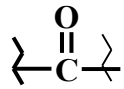
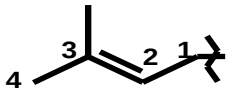
prefixes [substituents] + **parent structure** [carbon chain] + **suffixes** [(un)saturation and main functional group]



The root of the compound name is determined by number of carbon atoms in parent structure.

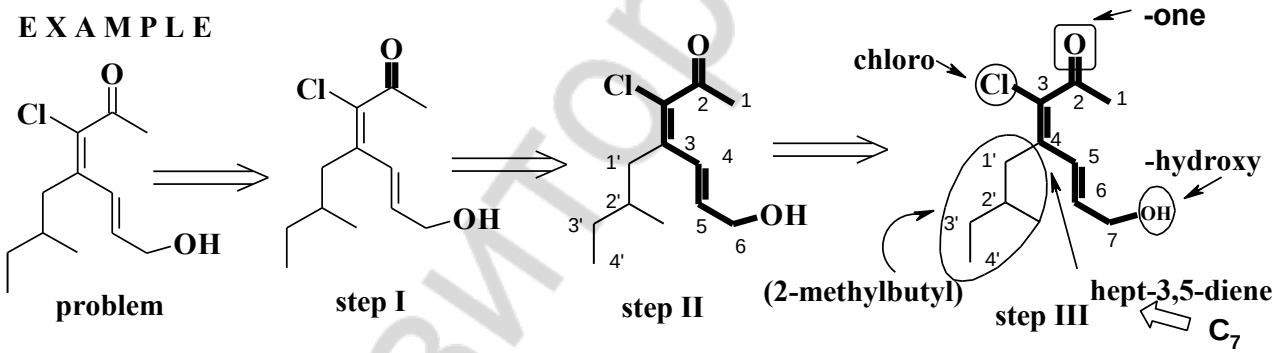
C_n	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}	C_{18}	C_{20}
Name	Meth	Eth	Prop	But	Pent	Hex	Hept	Oct	Non	Dec	Undec	Octadec	Icos

Groups with heteroatoms can be regarded either as functional groups or substituents depending of their priority. Only the main functional group will be named as functional and will be placed in the final position of the word. All the other groups will be substituents in addition to hydrocarbon substituents and few groups which never to be functional (e.g. nitro or chloro groups).

FUNCTIONAL GROUPS AND SUBSTITUENTS				
GROUP IN FORMULA		**WRITING IN NAME**		PRIORITY ORDER DOWN
Grafics	**Name (in text)**	**Functional group**	**Substituent**	
	Carboxyl group	-oic acid (carboxylic acid)	carboxy-	
	Aldehyde group	-al	formyl-	
	Keto group	-one	oxo-	
-OH	Hydroxyl group	-ol	hydroxy-	
-NH_2	Amino group	-amine	amino-	
GROUPS WHICH ARE EXCLUSIVELY SUBSTITUENTS				
NO_2	**Nitro group**	**nitro-**		
Cl (Br, I, F)	**Halide group**	**chloro- (bromo-; iodo, fluoro)**		
Hydrocarbon fragments		**core structure name + yl**		
		**(3-methylbut-2-enyl)-**		

To name the structure one should find the parent structure, then to number it and finally to indicate saturation-unsaturation and functional groups with suffixes and substituents with prefixes.

E X A M P L E



7-Hydroxy-4-(2-methylbutyl)-3-chlorohepta-3,5-diene-2-one

I STEP

To determine the parent structure we should follow the hierarchical system of rules (the rule placed above has the priority!).

Parent structure is continuous hydrocarbon chain (or cycle) **that**

1) carries the main functional group;
2) carries the maximum number of double (triple) bonds;
3) the longest;
4) carries the minimum number of chains attaches.

II STEP

One should indicate by a number the position of C-atoms in parent structure, using the lowest possible number for main functional group (if it's absent — for double bonds). For alkanes number the parent chain, starting at the end to result the set with the lowest numbers; thus the numbers 2, **3**, 5, 6 is to be chosen rather than 2, **4**, 4, 5.

III STEP

To name the parent structure we use the root for C_n taking in account the number of atoms. Then we indicate whether parent structure is saturated or unsaturated using -an(e), -en(e), yn(e) suffixes.

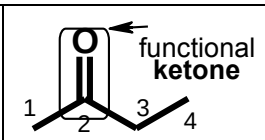
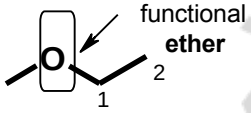
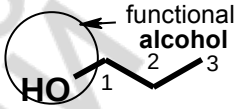
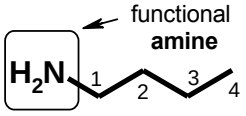
We name functional groups and substituents using the table above. The name of hydrocarbon groups can be constructed according to rules regarded above, followed by the addition of –yl suffix. For these indicate the position of the carbon attached to parent structure using the lowest possible number.

IV STEP

Finally we give the name to structure.

The first we list prefixes (which are names of substituents) in alphabetical order; next we name the parent structure (C_n) indicating by suffixes saturation/unsaturation character, followed by naming of the main functional group in final position.

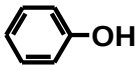
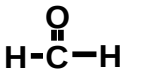
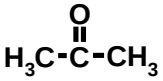
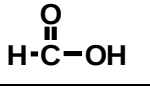
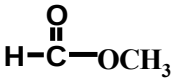
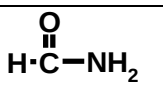
In **radico-functional** approach the characteristic group in the compound is expressed as one word (called the "functional class name"). The remainder of the molecule attached to that group is expressed in its radical form as another word which precedes the functional class name.

Approach				
Substitutive	Butan-2-one	Methoxyethane	Ethanol	Butanamine
Radico-Functional	Ethyl methyl ketone	Ethyl methyl ether	Ethyl alcohol	Buthylamine

Presence of functional group(s) in structure gives rise to classification of organic compounds.

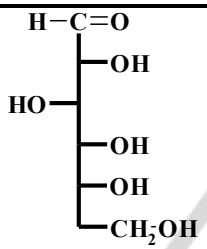
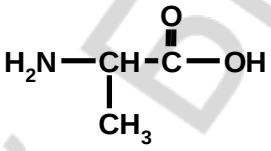
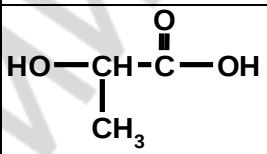
Hydrocarbons have no functional groups. They can be aliphatic or cyclic, saturated or unsaturated. Monofunctional compounds carry the only functional groups.

MONOFUNCTIONAL COMPOUNDS

Class name	**Functional group**		**Example**	
	Formula	**Name**	**Formula**	**Name**
ALCOHOLS	**-OH**	**Hydroxyl**	**CH_3OH**	**methanol**
PHENOLS	**-OH**	**Hydroxyl**		**phenol**
ALDEHYDES		**Aldehyde**		**Methanal (formaldehyde)**
KETONES		**Keto**		**Propanone (acetone)**
AMINES	**$-NH_2$**	**Amino**	**CH_3NH_2**	**Methanamine**
CARBOXYLIC ACIDS		**Carboxyl**		**Methanoic (formic) acid**
ESTERS		**Ester**		**Methyl formiate**
AMIDES		**Amide**		**Formamide**
NITRILES	**$-C\equiv N$**	**Nitrile**	**$CH_3C\equiv N$**	**Acetonitrile**

Polyfunctional compounds have few identical and heterofunctional compounds have few different functional groups.

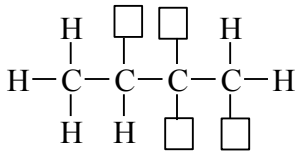
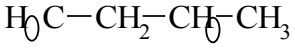
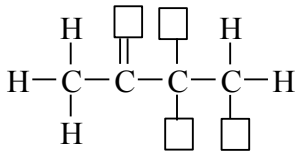
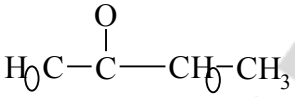
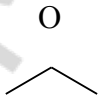
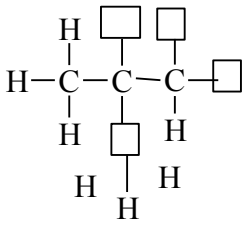
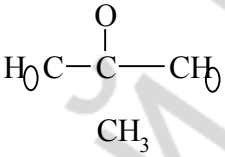
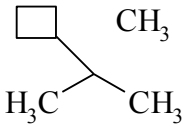
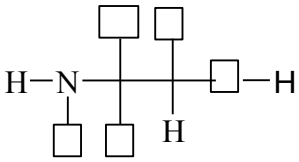
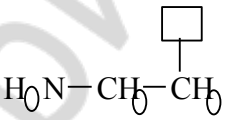
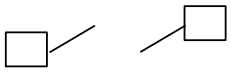
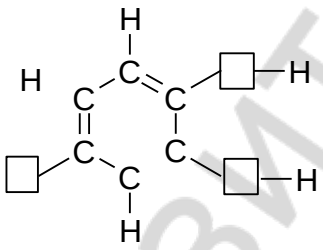
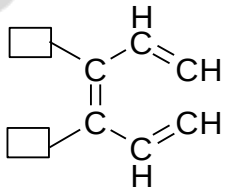
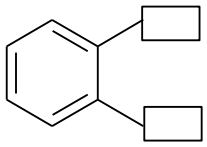
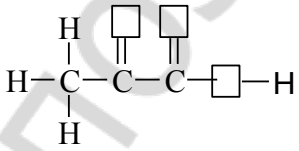
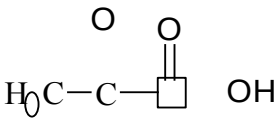
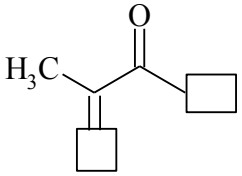
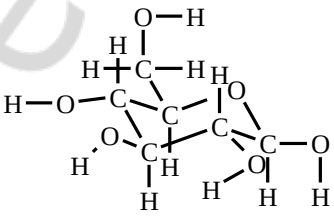
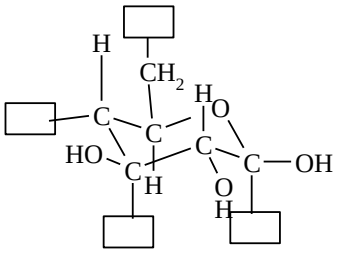
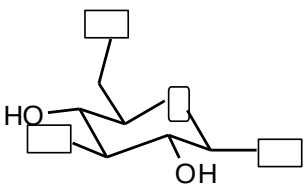
HETEROFUNCTIONAL COMPOUNDS

Class name	Functional group		Example	
	Formula	Name	Formula	Name
CARBOHYDRATES (SUGARS)	**-OH** **-C=O**	**Hydroxyl** **Aldehyde or Keto**		**Glucose**
AMINO ACIDS	**-NH_2** **-COOH**	**Amino** **Carboxyl**		**Alanine (2-amino-propanoic acid)**
HYDROXY ACIDS	**-OH** **-COOH**	**Hydroxyl** **Carboxyl**		**Lactic acid (2-hydroxy propanoic acid)**

The structure of the course is based on this classification and every new lab session you will meet the new class of compounds. First classes start from basic principles. Therefore the naming of organic compounds gives us the set of practice problems for the first laboratory session.

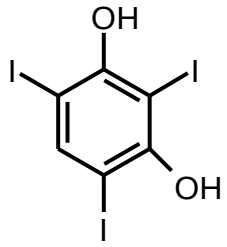
PRACTICE PROBLEMS

1. Complete the formulas of the following compounds.

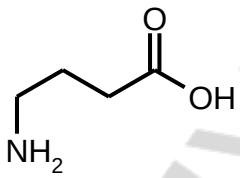
The name	*Kekule*	Condensed	Stick (line)*
Butane			
Butan-2-one			
2-Methyl-propan-2-ol			
2-Amino-ethan-1-ol			
Benzene-1,2-diol			
Pyruvic acid (2-oxopro-panoic)			
β-D-Gluco-pyranose			

* In stick (line) formulas any carbon atom can be indicated in condensed form.

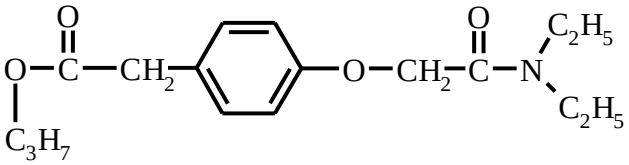
2. Find functional groups and other structural fragments in formulas of the pharmaceutical drugs presented.



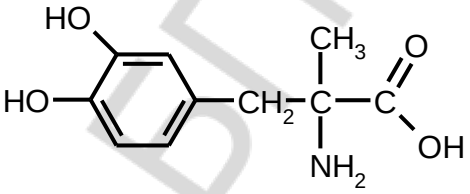
Riodoxolum



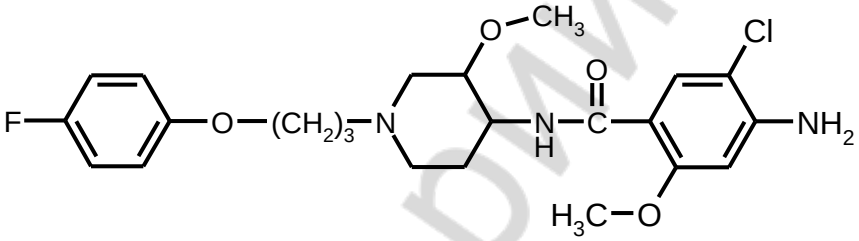
Gaballon (GABA)



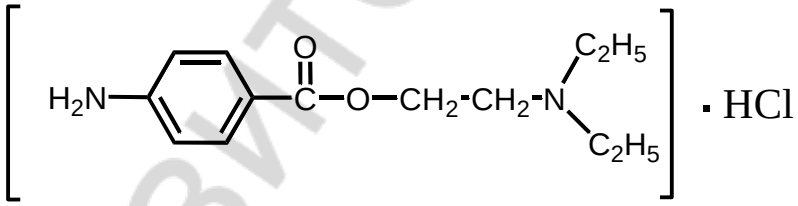
Fabantol



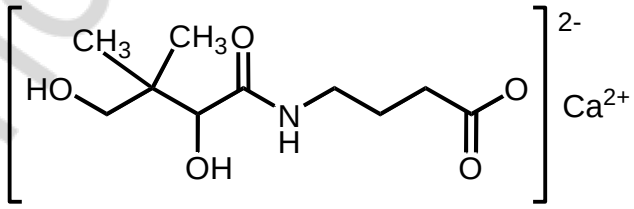
Metyldopa



Cisaprid

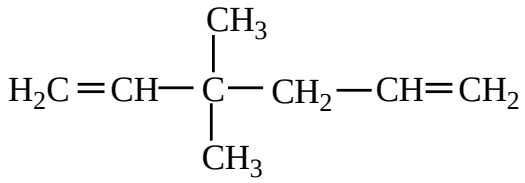
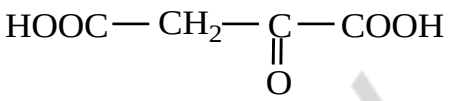
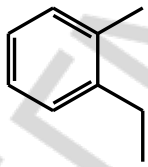
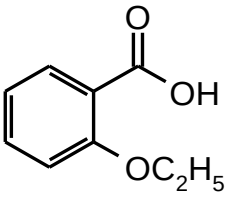
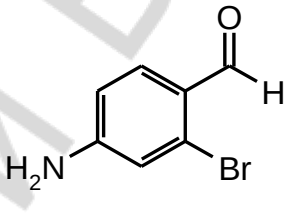
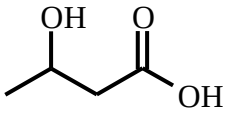
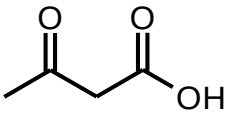
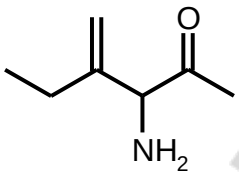
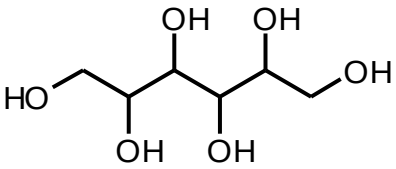
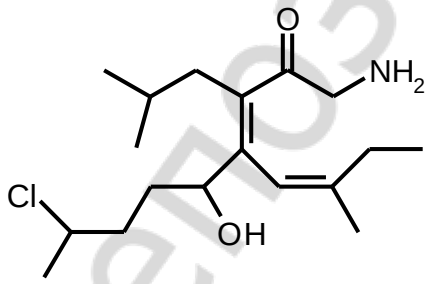
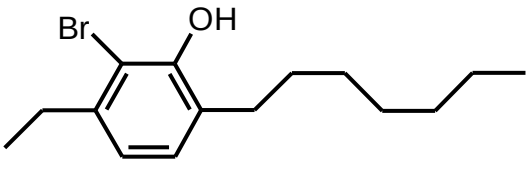
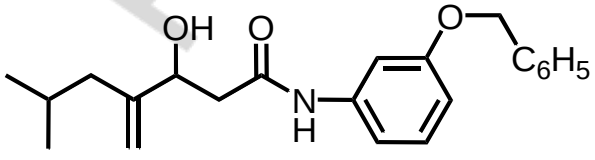
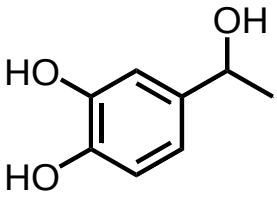


Procaine



Hopaten

3. Give the names of following compounds (IUPAC nomenclature).

4. Write the formulas of the following compounds.

2,3-Dimethylpentane	3-Methyl-4,4-diethylheptane
Cyclopentane	Propan-1,2,3-triol
3-Hydroxy-4,5-dihydroxymethyl-2-methylpyridine (vitamin B_6)	
Sodium 2-ethylpentanoate (sodium valproate, the active substance of *Depakene*, with antiepileptic action)	

5. Draw and name all the isomers of the compound with the formula C_4H_6.

6. Draw and name all the isomers of the compound with the formula C_8H_8O. Find functional groups and fragments.

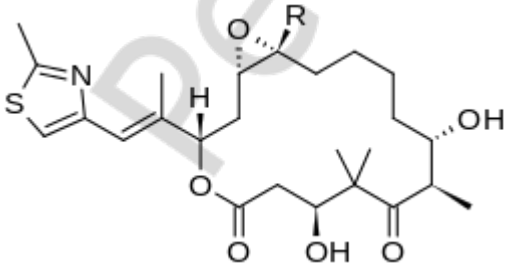
7. Draw and name all the isomers of the compound with the formula C_3H_6O.

8. Write the formulas of the following compounds. Give IUPAC names (substitutive approach).

Benzyldiethylamine	Diethyl ether	Ethane dicarbonic acid
Methyl ethyl ketone	*tert.*-Butyl alcohol	Nitroglycerine
γ-Oxybutyric acid	Phenyl acetone	Vinyl acetylene

9. Draw 3 bicyclic isomeric compounds with the formula $C_8H_{12}O_2$: the acid, the hydroxy ketone, the diol. Give their IUPAC names.

10. The *Epothilones* are a class of potential cancer drug, preventing cancer cells from dividing by interfering with tubulin. Analyze the formula of *Epothilones* A (R = H) and B (R = CH_3) and indicate functional groups and structural fragments.



Signature of teacher:

LABWORK № 2
CHEMICAL BONDING AND DISTRIBUTION OF ELECTRONES IN MOLECULES

Objective: to study the electronic configuration of organogenic elements and the process of covalent bond formation; to discuss the process of charge distribution in molecules.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.

Problems for discussion:

1. Chemical bonding in organic compounds.
2. Charge distribution in organic compounds. Induction and mesomerism. Electron donating and electron withdrawing substituents.
3. Conjugated systems. Conjugation energy.
4. Aromaticity. *Huckel*'s rule. Aromaticity of benzoic and non-benzoic systems.

PRACTICE PROBLEMS

1. Draw the model of the bond formation in methane and ethane using the concept of hybridization.

2. Draw the model of the bond (σ and π) formation in ethene and ethyne using the concept of hybridization.

3. Draw the formulas and discuss spatial structure of the buta-2,3-diene, hexa-2,4-diene and penta-1,4-diene. Use the concept of hybridization.

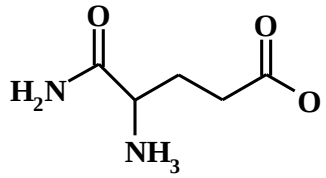
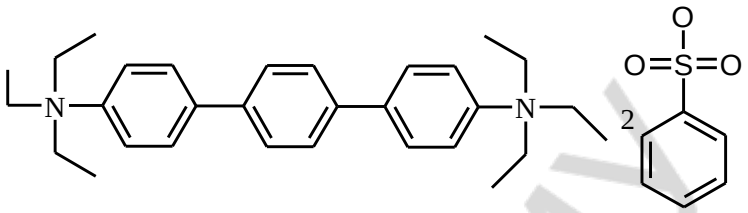
4. Convert name to structure and identify the type of conjugation.

Name	**Formula**	**Conjugation type**
Buta-1,3-diene		
Vinyl chloride (chloroethene)		
Propanoic acid		
Methyl propenoate		
Phenol		
Aniline (aminobenzene)		
2-(3,4-Dihydroxyphenyl)ethyl amine (*Dopamine*)		
Pyrrole		
Propenal		
Nitrosourea		
3-Hydroxy-6-methyl-2-ethyl pyridine succinate (acting principle of *Emoxypine*, is an antioxidant)		

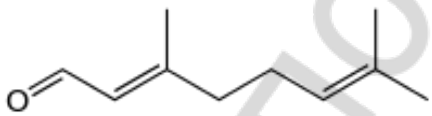
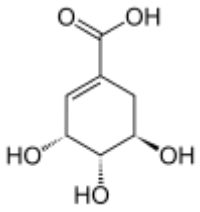
5. Fill the blank cells in the table.

Compound	Formula	Factors required for aromaticity
Naphthalene		
Phenanthrene		
Pyridine		
Pyrrole		
Pyridine		
Tropylium (cyclohepta-1,3,5-trienium) cation		
Thiophene		
Indole		

6. Indicate the charges on atoms of glutamine (proteinogenic amino acid) and *Tercuronium* (quaternary ammonium muscle relaxant).

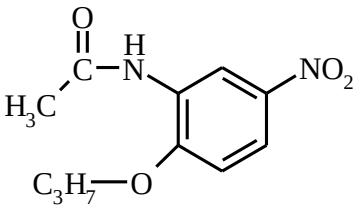
 ***Glutamine***	 ***Tercuronium***

7. Show graphically the influence of substituents on distribution of electrons in double bond. Indicate the effects (induction/mesomerism) and cumulative action of the substituents (donor/acceptor).

2-Methylbuta-2-ene	3,3,4-Trifluoropropene	Phenylacetylene
2- Methoxypropene	Cyclopent-2-enone (C=C bond)	*trans*-1-Nitrobuta-1-ene
Dimethyl sulfoxide	*cis*- Hept-2-enoic acid (C=C bond)	Ethyl cinnamate (C=O bond)
N-Ethenyl piperidine	*trans*-Oct-5-enoic acid (C=O bond)	Hexa-2,4-dienoic acid
Geranial 	Shikimic acid 	

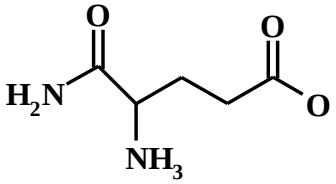
8. Show graphically the influence of each of functional groups on distribution of electrons in benzene ring of the molecule of vanillin (4-hydroxy-3-methoxybenzaldehyde).

9. Show graphically the influence of substituents on distribution of electrons in aromatic system. Indicate the effects (induction/mesomerism) and cumulative action of the substituents (donor/acceptor).

Phenol	N-Methyl aniline	Methyl benzoate
Salicylic acid	p-Aminophenol	p-Nitroaniline
p-Aminobenzenesulfonic acid	Cinnamic acid (3-(phenylpropenoic acid)	*Falimintum* 

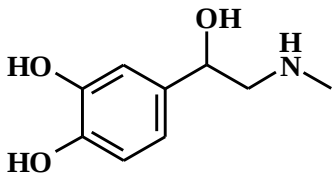
10. Compare the distribution of electrons in benzene rings of tyrosine (2-amino-3-(4-hydroxyphenyl) propanoic acid) and phenylalanine (2-amino-3-phenylpropanoic acid).

11. Assign charges to all appropriate atoms and formal charges to atoms forming the double bonds for glutamine (one of the proteinogenic* amino acids).

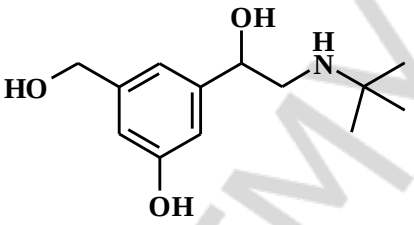


* Proteinogenic amino acids are incorporated biosynthetically into proteins during translation.

12. Show graphically the influence of functional groups on distribution of electrons in benzene ring of the molecules of *Epinephrine* (hormone and neurotransmitter, also used as medication) and *Salbutamo*l (a bronchodilator, which is a substance that dilates the bronchi and bronchioles, decreasing resistance in the respiratory airway and increasing airflow to the lungs. They are both in the List of Essential Medicines* proposed by World Health Organization).



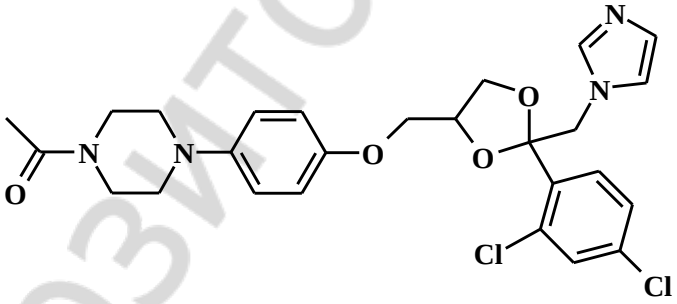
Epinephrine



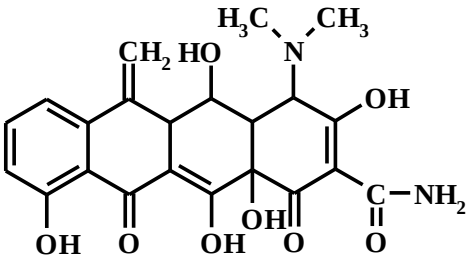
Salbutamol

13. Range following substances (phenol, 3-nitrobenzenesulfonic acid, benzene, 1,3-dinitrobenzene, anisole, benzyl alcohol) according to increase of charge in benzene ring. Explain your choice.

14. Find the aromatic fragments and indicate the conjugation types in *Ketoconazole* (a synthetic imidazole antifungal drug). Show graphically the influence of substituents on distribution of electrons in aromatic fragments and double bond.



15. Find the aromatic fragments and indicate the conjugation types in *Doxycycline* (tetracycline antibiotic). Show graphically the influence of substituents on distribution of electrons in aromatic fragments and double bond.



Signature of teacher:

* The list of the most effective and safe drugs covering the most important needs in a healthcare system.

LABWORK № 3
STEREOISOMERISM AND STEREOCHEMISTRY

Objective: to study spatial arrangement of atoms that form the structure of molecules and their manipulation.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.

Problems for discussion:

1. Configuration and conformations.
2. Spatial molecular models and formulas.
3. Chirality and symmetry of molecules.
4. Diastereomers and enantiomers.
5. Conformational analysis of aliphatic and cyclic compounds.
6. Stereochemistry in life systems.

PRACTICE PROBLEMS

1. Give definitions:

Stereoisomers are _____

_____

_____

Enantiomers are _____

_____

_____

Diastereomers are _____

_____

_____

Chirality is _____

_____

_____

Asymmetric carbon is _____

_____

_____

2. Write the formulas of the following compounds. In chiral molecules define asymmetric carbon atoms. In achiral molecules find the symmetry elements, excluding chirality.

Butane

3-Methylhexane

Propan-1,2-diol

Glycerol

Glycine (2-aminoethanoic acid)

Alanine (2-aminopropanoic acid)

Cyclohexanol

Cyclohex-2-en-1-ol

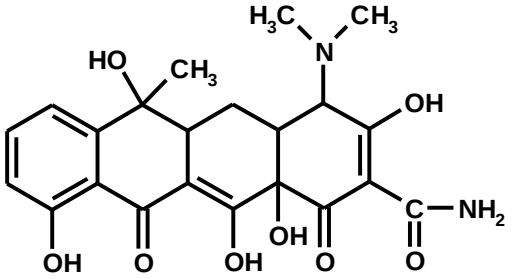
cis-Cyclohexane-1,2-diol

trans-Cyclohexane-1,2-diol

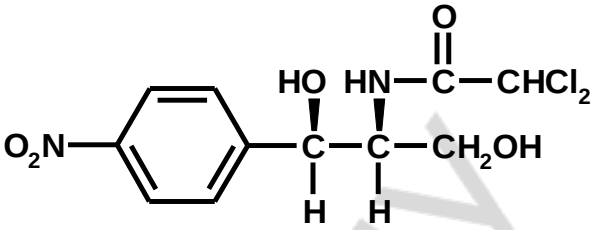
Carvone
(2-methyl-5-(1-methylethenyl)cyclohex-2-enone)

Menthol
(2-isopropyl-5-methylcyclohexanol)

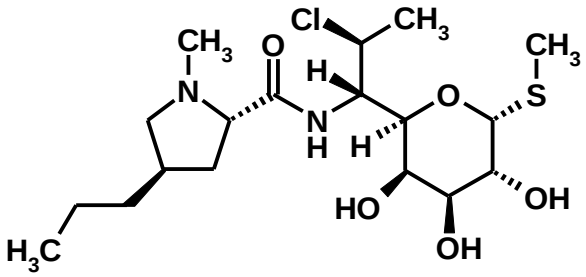
3. Find functional groups, structural fragments and chiral centers in pharmaceutical drugs



Sumycin (the first representative of *tetracycline* antibiotics)

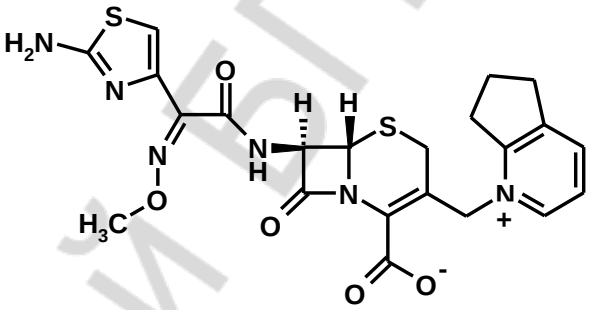


Chloramphenicol (antibiotic)



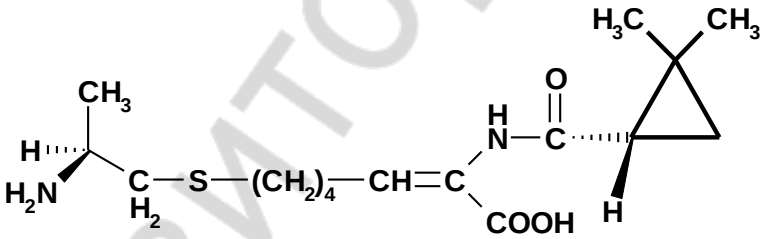
Clindamycin

(antibiotic with a primarily bacteriostatic effect; it is a bacteria protein synthesis inhibitor by inhibiting ribosomal translocation, in a similar way to macrolides)



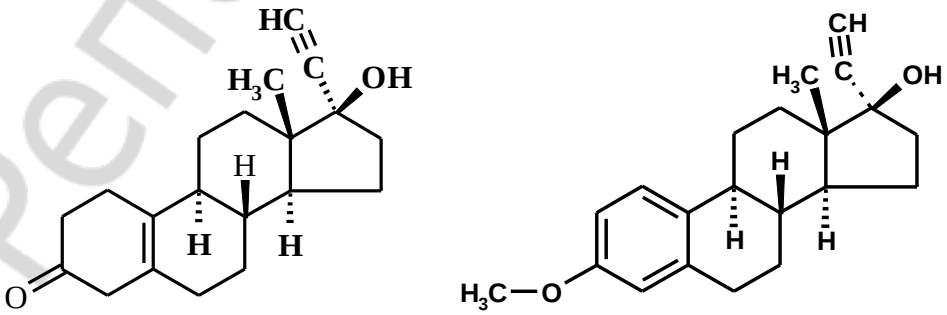
Cefpirome

(a fourth-generation c*ephalosporin*, which is a class of β-lactam antibiotics originally derived from the fungus *Acremonium*, which was previously known as *Cephalosporium*)



Cilastatin

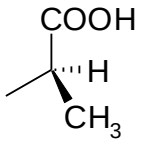
(a chemical compound which inhibits the human enzyme dehydropeptidase and can therefore be combined in *Primaxin* with β-lactam antibiotic *Imipenem* in order to protect it from degradation)



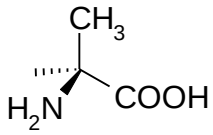
Norethynodrel and *Mestranol*

(components of the combined oral contraceptive *Enovid*)

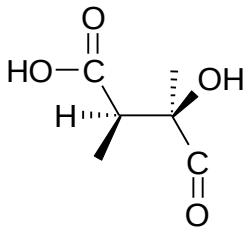
4. Finish formula drawing by adding missed fragments. For chiral compounds draw the second enantiomer.



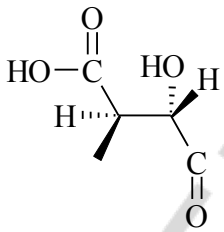
D-Lactic acid



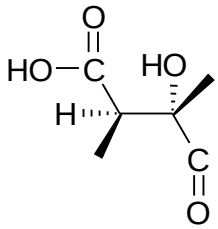
L-Alanine



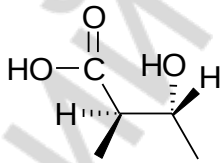
dextro-Tartaric acid



meso-Tartaric acid



levo-Malic acid



Methyl *meso*-tartrate

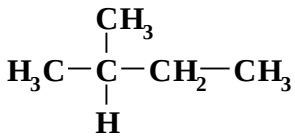
5. Give definition: **racemate** is _____

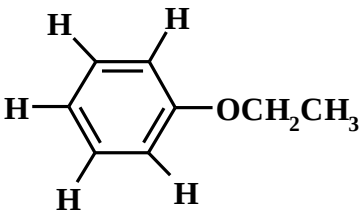
_____

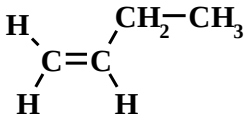
6. Draw the examples of π- and σ-diastereomers (2 for each type). Give the names.

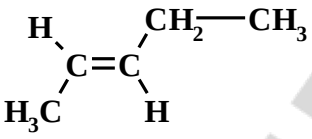
7. Write down the formulas of the isomeric pentanedienes and consider their spatial structure. Indicate which of these are diastereomers and enantiomers.

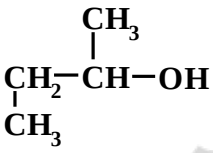
8. Define various structural types of protons in the following compounds. If there are two or more protons of the same type to indicate which of them are homotopic (H), enantiotopic (E) and diastereotopic (D).

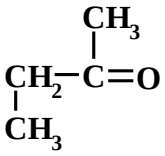


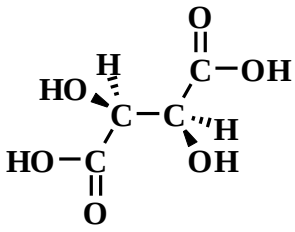


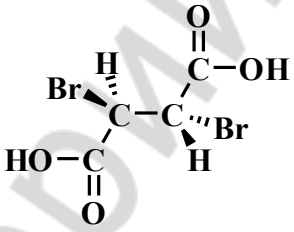






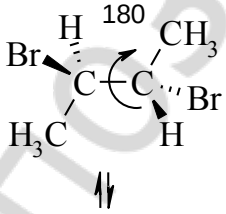


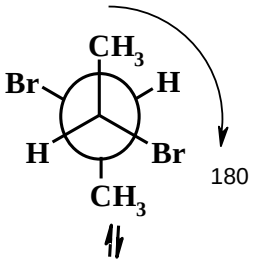




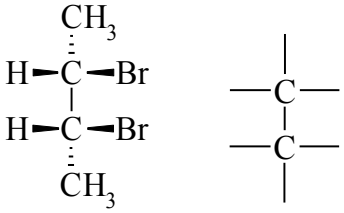
9. Transform perspective formula of *meso*-2,3-dibromobutane successively in *Newman* projection, and then in *Fischer* projection.

Staggered conformation



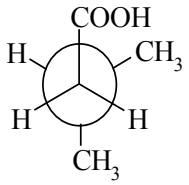


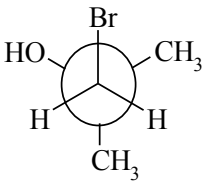
Eclipsed conformation

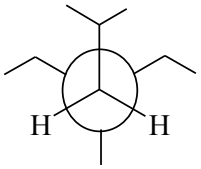


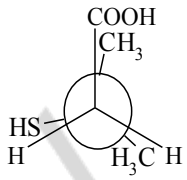
Newman projection *Fischer* projection

10. Draw the perspective formulas of substances, presented in *Newman* projections.









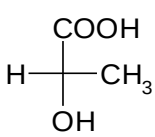
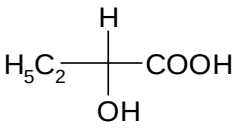
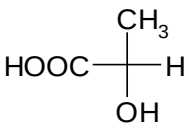
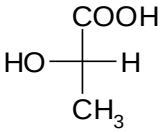
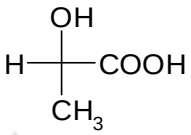
11. Write *Newman* projections for all staggered conformations (looking along the C_1-C_2 bond) of *Halothane* (trademarked as *Fluothane*, 2-bromo-1,1,1-trifluoro-2-chloroethane) which is inhaled as a general anesthetic.

12. Write *Newman* projections for all staggered and eclipsed conformations of γ-aminobutyric acid, looking down the C_2-C_3 bond.

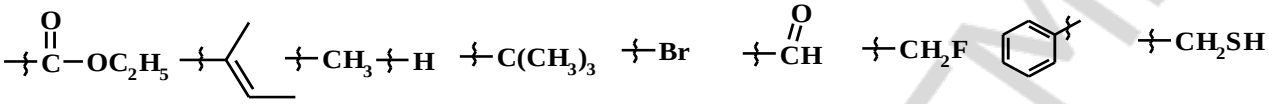
13. Write *Newman* projections for all conformations of butane, looking along the C_2-C_3 bond. Select the most stable and explain your choice.

14. Write and name *Newman* projections for all conformations of ethylene glycol, looking along the C_1-C_2 bond. Select the most stable and explain your choice taking in account the formation of intramolecular hydrogen bonds.

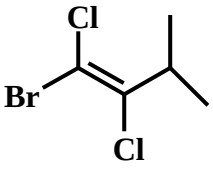
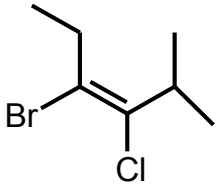
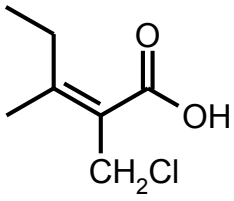
15. Find enantiomers from compounds presented below.

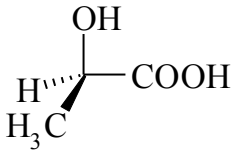
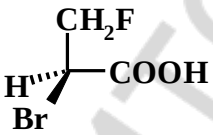
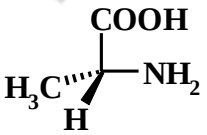
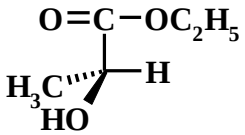
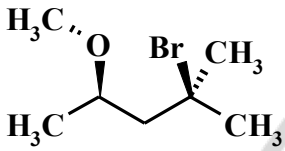
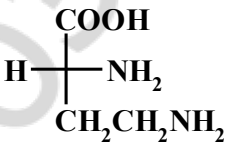
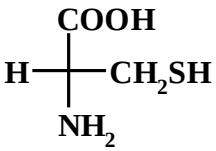
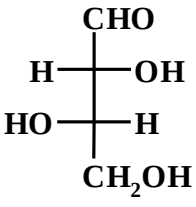
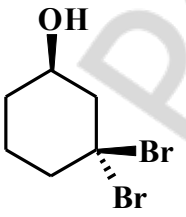
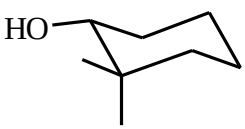
16. Rank priority of the groups (*Cahn–Ingold–Prelog* priority rules).



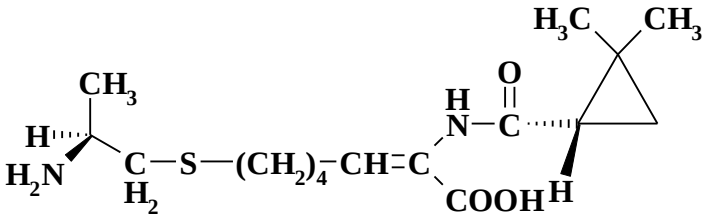
17. Name the substances (IUPAC names; E/Z and, if applicable, *cis*/*trans* discriptors).

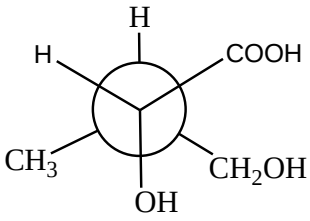
18. Determine configuration (R/S) of chiral centers. Indicate the priority of substituents. Assign, if applicable, L- and D-series.

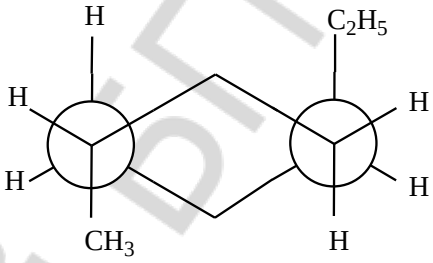











19. Assign the configuration (R/S) of chiral centers in *Cylastine* (*Thyenam* component).

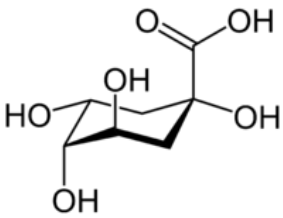


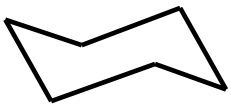
20. Give the names to substances (IUPAC names and stereochemical nomenclatures). Find (if it's possible) the plane(s) of symmetry.





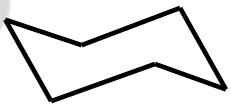
21. Natural quinic acid is a versatile chiral starting material for the synthesis of new pharmaceuticals. A medication *Tamiflu* for the treatment of influenza A and B strains has been successfully developed and launched into the market.
Complete consecutively templates presented below:



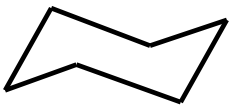


Draw only axial substituents

Draw only equatorial substituents



Draw all the substituents



Draw all the substituents in inverted form

22. Write both chair conformations for *cis*- 4-*tert*-butyl cyclohexanol and rank their relative stability. Identify axial groups by circling them.

23. Write all chair conformations for both *cis* and *trans* isomers of 1,2-dichlorocyclohexane. Rank all four conformations in terms of their expected relative stability. Assign the configuration of chiral centers.

24. Write chair conformation of *cis* cyclohexane-1,3-diol, which allows the formation of the intramolecular hydrogen bond.

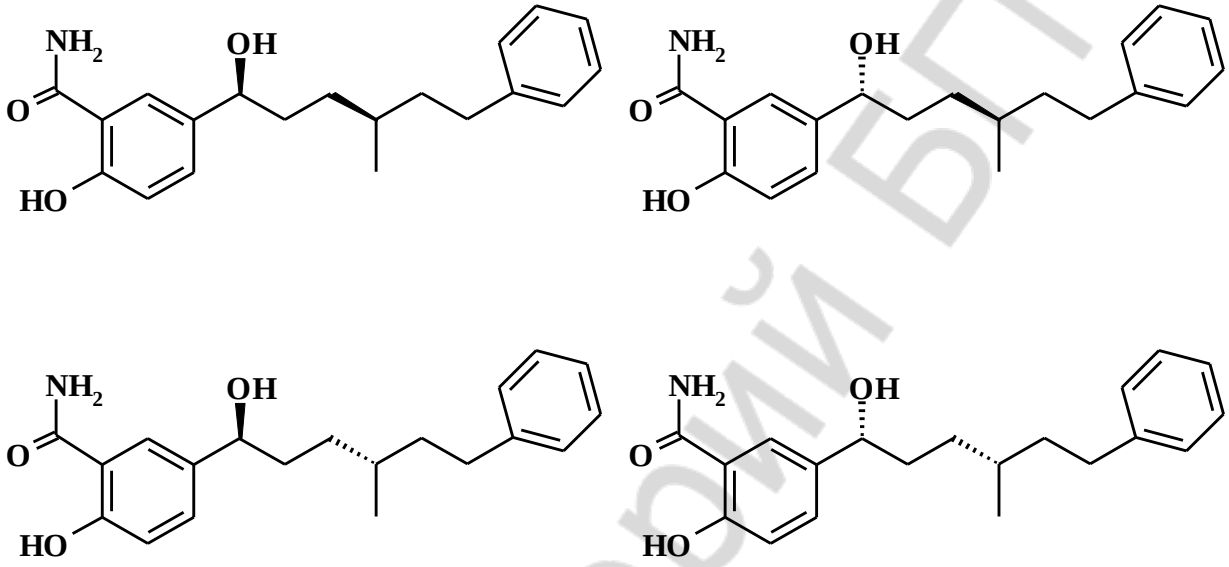
25. Write conformation of piperidin-4-ol, which allows the formation of the intramolecular hydrogen bond.

26. Write plane and chair conformations for both *trans*- and *cis*-decalins. Rank all isomers in terms of their expected relative stability.

27. There are some general principles of drug action that are applicable to many drugs. *Nobel* prize winner *Paul Ehrlich* develops the idea of receptor blockade concept. Binding is orthosteric in most cases, which means that the drug binds to the receptor within the same site as the receptor's physiological ligand. A drug that activates its receptor is referred to as an agonist, whereas an inhibitory drug is also called an antagonist. Therefore, only one or the other may have therapeutic value; for example, with histamine receptors, only antagonists are clinically useful.

Labetalol, an α- and β-adrenergic agent, is a mixture of four stereoisomers. The R,R-isomer carries most of the β-adrenergic (β-antagonist), whereas the S,R-isomer carries most of the α-blocking activity (α-antagonist). The R,S- and S,S-isomers are not active (or inert).

Find and indicate the corresponding structures from formulas shown below.



Signature of teacher:

LABWORK № 4
CHEMICAL REACTIVITY

Objective: to study classification and mechanisms of organic reactions.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.

2. *Машковский, М. Д.* Лекарственные средства / М. Д. Машковский. 16-е изд., перераб., испр. и доп. Москва : Новая волна, 2012.

Problems for discussion:

1. Different ways of organic reactions classification.
2. Classification of organic reactions by reaction change and reaction type.
3. Acidity and basicity.
4. The main principles of *Brønsted* and *Lewis* theories, examples of *Brønsted* and *Lewis* acids and bases.
5. Reactants and reagents.
6. Nucleophiles and electrophiles.
7. Reaction characteristics and factors that influence reactions (enegertics, electronic, steric, stereoelectronic and solvent effects.
8. Basic concepts about the mechanisms of organic reactions.
9. Steps of chemical reaction and intermediates, the arrow notation and writing of reaction mechanisms.

PRACTICE PROBLEMS

1. Write the examples of pharmaceuticals possessing the properties of -OH, -SH, -NH и -CH acids (you can use [2] for substance search). Explain your choice.

–OH acids (4 examples)

–SH acids (2 examples)

–NH acids (3 examples)

–CH acids (2 examples)

2. Write examples of pharmaceuticals possessing the properties of bases (you can use [2] for substance search). Explain your choice.

π Bases (3 examples)

p Bases (4 examples)

3. Write the following compounds and rank their acidity, from 1 (most) to 4 (least). Write corresponding conjugated bases and rank their basic properties.

Acetic, lactic, β-hydroxybutyric and γ-hydroxybutyric acids

Methyl, ethyl, trifluoromethyl and *tert.*-butyl alcohols

Phenol, picric acid, 4-nitrophenol, 3,4-dimethoxyphenol

Butylamine, ammonia, pyrrole, pyridine

Ethanol, ethanthiol, ethylamine

Glycerol, ethylene glycol, resorcinol, 2-ethoxyethanol

4. Write 3 pharmaceuticals [2], possessing the properties of amphoteric substances.

5. Write 3 pharmaceuticals [2], possessing the properties of *Lewis* acids.

6. Give definition.

Free radical is _____

_____

Write 4 unstable and two stabilized radicals.

7. Give definition.

Nucleophile is _____

_____

Give 2 examples (for each problem) of reagents possessing the properties of nucleophiles:

ions with lone electron pair;

neutral molecules with lone electron pair;

neutral molecules which get lone electron pair in heterolysis.

8. Give definition.

Electophile is_____

_____

Give 2 examples (for each problem) of reagents possessing the properties of electophile:

ions with free (vacant) orbital;

neutral molecules with free (vacant) orbital;

neutral molecules which gets vacant orbital in heterolysis.

9. Write chemical reactions and classify each as by structural change type (addition, elimination or substitution) and reagent type (nucleophilic, electrophilic or radical):

a) reaction of cyclohexane with chlorine under UV irradiation

b) reaction of 2-methylpent-2-ene with bromine in tetrachloromethane as solvent

c) reaction of pent-1-yne with chlorine

d) reaction of chlorocyclohexane with butyllithium

e) reaction of chlorocyclohexane with aqueous sodium hydroxide

f) reaction of 1-bromo-1-methylcyclohexane with alcoholic sodium hydroxide

g) cyclopentanone hydrogenation in presence of palladium

i) acid catalyzed reaction of isobutiric acid with ethanol

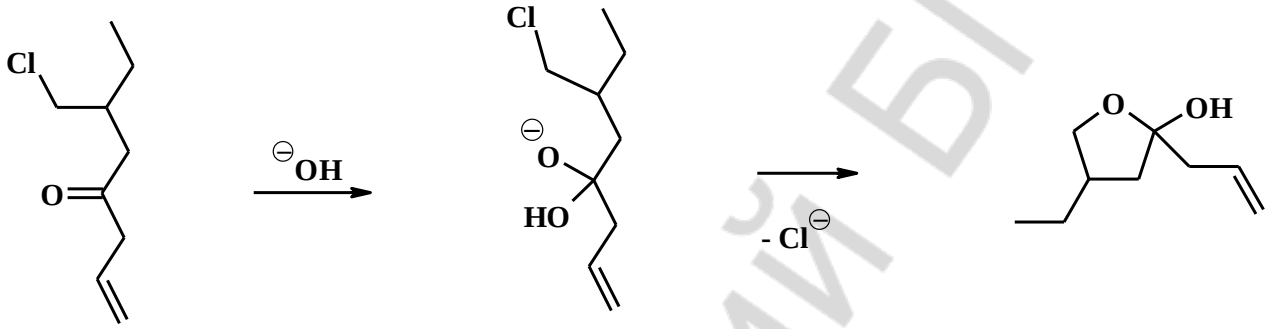
j) reaction of ethyl lactate with isoamyl alcohol

k) iron catalyzed reaction of benzene with bromine

l) the acid-base reactions of lactic acid with sodium hydroxide and methylamine

m) the acid-base reactions of 4-aminobutanoic acid with ammonium carbonate, benzyl amine, acetic acid.

9. Draw arrows to show electron transfer in the following two steps. Draw a circle around the nucleophilic atom in step 1 and in step 2.



10. Write pharmaceuticals [2]. Find reactivity centers. Write reaction of hydrochloride formation.

Diphenhydramine (antihistamine)

Chloramphenicol (antibiotic)

Quinidine (antiarrhythmic agent)

EXPERIMENTAL SECTION

CHEMICAL PROPERTIES AND QUALITATIVE FUNCTIONAL ANALYSIS

The methods available for the identification of the functional groups involve chemical reactions that are characteristic of the individual groups. However within the past few years numerous instruments have become available that provide considerable information regarding many functional groups. Most of these instrumental methods make use of some type of spectroscopy. The instrumental methods which are most useful for the qualitative analysis of organic compounds are ultraviolet and visible absorption spectroscopy, infrared spectroscopy, nuclear magnetic spectroscopy, and mass spectroscopy. Therefore, chemical methods of identification are still in use. Organic compounds are generally recognized by the detection of the functional group that is present in the molecule. For example, detection of the carbonyl group indicates an aldehyde or a ketone; the presence of nitrogen with basic properties indicates the presence of amine; detection of hydroxyl groups indicates either alcohols or phenols.

In this lab section we're beginning to study of functional group detection and will pursue the tradition in next Lab sessions. You will use in your educational problems both chemical methods and instrumental methods to detect the structure of organic compounds.

Experiment 1. Preparation of sodium ethoxide and its hydrolysis.

Place 10 drops of ethanol*[*] in a dry test tube, and add a small piece of sodium metal* with a tweezers (You must previously remove kerosene from the Sodium surface by placing it between sheets of filter paper). Close the tube with a stopper and gather the hydrogen formed. Bring the tube to the burner and remove the plug. A mixture of hydrogen and air burns with a characteristic "barking" sound.

Dissolve the white precipitate of sodium ethoxide in 3–4 drops of ethanol* and add 1 drop of 1 % phenolphthalein*. The indicator remains colorless. After adding 1–2 drops of water in tube magenta coloration appears.

Write a reaction scheme of sodium ethoxide formation, followed by its hydrolysis. Why does water dissolves sodium ethoxide?

Whether you can detect acidic properties of isoamyl alcohol using common acid base (pH-) indicators?

Experiment 2. Preparation of sodium phenoxide and its acidic hydrolysis

Place 10 drops of phenol-water* emulsion in a test tube and shake the mixture. Add dropwise 10 % solution of sodium hydroxide (21) to emulsion till the solution become clear. After adding of a few drops of 10 % sulfuric acid (23) you will observe the formation of opaque emulsion.

Write a reaction scheme for formation and hydrolysis of sodium phenoxide. Why does phenol react quantitatively with sodium hydroxide in contrary to ethanol?

* Notice: reagents marked with asterisk (*) are in the fume hood.

Why does the addition of sulfuric acid lead to formation of turbid emulsion? Write a reaction scheme.

Experiment 3. Detection of acidic properties of stearic acid.

The redox reaction between iodide and iodate slightly acidic medium leads to free iodine formation, and is used to detect weak organic acids (in particular fatty acids, such as palmitic, stearic, etc.). These acids are not detected by acid-base indicators.

In each of the two test tubes add 2 drops of 10 % potassium iodide (20) solution and 2 drops of 4 % potassium iodate (1) solution. Then, add 2 drops of 10 % alcoholic solution of stearic acid* to one of them. Heat both tubes for 1 minute in a boiling water bath. After cooling, add to each tube 2 drops of starch emulsion*. Compare coloring in both tubes.

Write a scheme of redox reaction between iodide (NaI) and iodate ($NaIO_3$). Explain the role of steric acid in this reaction.

Experiment 4. Basic properties of aliphatic and aromatic amines.

Place 2 drops of water in the two test tubes. Add to the first tube 1 drop of aniline*, and to the second — 1 drop of diethyl amine*. Agitate both tubes. Use universal indicator or *red litmus* to detect approximately pH of both solutions.

Add 1 drop of 10 % hydrochloric acid (9) to aniline emulsion in first tube. You can observe the formation of transparent solution. Then add 3 drops of saturated aqueous picric acid solution (5) to a solution of diethyl amine* in the second tube, agitate the mixture and cool the tube in a glass with a cold water, in few minute diethyl amine picrate precipitate is formed.

Compare basicity and solubility in water of diethyl amine and aniline.

Explain the formation of transparent solution after the addition of hydrochloric acid to aniline emulsion. Write the scheme of the reaction.

Write the scheme of the reaction between diethylamine and picric acid (2,4,6-trinitrophenol).

Signature of teacher:

LABWORK № 5
SEPARATION AND PURIFICATION OF SUBSTANCES IN SOLVENT EXTRACTION

Objective: to study separation and purification of substances in solvent extraction.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.

Problems for discussion:

1. The main classes of biologically active substances isolated from natural raw materials, their acidic and basic properties.
2. Methods of separation and purification of substances from natural raw materials.
3. Solvents and solubility in organic and bioorganic chemistry.

EXPERIMENTAL SECTION

Experiment 1. Extraction of colorings from pine needles.

1.1. Solid-phase extraction.

In this section you extract the pigment from pine needles by using of organic solvent.

- The needles were crushed mechanically into a powder form using a mortar and a pestle.
- The pine needle powder (2–5 g) is stirring in 20 mL of toluene* (use 50 mL conical flask also known as an *Erlenmeyer* flask) for 10 min and then keep the extract for 5 min.
- The extract is decanted from precipitate into glass (50–100 mL).
- The precipitate is extracted for 3 more times using for each 10 mL of toluene*.

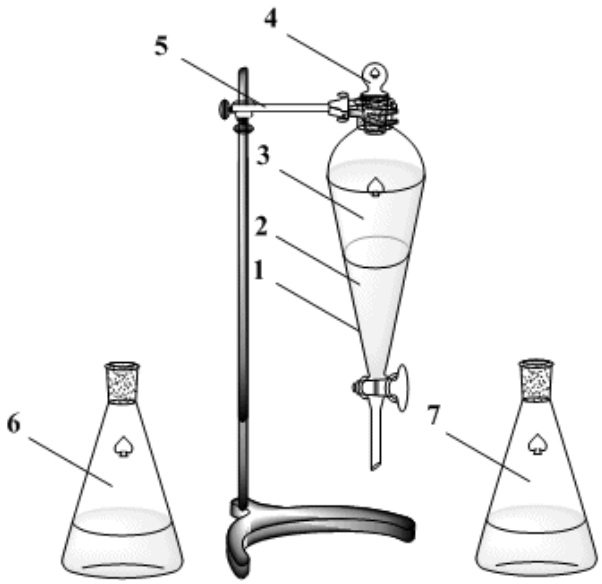
1.2. Liquid-phase extraction.

In this section you purify the pine extract from carboxylic acids. The procedure includes: 1) liquid-phase extraction to aq. sodium hydroxide solution; 2) washing the traces of base from pine extract.

Use separatory funnel (sep funnel) for liquid-phase extraction. Before extraction examine funnel.

- Examine the junction of stopcock with funnel for free rotation;
- Fix the funnel on tripod bars;
- Pour 10-20 mL of water into the funnel and examine whether the cock controls the flow of liquid in proper way in closed and opened state;

After funnel being examined you can proceed the extraction.



1. Sep funnel
2. More dens phase
3. Less dense phase.
4. Stopper
5. Holder.
6. Glass for pine extract fraction.
7. Glass for washing extract fraction.

1. Fix the sep funnel (50–100 mL) on stand, closing the stopcock.

2. Transfer the toluene pine extract to a sep funnel and add 5–10 mL of diluted aq. NaOH*. Note which layer is organic and which is aqueous.

3. Stopper the funnel, invert it and open the stopcock to vent the vapors. Alternate between gently shaking the funnel and venting vapors by opening the stopcock. Toward the end of the extraction, you may shake more vigorously to be sure the extraction is complete. Place the sep funnel in a ring clamp, allow the layers to separate completely, then drain the lower layer into a 50 mL conical flask labeled Flask A. Add another 5–10 mL of aq. NaOH* to the sep funnel, shake the mixture as before and add this lower layer to Flask A. Make a note of the contents of Flask A in your notebook.

1.3. Washing NaOH from extract.

Add 10 mL of water to the sep funnel, shake the mixture thoroughly with venting as above, allow the layers to separate, and drain the lower layer into a conical flask labeled Flask B. Add another 5 mL of water to the sep funnel, shake the mixture as before and add this lower layer to Flask B. Make a note of the contents of Flask B in your notebook. Control the process with indicator till pH will be 7.

At this point, a significant amount of water is present in the ether layer. It can be removed by performing of anhydrous sodium sulfate* (if it’s absent you can use magnesium chloride as an alternative) as drying agent to form hydrate form.

Measure the volume of the extract obtained and fix results and observations from experiment in notebook.

Experiment 2. Extraction of yellow colorants from citrus peel.

1. The citrus peels are cut mechanically into a pieces using a knife or scissors.
2. Place citrus peel mass in a conical flask and add 50 mL of ethanol*.
3. Stir the mixture under reflux for 30 min.
4. The extract is decanted from precipitate into glass (50–100 mL).
5. The precipitate is extracted for 3 more times using for each 10 mL of ethanol*.

Measure the volume of the extract obtained and fix results and observations from experiment in notebook.

Write down the formula of basic colorants belonging to the citrus peel. Determine the chiral centers and the main reaction, the chromophore group.

Signature of teacher:

LABWORK № 6
TEST № 1 "STRUCTURE AND NOMENCLATURE OF ORGANIC COMPOUNDS"

Remind the program material from the theme 1 to 5.

Recommended literature: study the literature from the themes 1 to 5.

Questions to the concluding test:

1. Constitution and isomerism of organic compounds.
2. Classification of organic compounds.
3. IUPAC nomenclature of organic chemistry.
4. Organic chemistry laboratory: equipment, glassware and reagents.
5. Chemical bonding in organic compounds.
6. Charge distribution in organic compounds. Induction and mesomerism. Electron donating and electron withdrawing substituents.
7. Conjugated systems. Conjugation energy.
8. Aromaticity. *Huckel's* rule. Aromaticity of benzoic and non-benzoic systems.
9. Configuration and conformations.
10. Spatial molecular models and formulas.
11. Chirality and symmetry of molecules.
12. Diastereomers and enantiomers.
13. Conformational analysis of aliphatic and cyclic compounds.
14. Stereochemistry in life systems.
15. Classification of organic reactions (by reaction change and reaction type).
16. Variables of organic reactions Acidity and basicity (the main principles of *Brønsted a*nd *Lewis* theories, examples of *Brønsted* and *Lewis* acids and bases).
17. Reactant and reagents.
18. Nucleophiles and electrophiles.
19. Reaction characteristics and factors that influence reactions (enegertics, electronic, steric, stereoelectronic and solvent effects.
20. Mechanisms of organic reactions (basic concepts, steps of chemical reaction and intermediates, the arrow notation and writing of reaction mechanisms).
21. The main classes of biologically active substances from natural raw materials. Their acidic and basic properties.
22. Methods of separation and purification of substances from natural raw materials.
23. Solubility and use of solvents in organic chemistry.

LABWORK № 7
INSTRUMENTAL METHODS OF STRUCTURE DETERMINATION. INFRARED SPECTROSCOPY

Objective: to study the basic concepts and IR spectroscopy techniques for organic compounds analysis.

Recommended literature

1. *Chernykh, V. P.* A. Applied infrared spectroscopy : a manual for students of higher schools / V. P. Chernykh, ed. by V. P. Chernykh. Kharkiv : NUPh, 2014. 152 p.

2. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.

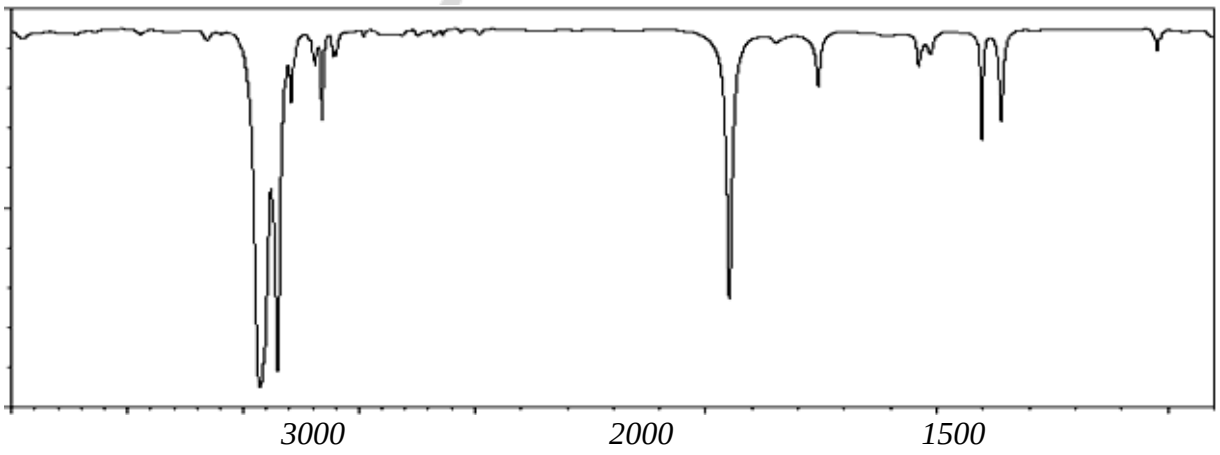
Problems for discussion:

1. Instrumental methods of organic compounds analysis.
2. Basic concepts of optical spectroscopy.
3. Spectrum of electromagnetic waves.
4. Ultraviolet spectroscopy and spectroscopy in the visible region. Types of electronic transitions.
5. The chromophore group. The displacement of the absorption bands.
6. Infrared spectroscopy
7. Molecular vibrations (stretching, bending). Interpretation of major absorption frequencies of functional groups.
8. The use of characteristic bands and lines from “fingerprints” for identification of organic compounds.

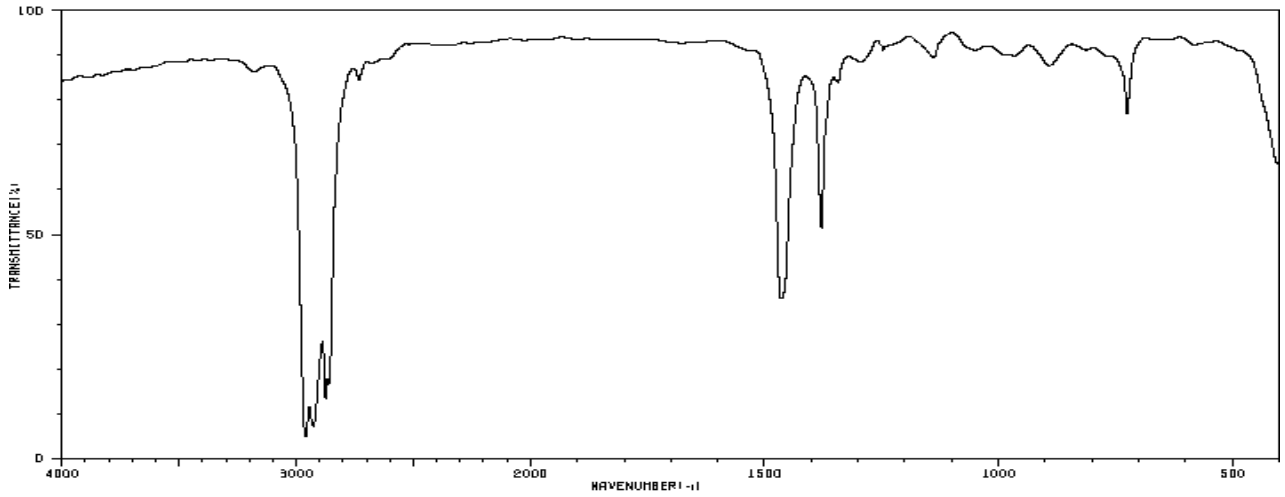
PRACTICE PROBLEMS

1. Analyze the stretching vibrations of C-H in spectra of following compounds. Explain the difference. Explain why in the spectra of hexane and methylcyclohexane bands of medium intensity at 1379 cm^{-1} and 1376 cm^{-1} are observed, and why these bands are absent in the spectrum of cyclohexane.

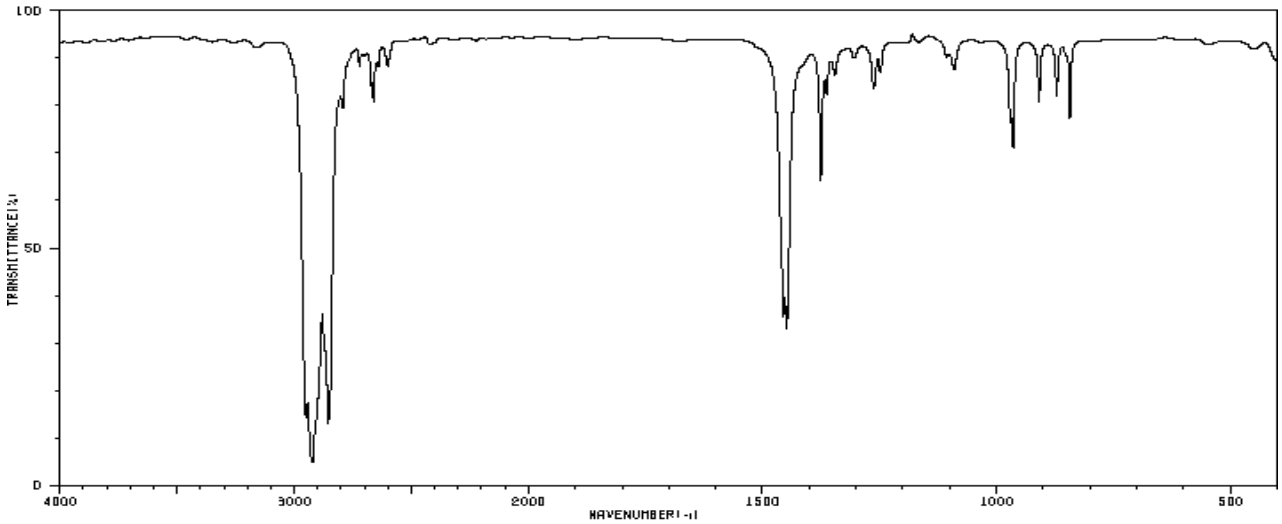
IR spectrum of cyclohexane 2953, 2875, 1450 cm^{-1}.



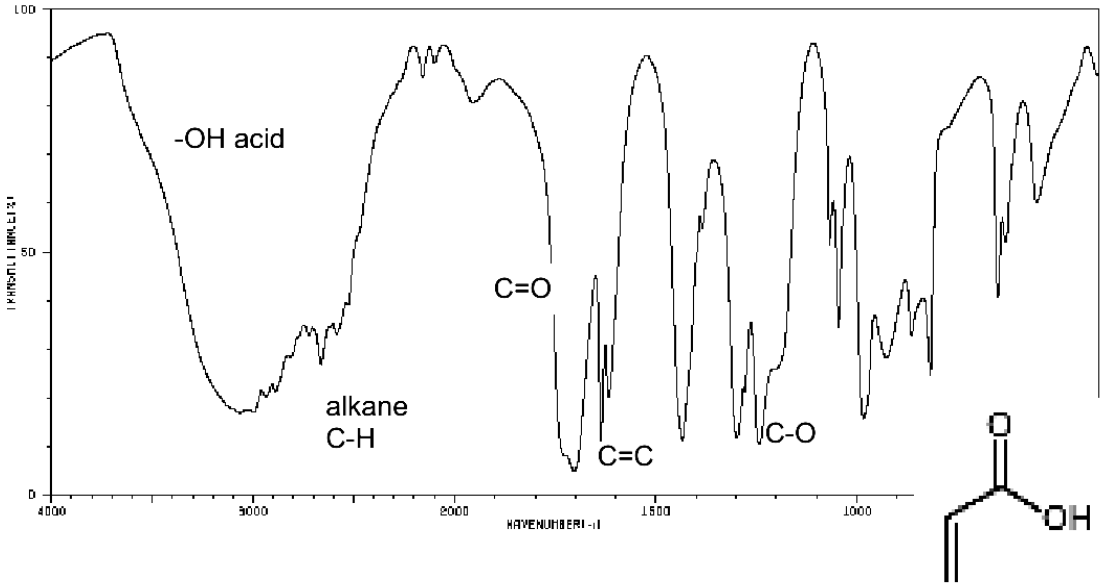
IR spectrum of methylcyclohexane 2962, 2872, 2852, 2848, 1451, 1379 cm^{-1}.

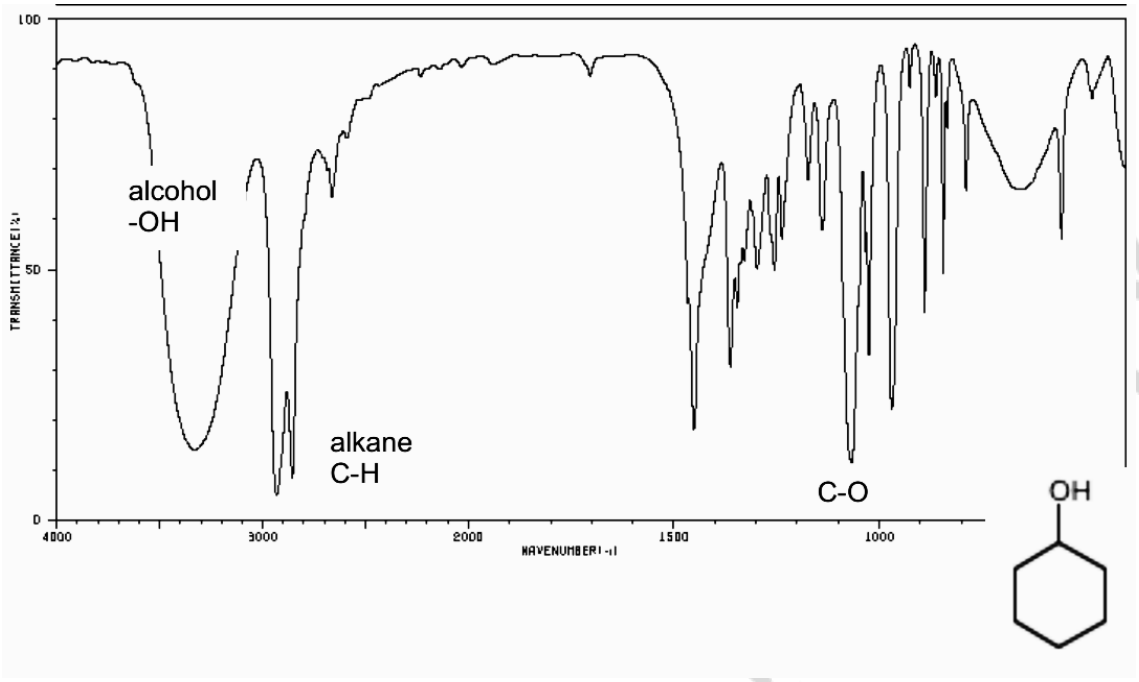


IR spectrum of methylcyclohexane 2922, 2883, 1449, 1376 cm^{-1}.



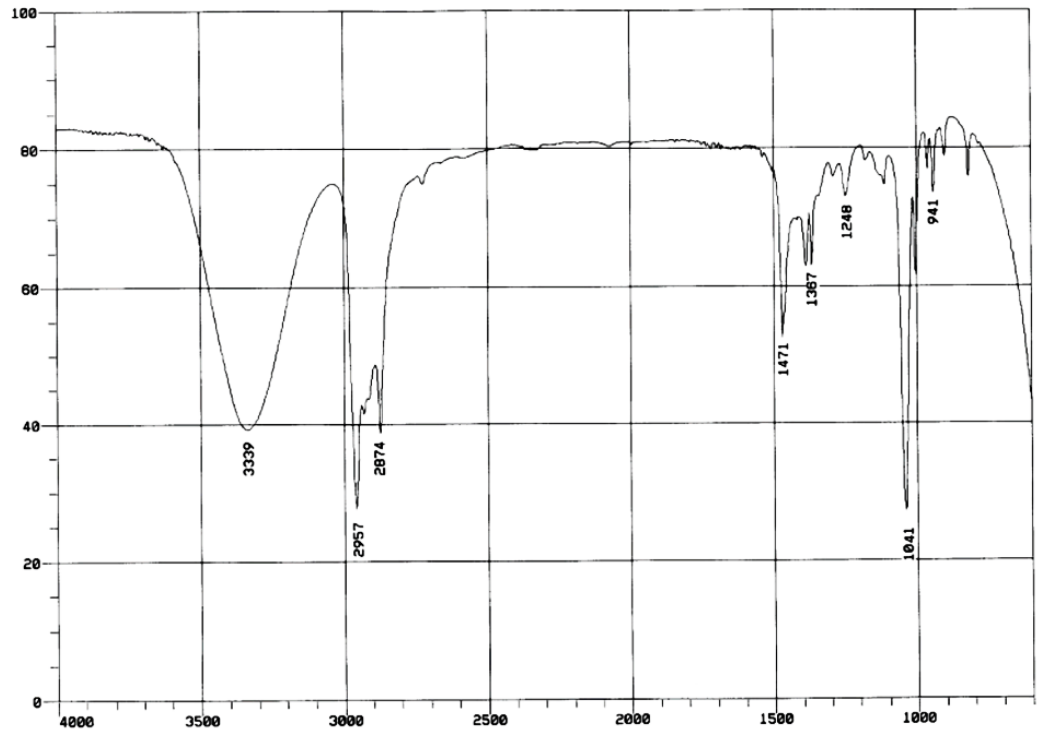
2. For each of the following IR spectra, select three IR peaks and label the functional groups to which they correspond.



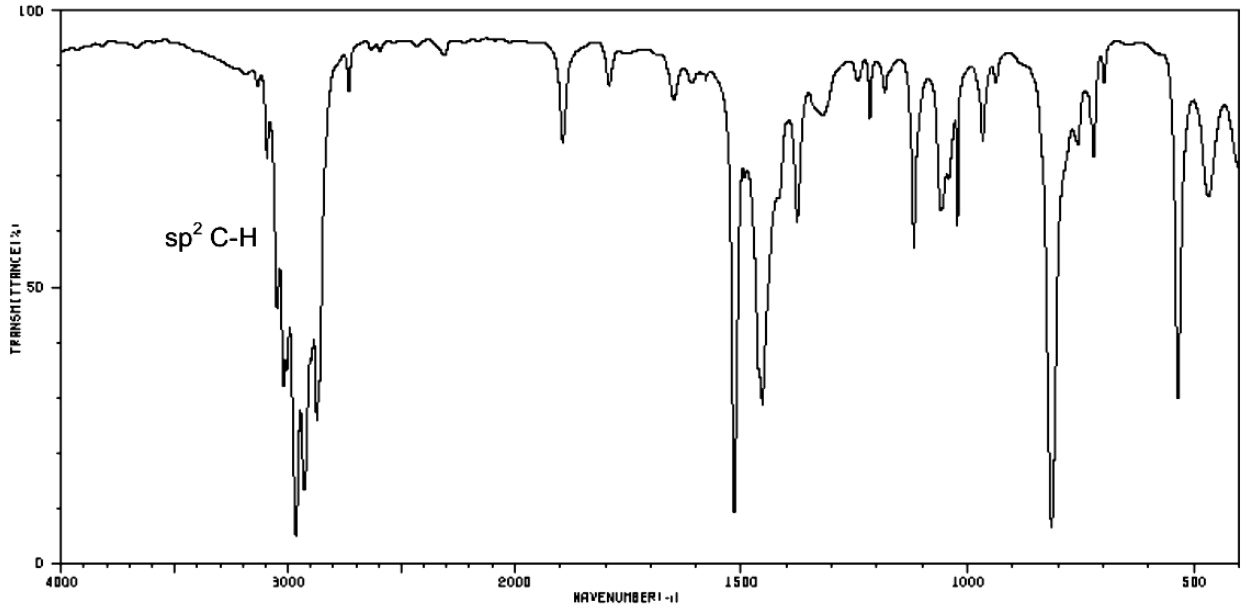


3. You find a bottle on the shelf only labeled C_3H_6O. You take an IR spectrum of the compound and find major peaks at 2950, 1720, and 1400 cm^{-1}. Draw a structural formula of the substance that was found in the bottle.

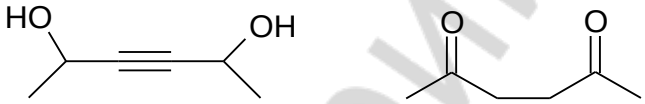
4. Find the structure for the following molecules $C_4H_{10}O$.

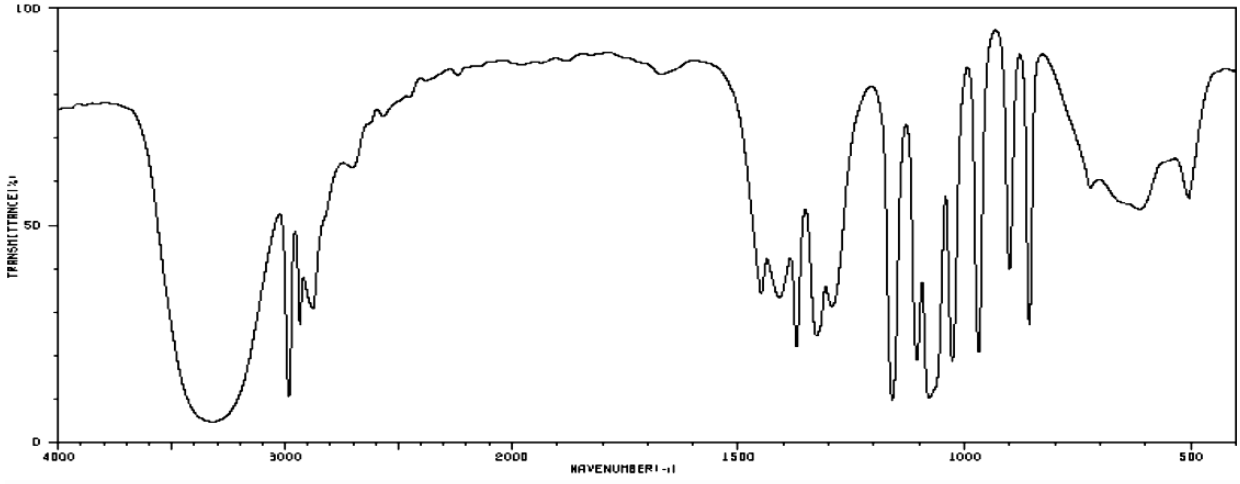


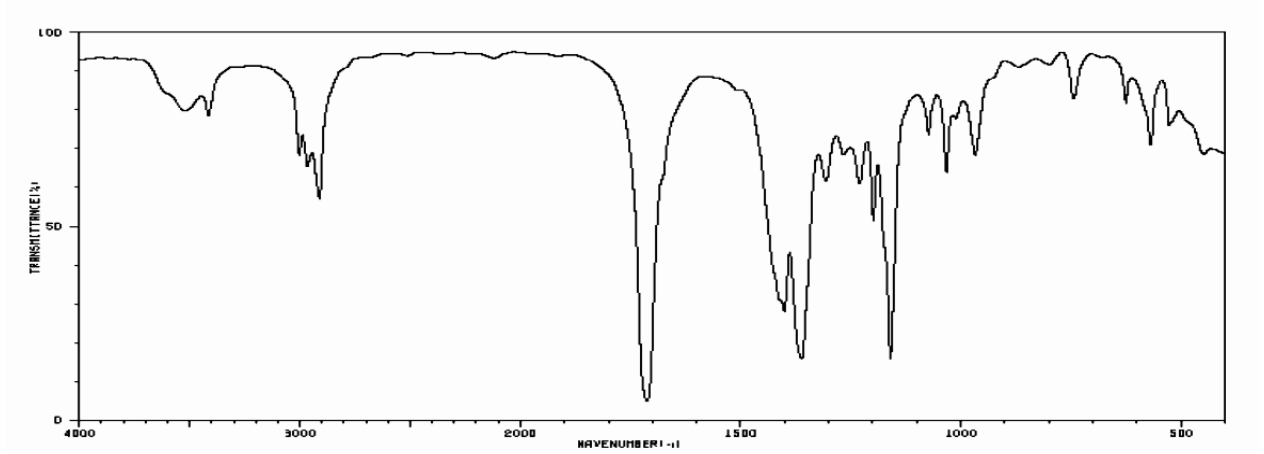
5. Use the IR data to determine the structure of the molecule C_9H_{12}.



6. Both of the following molecules have the formula $C_6H_{10}O_2$. Match each compound to its corresponding spectrum, and give an evidence for your choice.

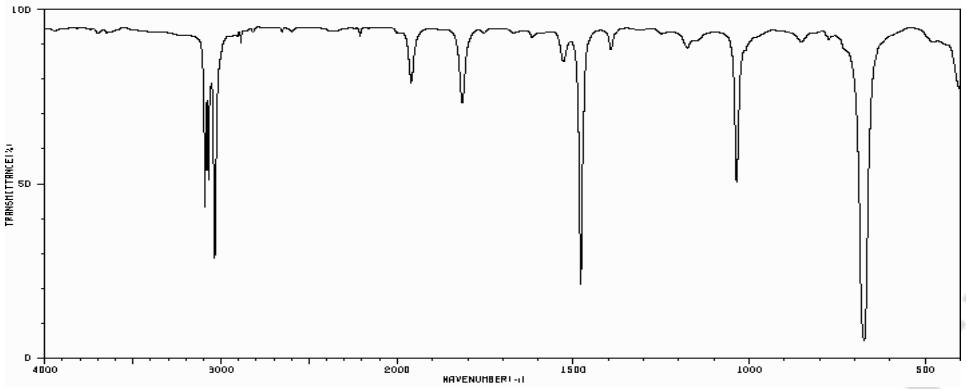




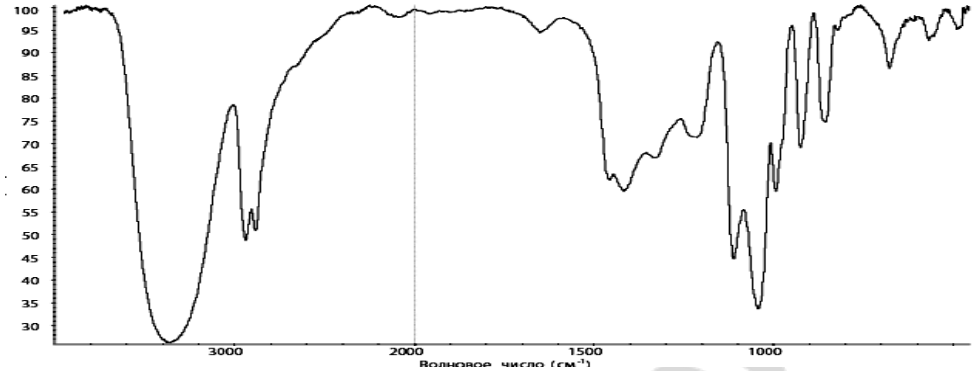


7. Analyze the following IR spectra given bellow and explain the origin of the absorption bands.

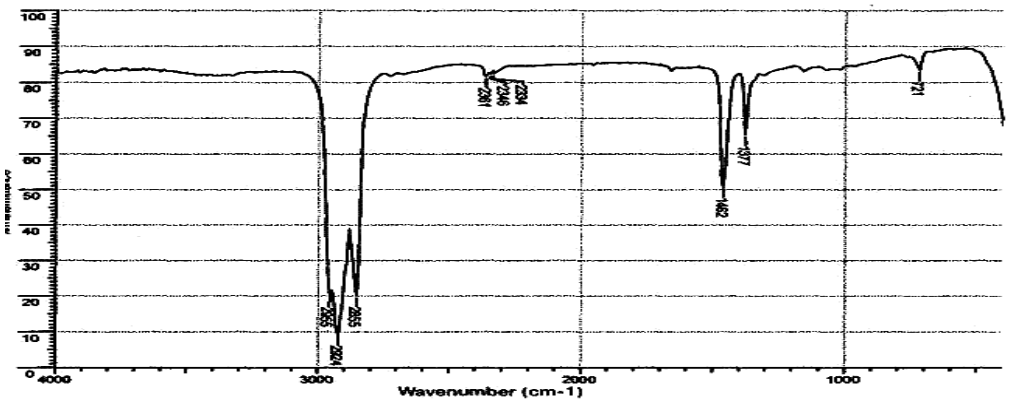
Benzene



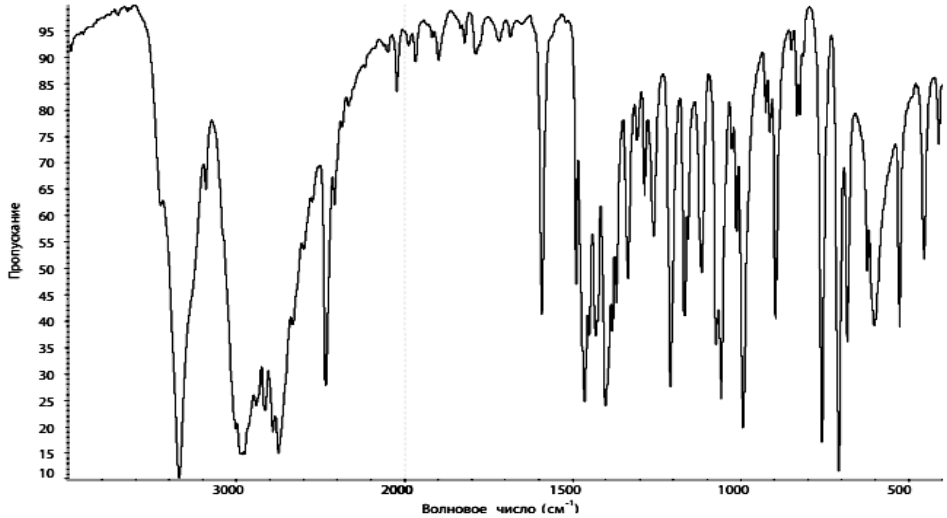
Glycerol

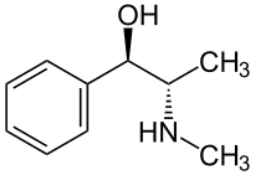


Vaseline oil



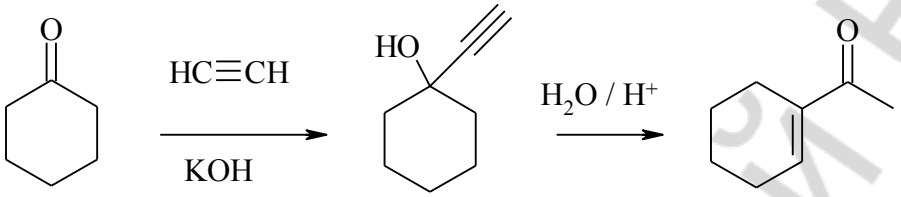
Component of pharmaceutical drug *Ephedrine.*



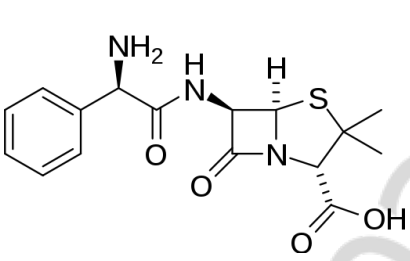


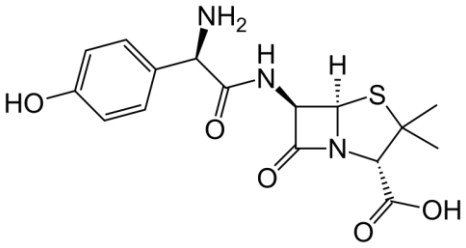
8. Cyclohexene and hex-1-yne both have the molecular formula C_6H_{10}. How would you use infrared spectroscopy to distinguish between the two compounds?

9. What characteristic frequencies in the IR spectrum can be used to monitor the progress of two step reaction which include *Favorsky* reaction (nucleophilic attack of a terminal alkyne) followed by the arrangement of *Kucherov* type?



10. Propose characteristic frequencies which can be used to distinguish IR spectra of *Ampicillin* and *Amoxicillin*?





Signature of teacher:

LABWORK № 8
NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Objective: to study basic concepts and techniques of ^{1}H NMR and ^{13}C NMR spectroscopy.

Recommended literature

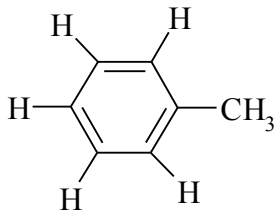
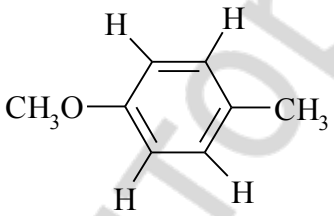
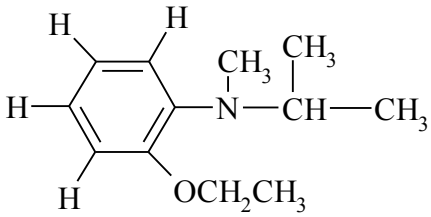
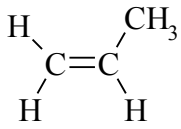
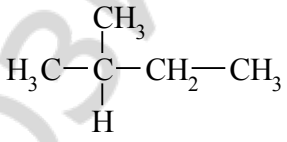
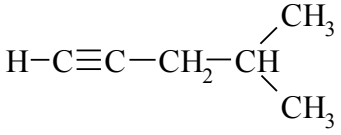
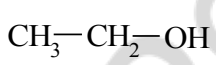
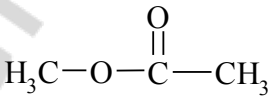
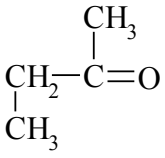
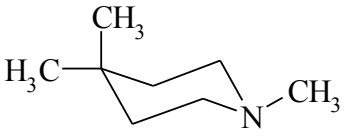
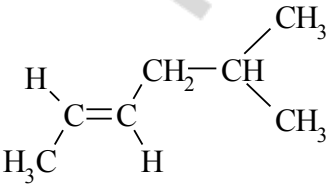
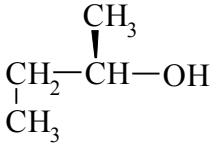
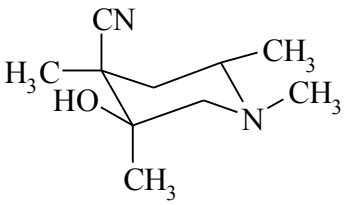
1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.

Problems for discussion:

1. The basic concepts of nuclear magnetic resonance spectroscopy.
2. ^{1}H NMR spectroscopy.
3. Chemical shift.
4. Spin-spin interactions and coupling constants.
5. Integration.
6. ^{13}C NMR spectroscopy.
7. Solvents for NMR spectroscopy.

PRACTICE PROBLEMS

1. Define various structural types of protons in the following compounds. If there are two or more protons of the same type to indicate which of them are homotopic (H), enatiotopic (E) and diastereotopic (D). Which of them are magnetically equivalent.

2. Predict chemical shifts, integrity and spin-spin coupling in ^{1}H NMR spectrum of 3,5-dimethoxyacetophenone* (consider only the spin-spin interaction of geminal and vicinal proton — ^{2}J and ^{3}J). Explain the coupling.

3. Predict chemical shifts, integrity and spin-spin coupling in ^{1}H NMR spectrum of 3,5-*para*-methylaniline*.

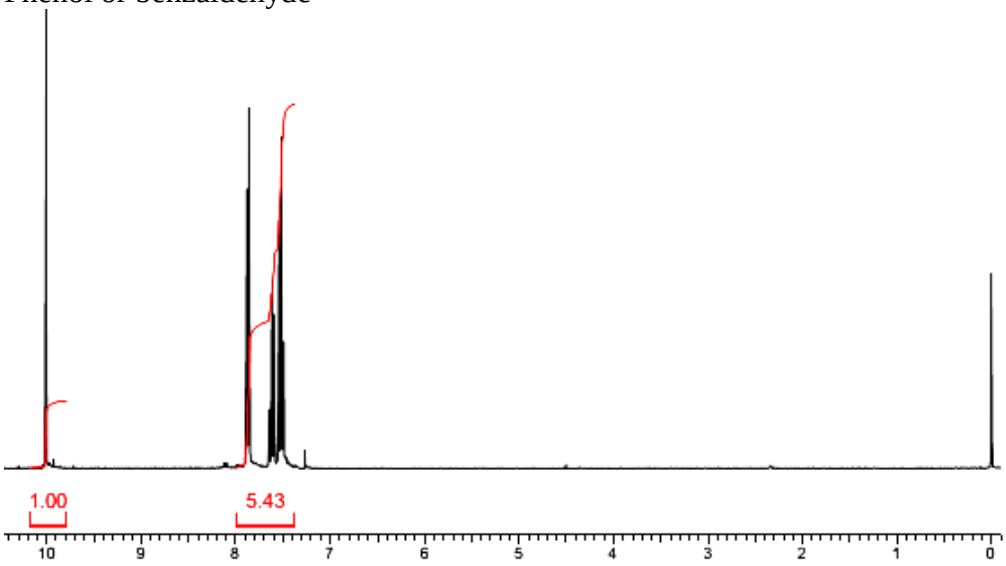
4. Predict chemical shifts, integrity and spin-spin coupling in ^{1}H NMR spectrum of methoxybenzene*. Explain the coupling.

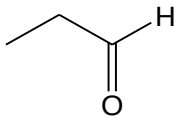
5. Predict chemical shifts, integrity and spin-spin coupling in ^{1}H NMR spectrum of isopropyl ethyl ether*. Explain the coupling.

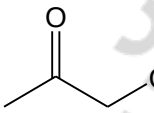
* Consider only the spin-spin interaction of geminal and vicinal proton — ^{2}J and ^{3}J.

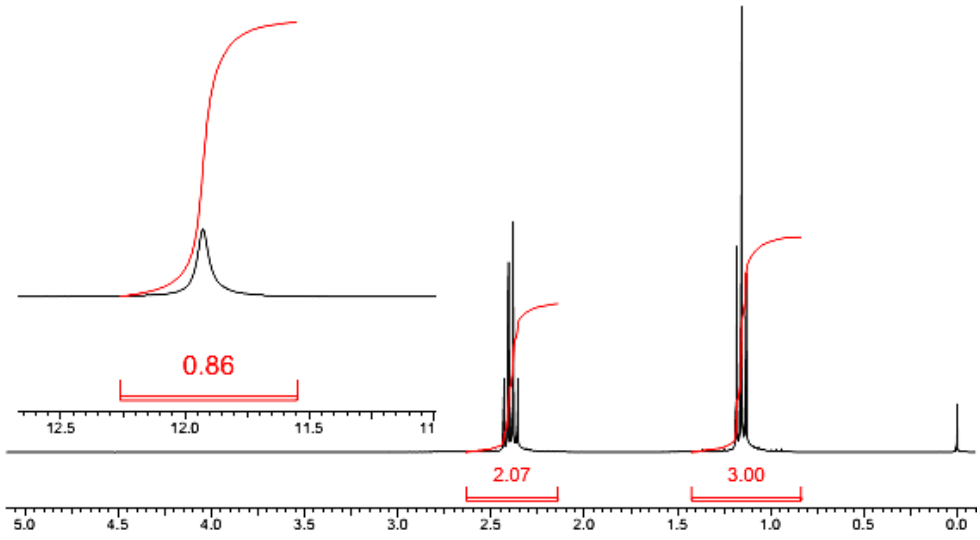
6. Find the compound corresponding the spectrum proposed. Explain your choice.

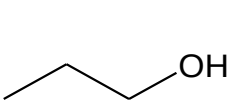
Phenol or benzaldehyde

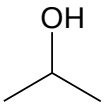


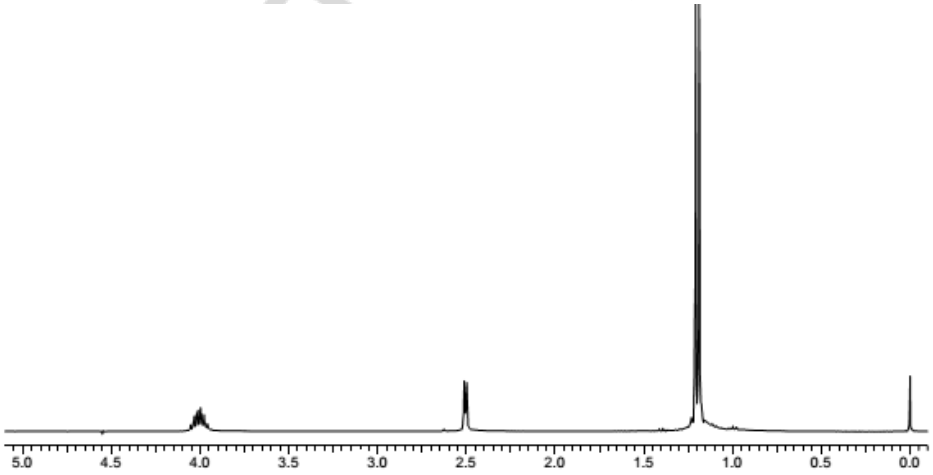












7. Based on chemical shifts, integrity and coupling distinguish the substances proposed by means of NMR ^{1}H spectroscopy.

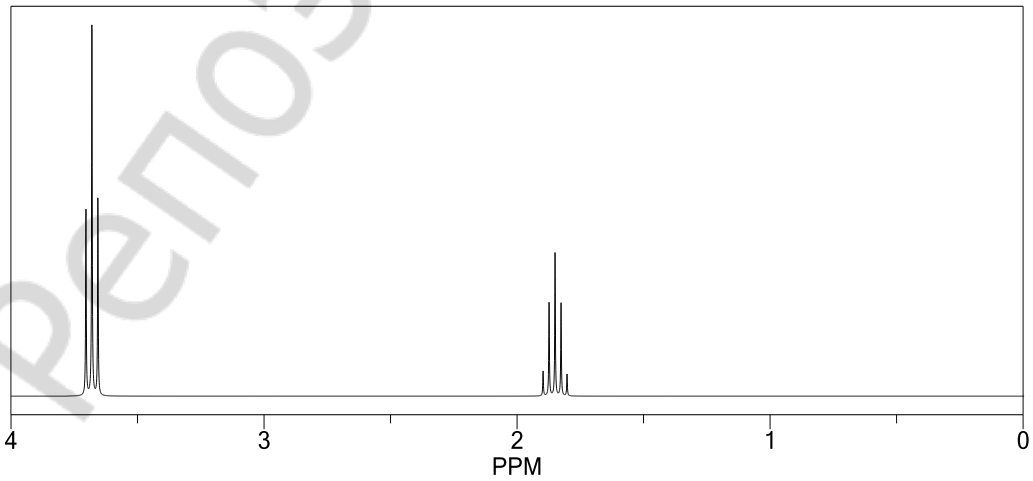
Diethyl ether and methyl ethyl ether

Methanal and acetone

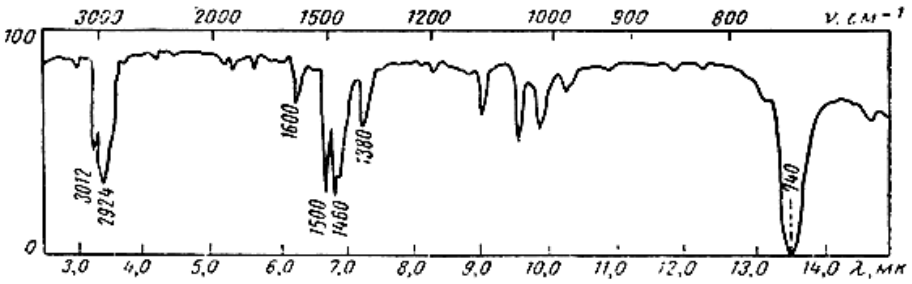
Benzene, toluene, *para*-xylene

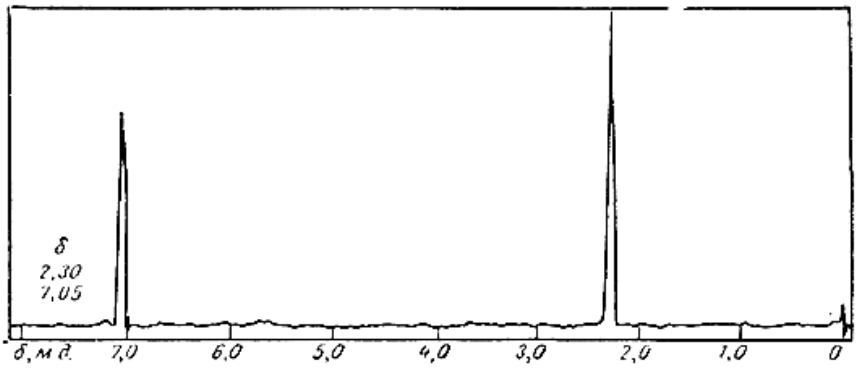
Salicylic and acetylsalicylic acids

8. Which of isomeric dichloropropanes correspond NMR ^{1}H spectrum proposed. Explain your choice.

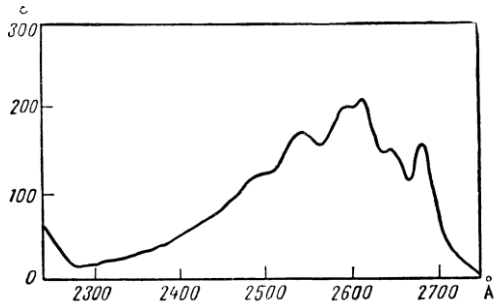


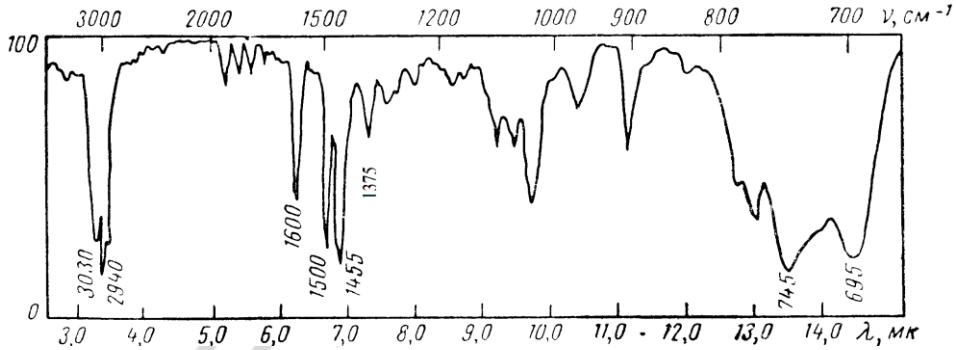
9. Determine the structure of the compound C_8H_{10} based on IR and NMR ^1H spectra.

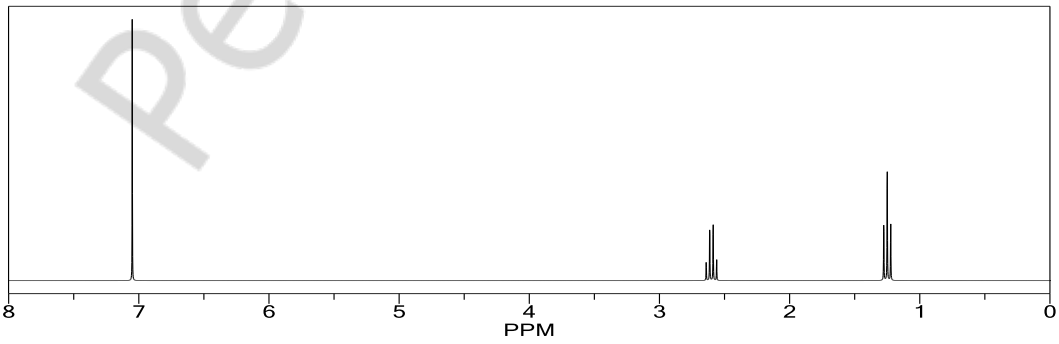




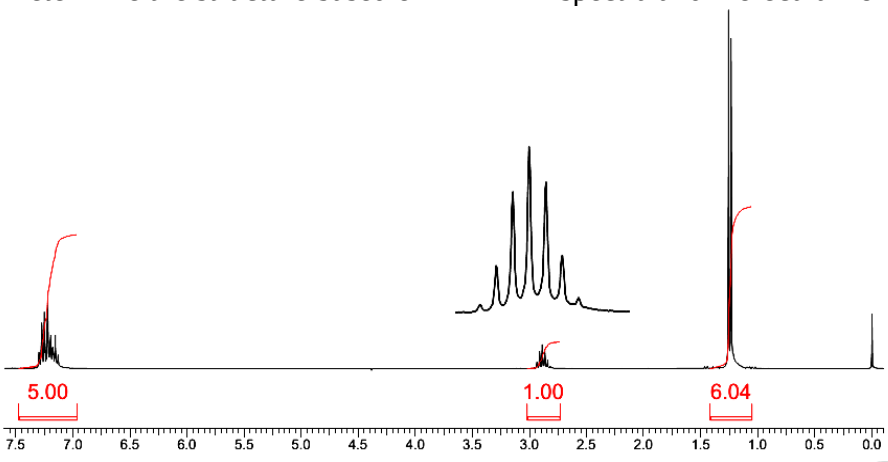
10. Determine the structure of the compound C_8H_{10} based on UV, IR and NMR ^1H spectra.



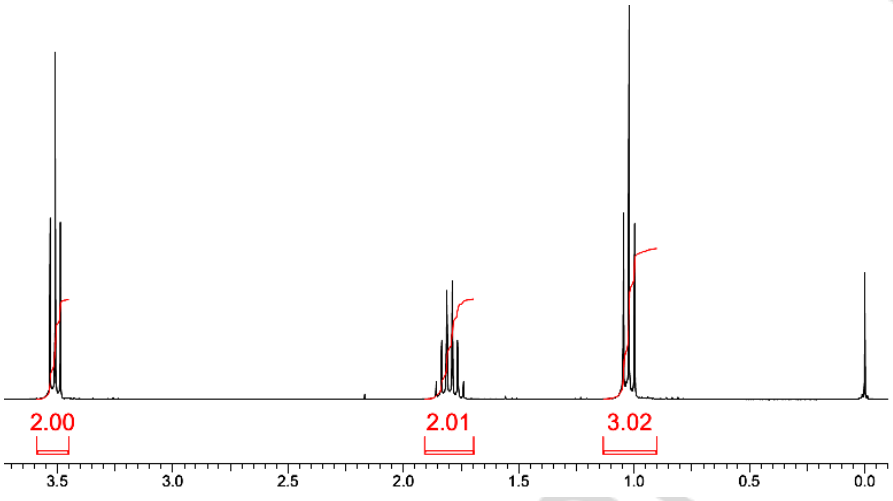




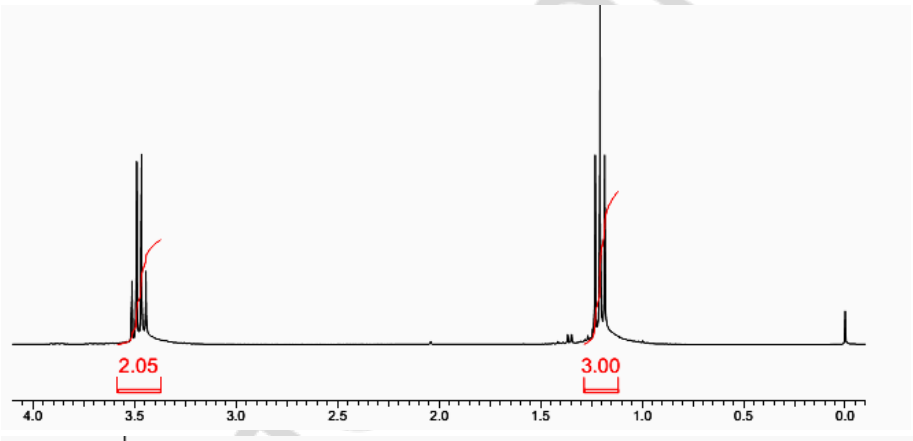
11. Determine the structure based on NMR ^{1}H spectra and molecular formula.



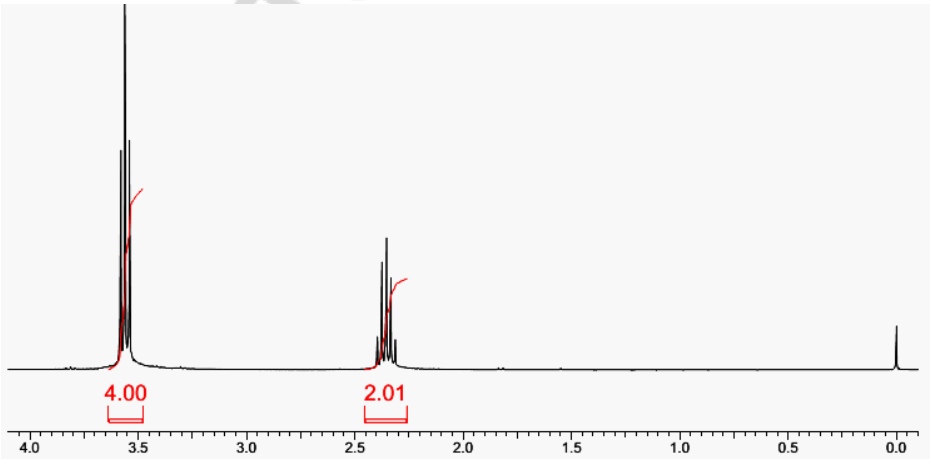
C_9H_{12}



C_3H_7Cl

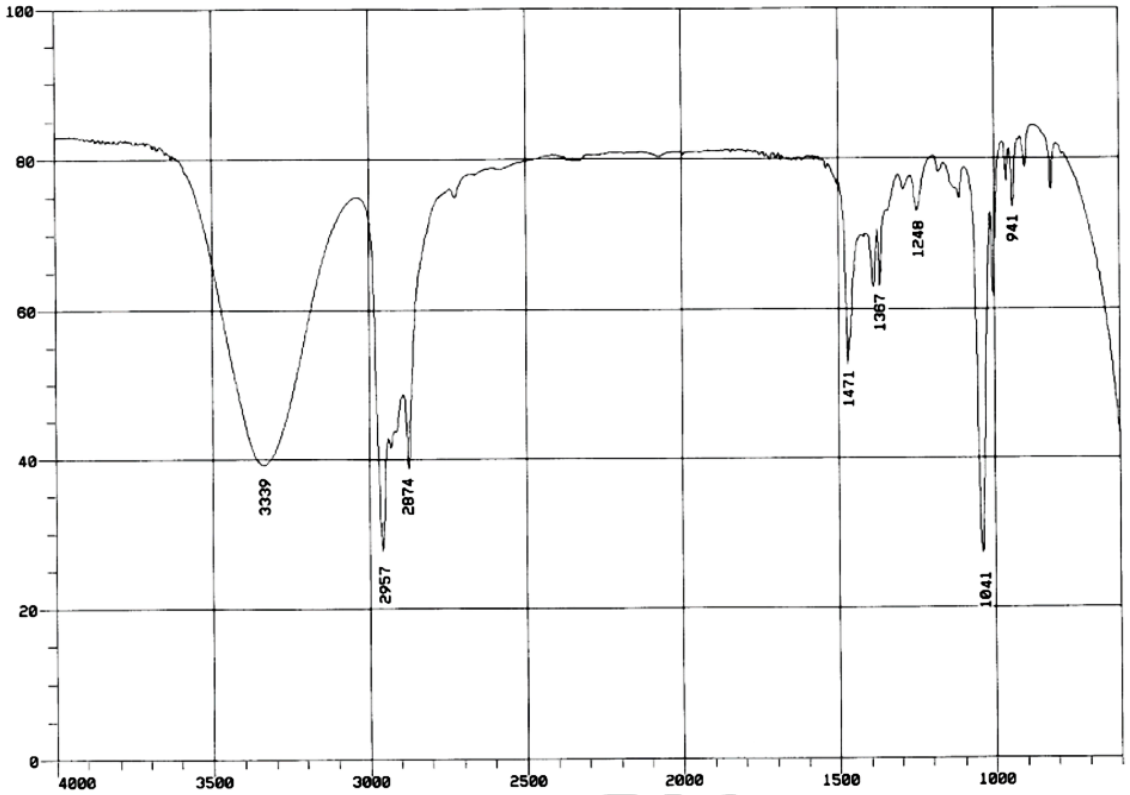


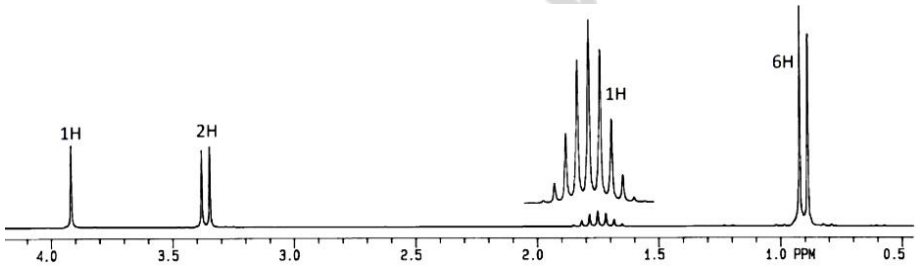
$C_4H_{10}O$



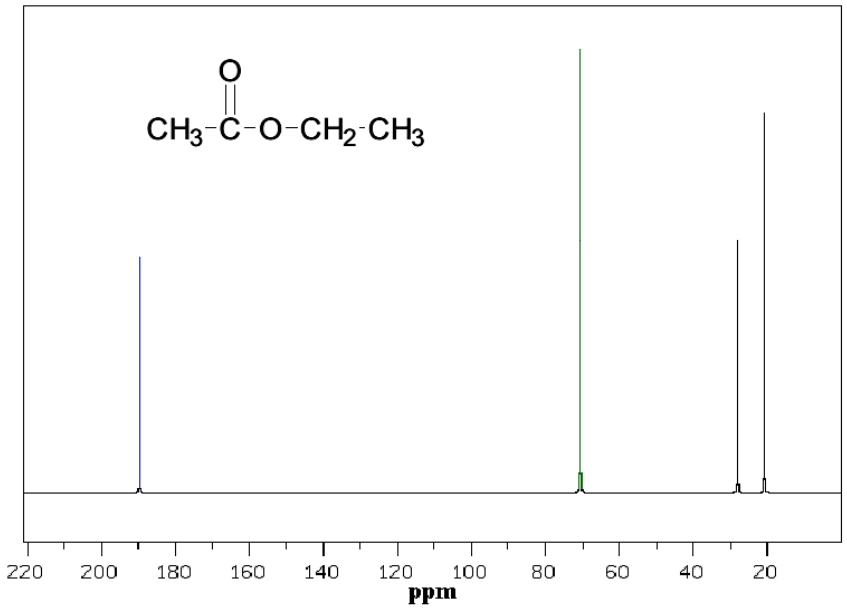
$C_3H_6Br_2$

12. Determine the structure of compound $C_4H_{10}O$ based on spectra proposed.





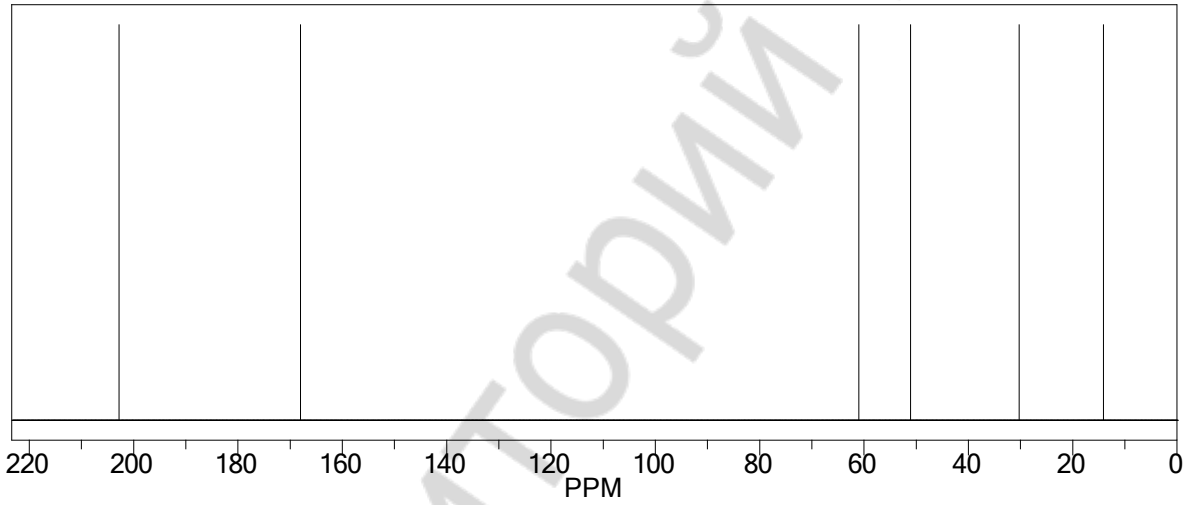
13. Explain the shifts in NMR ^{13}C spectrum*



* Spectrum both carbon and proton decoupled.

14. Predict chemical shifts in NMR ^{13}C and ^{1}H spectra of 1-methyl-3-methoxybenzene.

15. Explain the shifts in decoupled NMR ^{13}C spectrum of acetoacetic ester. Predict the coupling $^{1}J_{CC}$, $^{2}J_{CC}$, $^{3}J_{CC.}$



Signature of teacher:

LABWORK № 9, 10
NONAROMATIC HYDROCARBONS

Objective: to study the structure and properties of nonaromatic hydrocarbons.

Recommended literature

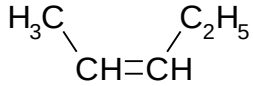
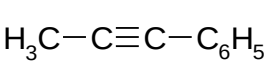
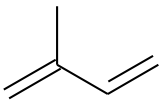
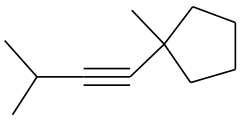
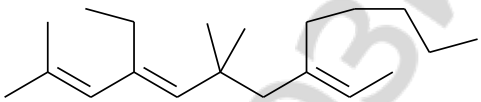
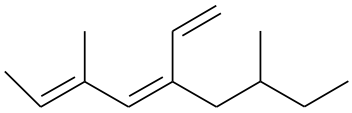
1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.

Problems for discussion:

1. Structure and nomenclature of hydrocarbons.
2. Addition reaction to multiple bond.
3. Allylic substitution in alkenes.
4. Substitution of acetylenic hydrogene.
5. Addition reactions to dienes.
6. Redox reactions of hydrocarbons.
7. Polymerization of unsaturated hydrocarbons.
8. Hydrocarbon identification.

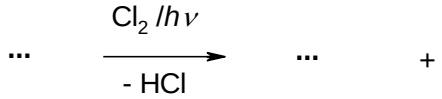
PRACTICE PROBLEMS

1. Give IUPAC names to following compounds.

2. Discuss and write all steps of the mechanism of methane chlorination under irradiation.

3. Write and name all of the structural isomers which are formed in monochlorination of 2-methylbutane during irradiation. Calculate the ratio of isomers (rates of substitution for primary / secondary / tertiary hydrogens correspond as 1/3/8). Indicate chiral centers in halides. For chiral halides draw stereoformulas of enantiomeric pairs and designate the configuration (R-/S-) of chiral centers.



2-Methylbutane

4. Draw examples of cumulated, conjugates and unconjugated dienes C_6H_{10}. Give them the names.

5. Draw a pair of diastereomers for:

3,5-Dimethylhex-3-ene

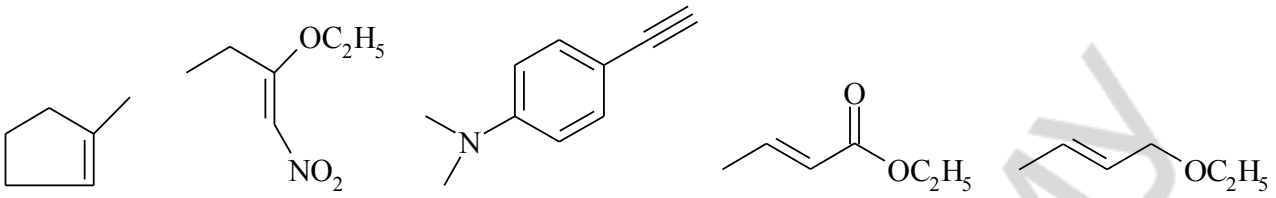
Pent-2,4-diene

6. Draw a pair of enantiomers for:

3-Methylcycloxene

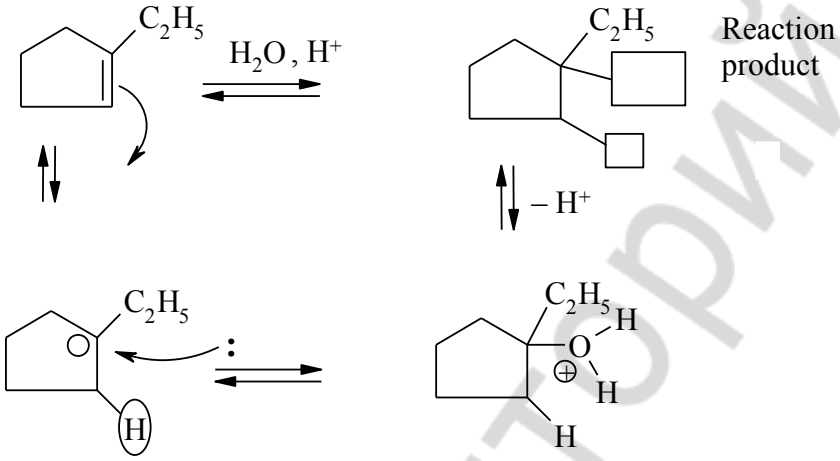
Pent-2,3-diene

7. Show graphically the influence of substituents on distribution of electrons in double bond. Indicate the effects (induction/mesomerism) and cumulative action of the substituents (donor/acceptor).

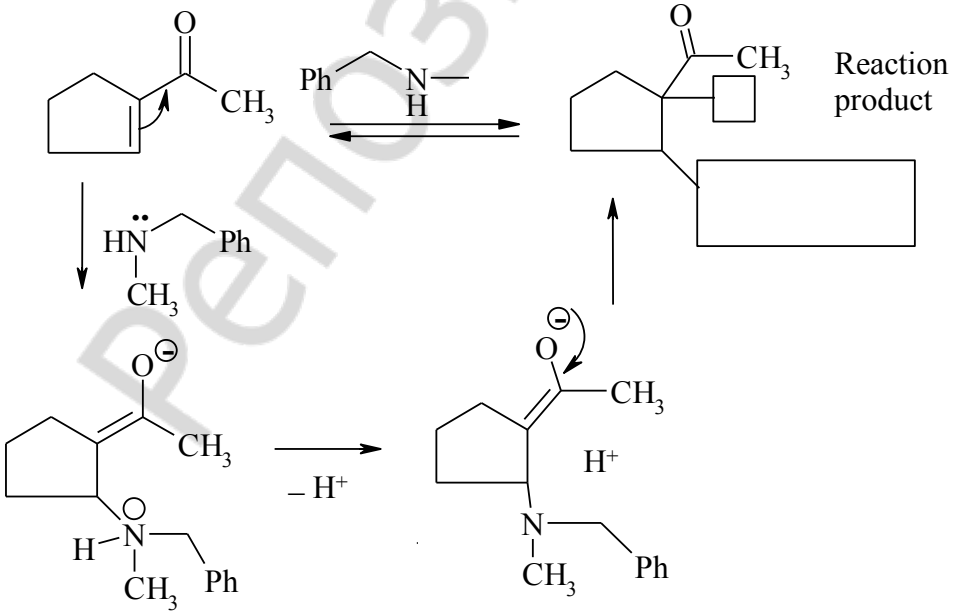


8. Complete the following schemes (add atoms, arrows, charges). Discuss the mechanism and predict the selectivity. Explain why amination is possible only to double bond substituted with acceptor.

Hydration



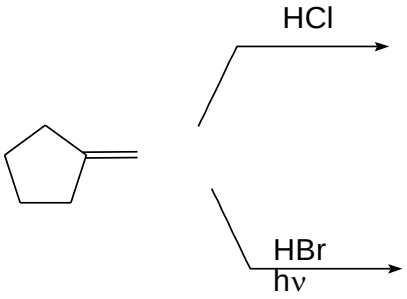
Amination



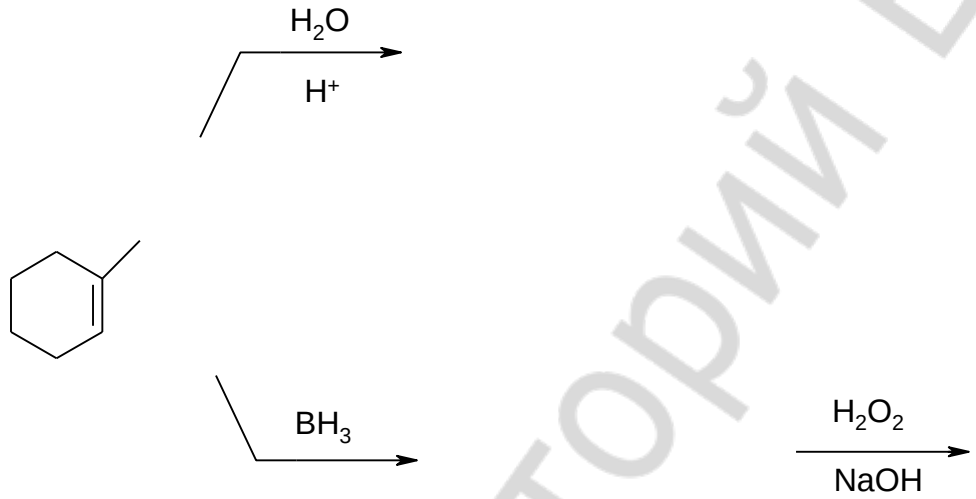
9. Write constitutional formulas of substrates and products of addition reactions.

Hydrocarbon	Reagent	Product formula and name
Pentene	$\xrightarrow{Br_2}$	
But-2-ene	$\xrightarrow{HCl}$	
Propine	$\xrightarrow{HCl(equim.)}$	
But-2-yne	$\xrightarrow{HCl(ex.)}$	
2-Methylbut-1-ene	$\xrightarrow{H_2O/\,H^+}$	
1-Methylcyclohexene	$\xrightarrow{C_2H_5OH/H^+}$	
But-1-yne	$\xrightarrow{H_2O/\,H^+,\ Hg_2^{+}}$	
But-2-yne	$\xrightarrow{C_2H_5OH/H^+}$	
hex-3-yne	$\xrightarrow[t]{C_6H_5CH_2NHCH_3}$	
But-2-ene	$\xrightarrow{KMnO_4/\,H^+,\ 0^oC}$	
1-Ethylcyclohexene	$\xrightarrow[(ROOR)]{HBr}$	
Cyclopentene	$\xrightarrow{C_6H_5COOOH}$	

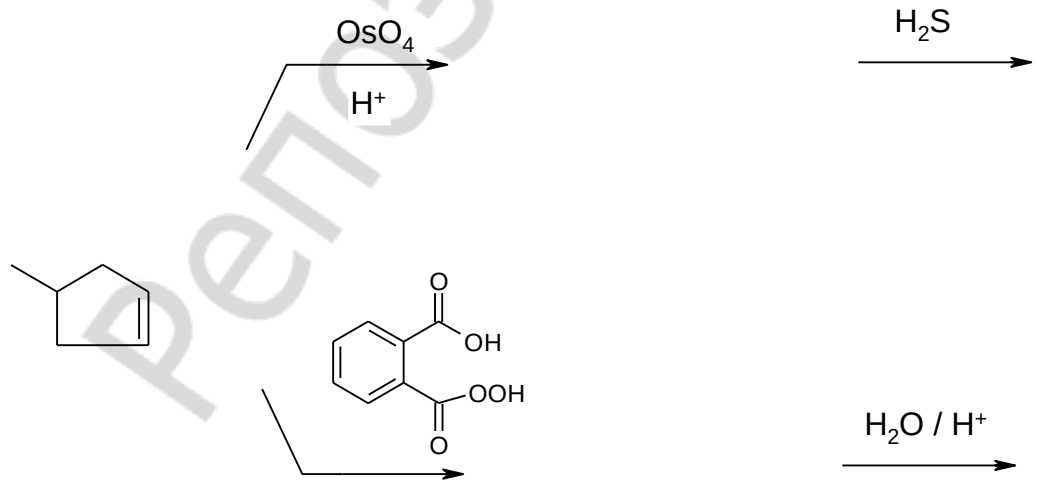
10. Write reaction schemes of hydrohalogenation. Describe the mechanisms and explain the regioselectivity (preference for the formation of one constitutional isomer over another).



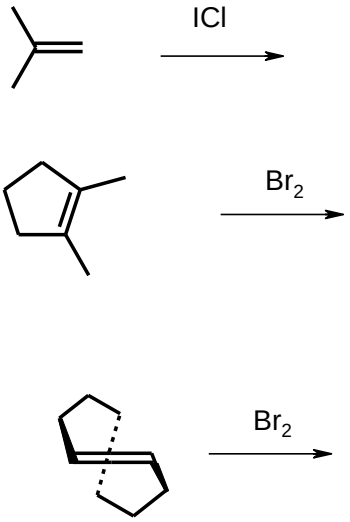
11. Write reaction schemes of alcohol formation. Using diagrams, mechanisms with curly arrows, and/or short paragraphs, explain the regioselectivity of both processes.



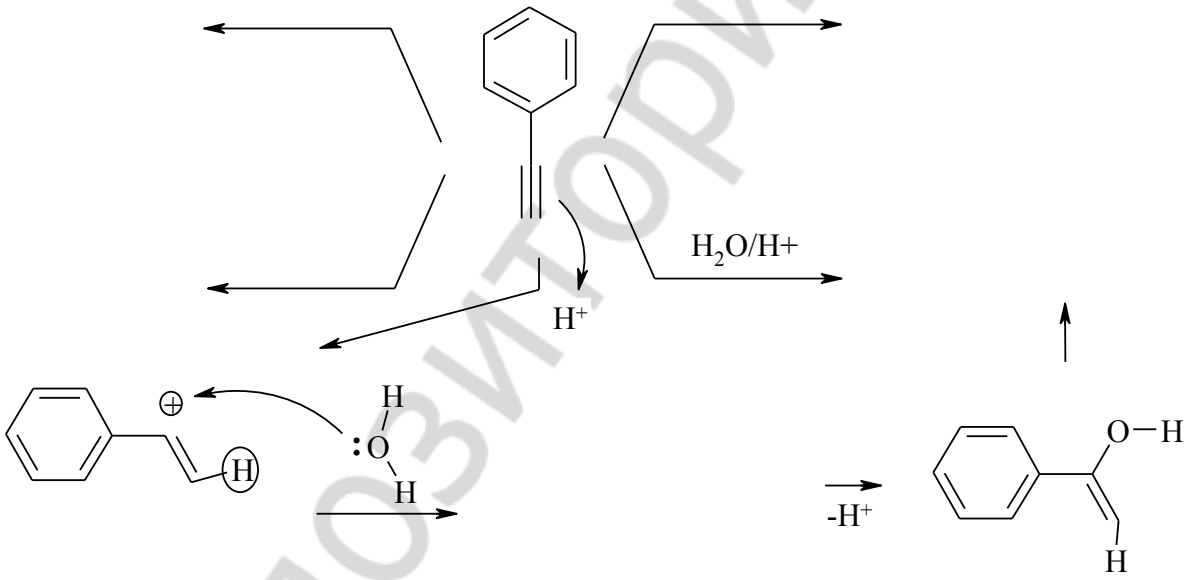
12. Write reaction schemes of diol hydroxylation. Using diagrams, mechanisms with curly arrows, and / or short paragraphs, explain the selectivity of both processes.



13. Write reaction schemes of halogenations. Describe the mechanisms and explain the selectivity.



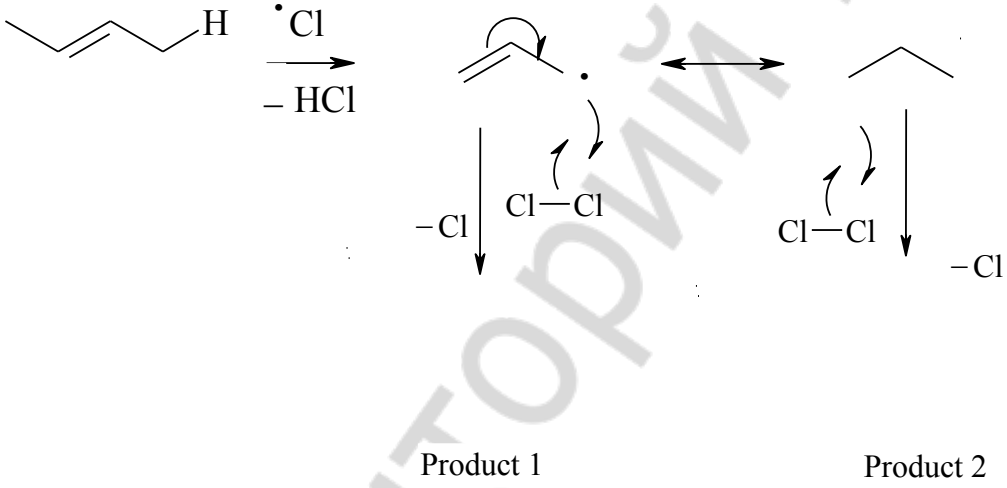
14. Finish the schemes of acid catalyzed reactions of phenyl acetylene with water, ethanol, acetic acid and isopropylamine. Complete the mechanism for *Kucherov* reaction.



15. Write reaction schemes of nucleophilic addition of sodium phenoxide, diisopropylamine, phenyl mercaptane to ethinylcyclohexane.

16. Explain the mechanism of the reaction between cyclopentylacetylene and morpholine.

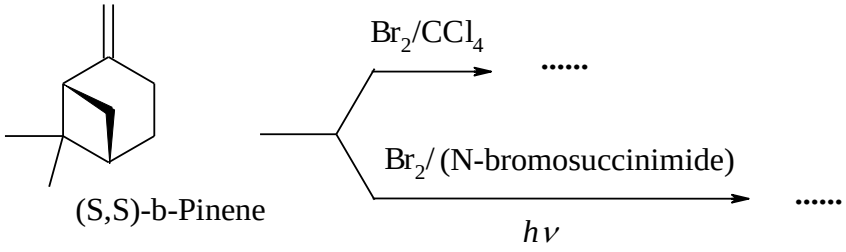
17. Complete the scheme of allylic substitution of but-2-ene. Explain the stability of intermediate allylic radical and formation of isomeric halides.



Product 1 Product 2

18. Write reaction schemes for allylic hydroxylation (SeO_2) and bromination (N-bromosuccinimide) of hex-1-ene. Explain the mechanism and factors facilitating the substitution of allylic hydrogen.

19. Write reaction schemes of bromination of β-pinene. Explain chemoselectivity.



20. Write constitutional formulas of substrates and products of the acetylenic hydrogen substitution.

Alkyne	Acetylenide anion	Product
Propyne	$NaOCH_3$	C_2H_5Br
Ethyl acetylene	$NaNH_2$	Br
Ethyne	NaOH	O
Acetylene	$Ag(NH_3)_2OH$	

21. Write reaction schemes for 1,2- and 1,4-additions (bromination and hydrogenation) to cyclohexa-1,3-diene. Explain the regioselectivity of the process.

22. Draw *s-cis* and *s-trans* forms of 2,3-dimethylpenta-1,3-diene. Write *Diels-Alder* reaction of this substance with methoxyethene

23. Write *Diels-Alder* reaction for next reactants:

2,3-Dimethylbut-1,3-diene and nitroethene

2,3-Dimethoxybut-1,3-diene and acrylonitrile

Cyclohex-1,3-diene and methyl acrylate

24. Write reaction schemes and give the names of the polymerization products from next monomers:

Vinyl chloride $\longrightarrow$

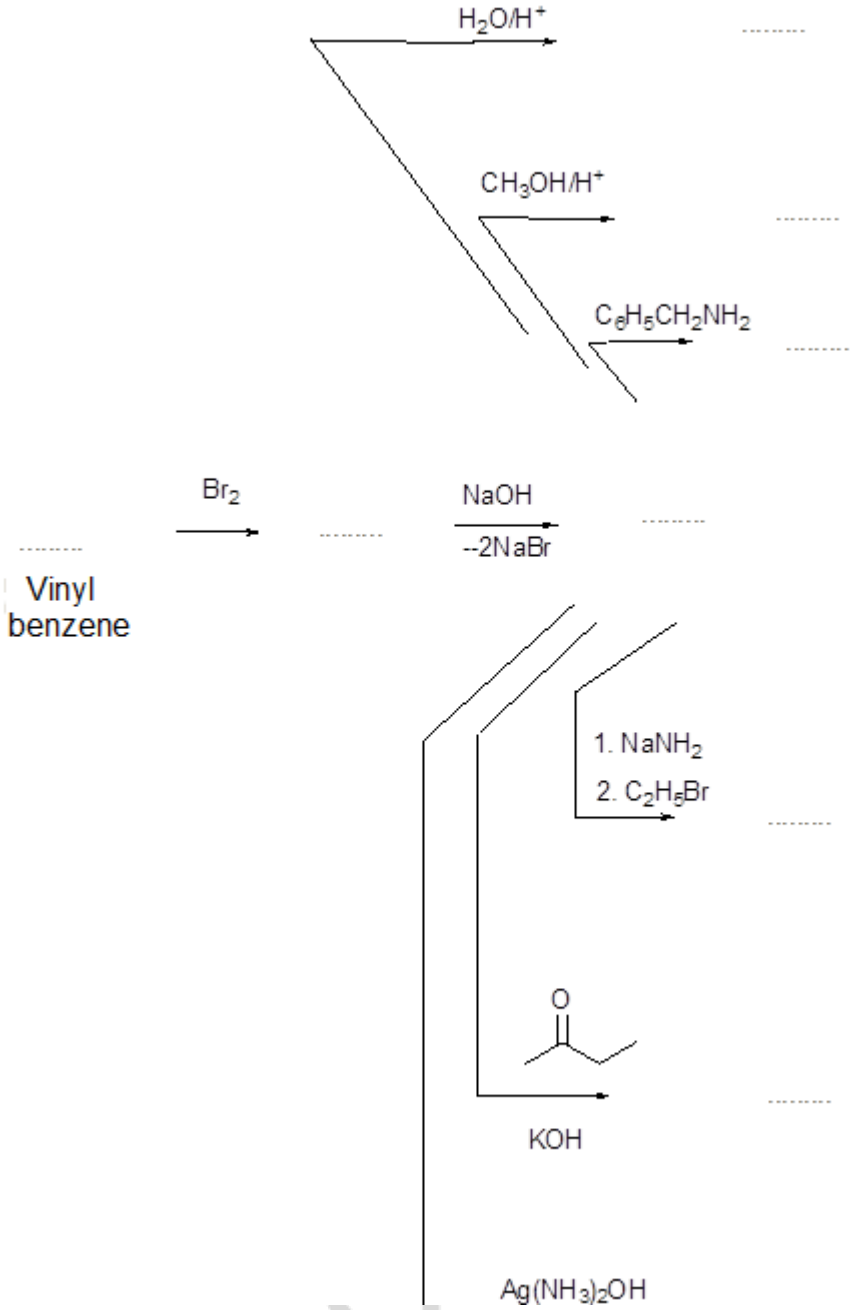
2-Methylbut-2-ene $\longrightarrow$

25. Explain radical mechanism for propene polymerization.

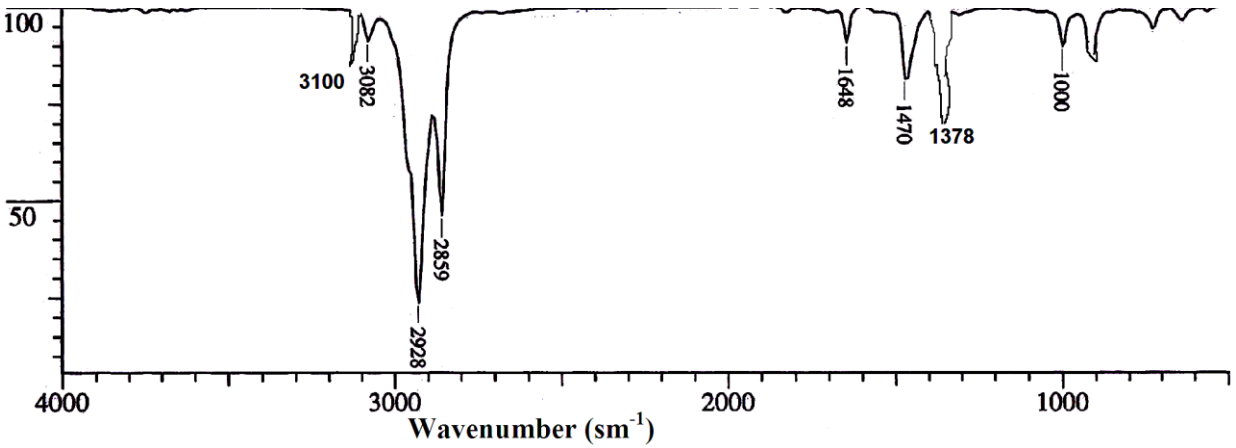
26. Write reaction schemes for 1,2- and 1,4-addition polymerization of isoprene.

27. Write reaction scheme for copolymerization of buta-1,3-diene and styrene (head-tail).

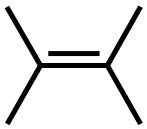
28. Fill the blanks in scheme.



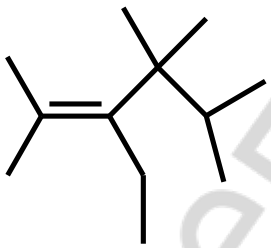
29. Draw the constitutional formular of the substance which IR-spectrum is shown below. Explain the position of bands.



30. Predict chemical shifts (approximately), coupling and integrity of NMR ^{1}H spectra for substances shown. Explain the answer.



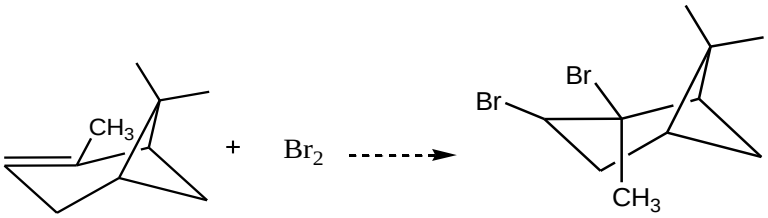
0 ppm.



0 ppm.

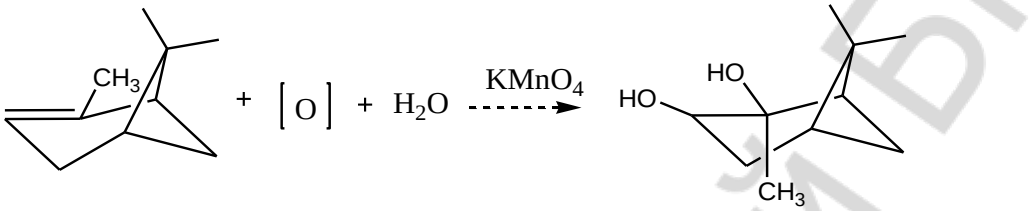
EXPERIMENTAL SECTION

Experiment 1. Chemical test on double bond with bromine water.



Place 2 drops of α-pinene* in a dry test tube followed by addition of few drops of bromine water*. Shake the mixture. Fix the change of bromine water color.

Experiment 2. Chemical test on double bond with potassium permanganate.



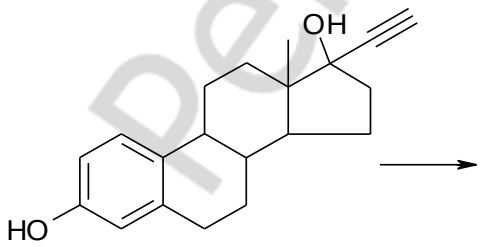
α-pinene α-pinene glycol

Place 2 drops of α-pinene* in a dry test tube followed by addition of few drops of potassium permanganate (14) solution. Shake the mixture. Fix the change of potassium permanganate solution color.

Explain why did both solutions become colourless?

Explain why is potassium permanganate oxidation for diol syntheses limited?

Complete the scheme of the reaction between ethynylestradiol with an ammonia solution of copper (I) chloride.



Signature of teacher:

LABWORK № 11
AROMATIC HYDROCARBONS

Objective: to study the structure and properties of aromatic hydrocarbons.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.

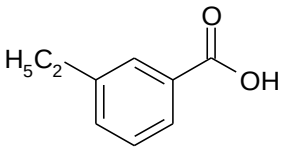
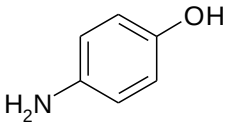
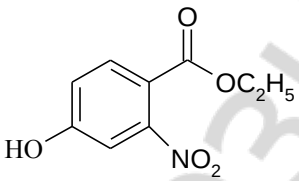
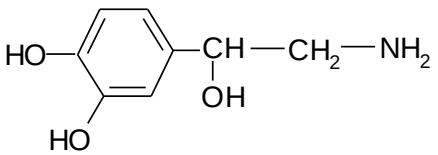
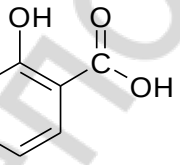
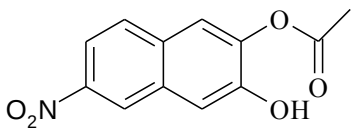
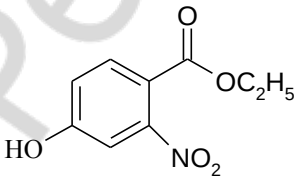
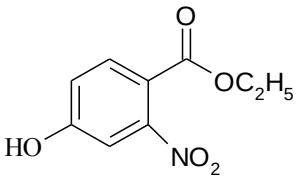
2. *Машковский, М. Д.* Лекарственные средства / М. Д. Машковский. 16-е изд., перераб., испр. и доп. Москва : Новая волна, 2012.

Problems for discussion:

1. Structure and nomenclature of aromatic hydrocarbons.
2. Aromaticity of arenes.
3. Reactivity of aenes: reactions on benzene ring vs reactions on side chain.
4. Radical substitution in side chain.
5. Addition and oxidation of ring fragment.
6. Mechanism S_EA: general scheme, the influence of substituent and nature of electropjile.
7. Examples of aromatic halogenation, nitration, sulfonation, alkylation and acylation.
8. Chemical and instrumental detection of arenes.

PRACTICE PROBLEMS

1. Give IUPAC names to following compounds.

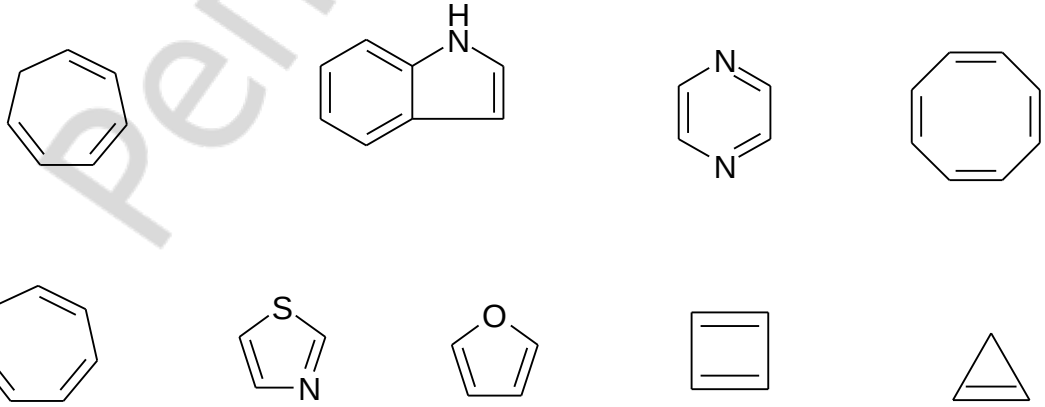
	
	
	
	

2. Convert name to structure. Give IUPAC names (substitutive approach).

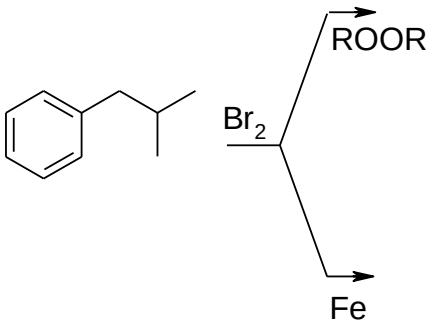
Benzyl chloride	*p*-Sulfobenzoic acid
2,3-Dihydrophenanthrene	Phthalic acid
Anthracene	Anthraquinone
1,4-Dibromo-1,4-dihydronaphthalene	α-Naphthylamine

3. Draw formulae of all the isomers (including stereoisomers) of monosubstituted benzene ($C_{10}H_{14}$). Give the names.

4. Determine which of the following compounds contain aromatic fragments. Discuss their aromaticity in terms of the *Hückel* concept.



5. Write the reaction of isobutyl benzene with bromine in different conditions. Explain the regioselectivity and indicate the type of the reagent and reaction.

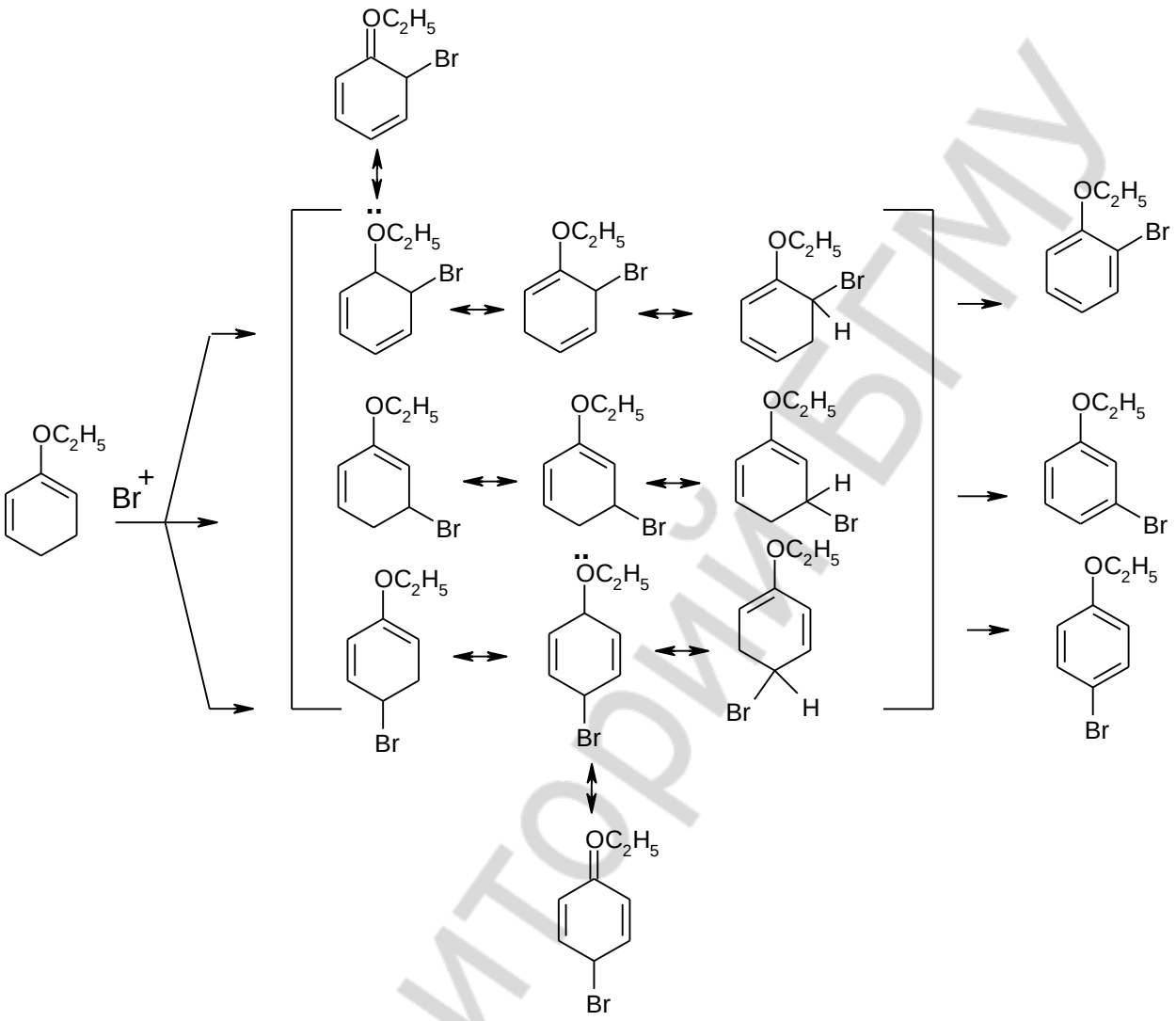


6. Write the products of toluene oxidation by SeO_2, MnO_2 and $KMnO_4$. Explain why toluene is less toxic compare to benzene under enzymatic oxidation *in vivo.*

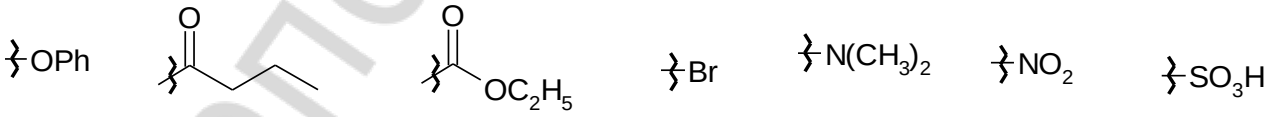
7. Write the reactions schemes of oxidation and reduction of naphthalene in drastic and mild conditions.

8. Write the reactions schemes of bromination, oxidation and *Diels-Alder* addition to anthracene. Explain the mechanism.

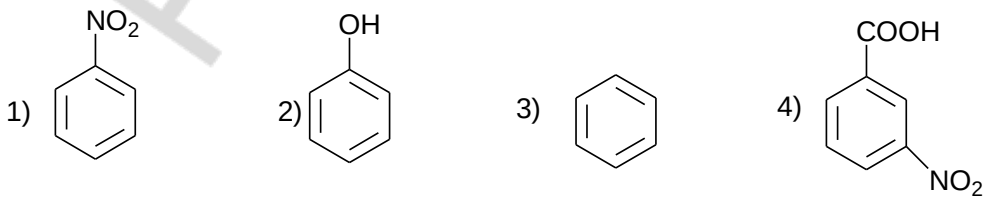
9. Draw arrows and charges to show electron-movement in the following two steps (draw arrows for each step and for all the resonance hybrids). Detect electrophile, rate limiting step and explain the formation of major products.



10. For the following substituents, classify each as electron-donating or electron-withdrawing ("D" or "W"); as activating or deactivating ("act" or "dea"); and as *ortho-para* directing or *meta* directing ("*o/p*" or "*m*").

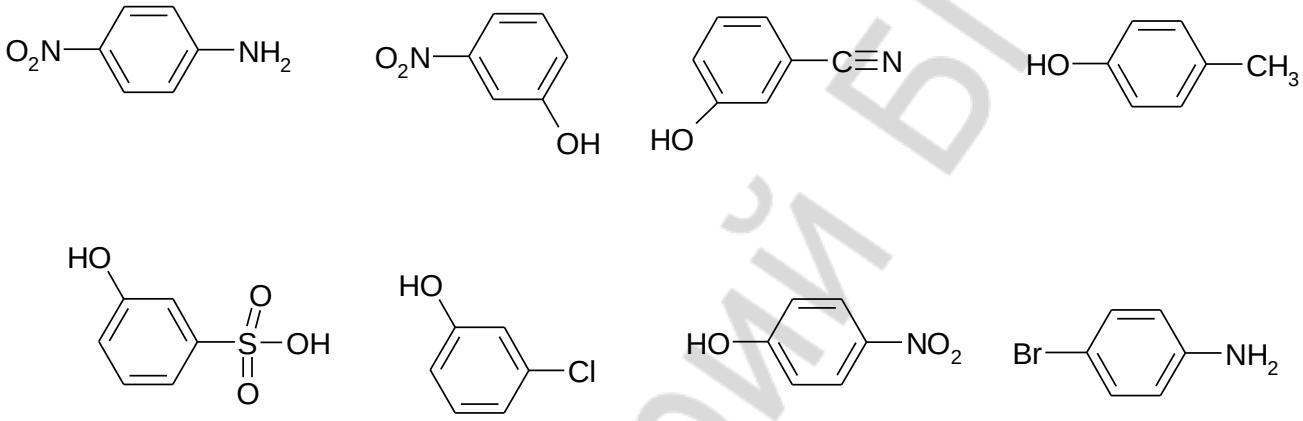


11. Rank substances in context of their reactivity in electrophilic substitution



12. Explain why ester (-OCOR) and amide groups (-NHCOR) are less activating than ether (-OR) and amino ($-NH_2$) groups; and why amino ($-NH_2$) is better activator than alcohol (-OH) group.

13. Predict the regioselectivity for further substitution of disubstituted benzenes by looking at the cumulative effects of both substituents. As a suggested method, look at each of the substituents, label their directing effects, then indicate the sites where they would promote reactivity with small arrows.



14. Design a synthetic scheme leading to pure 2-bromobenzoic acid from toluene based on protection group strategy.

15. Design a synthetic scheme to obtain 1-bromo-2-isoamyl-4-nitrobenzene starting from benzene.

16. Discuss mechanisms of alkylation reactions. Propose catalysts to generate electrophiles.

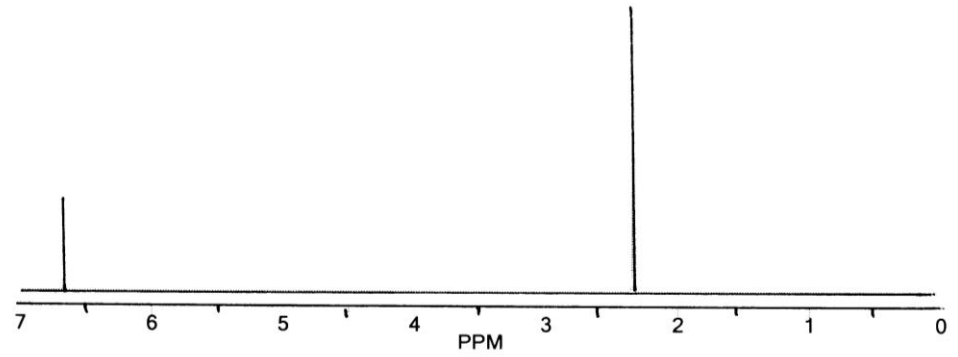
Benzene with propene

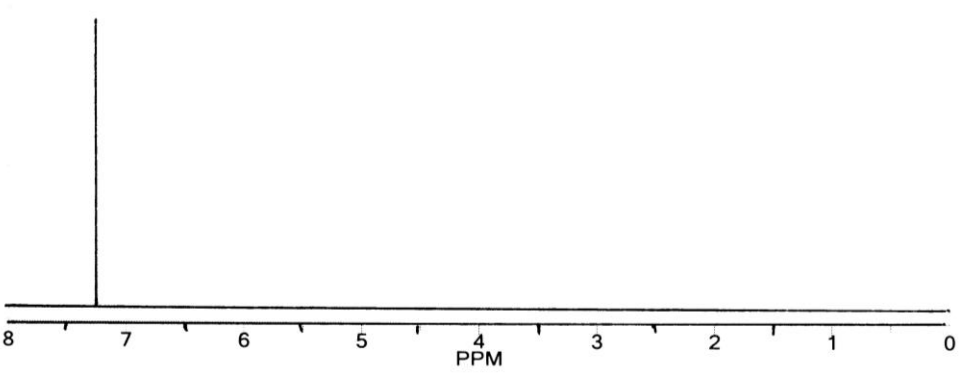
Methoxybenzene with *tert.*-butyl alcohol

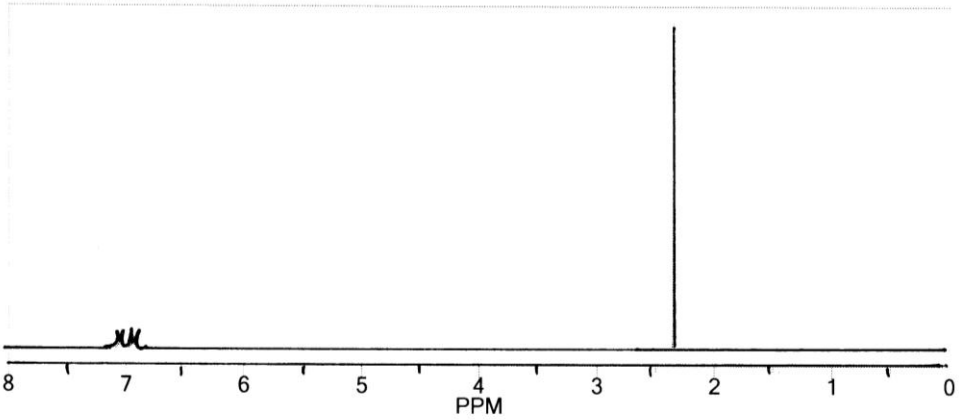
Intramolecular cyclization of (5-bromohexyl)benzene

Explain why alkylation is not applicable to synthesize 7-methyloctylbenzene from benzene. Propose the synthetic scheme *via* acylation reaction.

17. Distinguish spectra for benzene, 1,2-dimethylbenzene and 1,3,5-trimethylbenzene. Explain your choice.







18. Predict for *para*-diacetoxybenzene frequency bands in IR spectrum as well as chemical shifts, J-coupling and integrity in the ^{1}H NMR spectrum.

EXPERIMENTAL SECTION

Experiment 1. Ignition test for high degrees of unsaturation.

Heat a small samples benzoic acid (44) on a spatula. First, hold the sample near the side of a *Bunsen* burner to see if it melts normally and then burns. Heat it in the flame. Do the same with samples of α-pinene*, and hexane*. Give observations. Aromatic compounds often burn with a smoky flame.

A sooty yellow flame is an indication of an aromatic ring or other centers of unsaturation.

Experiment 2. Bromination test on arenes.

Place 3 drops of bromine water* in 3 test tubes, then add to the first tube 2 drops of benzene*, and to the second — 2 drops of toluene*, and to the third 2 drops of or aniline*. Shake both tubes vigorously.

The disappearance of the yellow coloring means the positive test.

How to promote the bromination of benzene?

Experiment 3. Permanganate test on arenes.

Place in two tubes 2 drops of 2 % aq. $KMnO_4$ (14) and 2 drops of H_2O followed by the addition 2 drops of benzene to the first and 2 drops of toluene to the second tube. The disappearance of the pink-violet coloring means the positive test. Explain why we see no positive test for both tubes. Add to each tune 2 drops of 10 % sulfuric acid and heat the mixtures. Fix the change of coloring in one of the tubes. Explain the observation.

Signature of teacher:

LABWORK № 12
COLLOQUIUM № 1. STRUCTURE, REACTIVITY AND IDENTIFICATION OF HYDROCARBONS. ACADEMIC RESEARCH № 1

Objective: to systematize the knowledge of the structure and reactivity of hydrocarbons and challenge the skills of qualitative chemical tests on hydrocarbons.

Remind the program material from the theme 7 to 11.

Recommended literature: study the literature from the themes 7 to 11.

EXPERIMENTAL SECTION

An example for experimental problem:

1. Propose and proceed chemical tests to distinguish hex-1-yne-1 and hex-2-yne.
2. Identify chemically the proposed substance.
3. Predict spectral characteristics (UV, IR, NMR-spectra) of the proposed substance.

ACADEMIC RESEARCH № 1

Signature of teacher:

LABWORK № 13
ORGANIC HALIDES

Objective: to study the structure and properties of halogenated hydrocarbons.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.

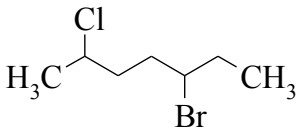
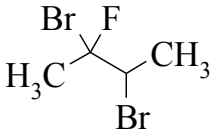
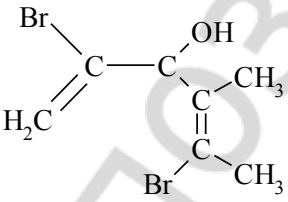
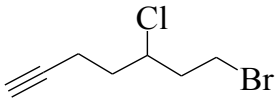
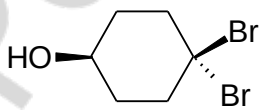
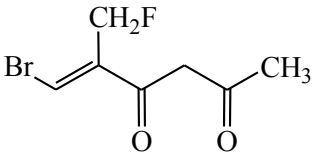
2. *Машковский, М. Д.* Лекарственные средства / М. Д. Машковский. 16-е изд., перераб., испр. и доп. Москва : Новая волна, 2012.

Problems for discussion:

1. Structure and nomenclature of halogenated hydrocarbons
2. Competitive mechanisms of nucleophilic substitution and elimination.
3. S_N1, S_N2 mechanisms.
4. Allyl and benzyl halides. Reasons for higher reactivity in nucleophilic substitution reactions.
5. Reactivity of vinyl and aryl halides.
6. Chemical and instrumental detection of organic halides.

PRACTICE PROBLEMS

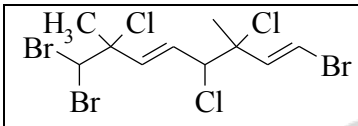
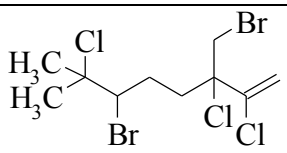
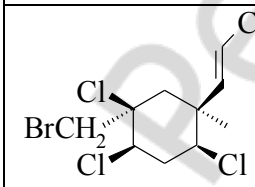
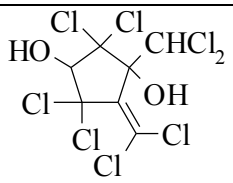
1. Give IUPAC names to following compounds.

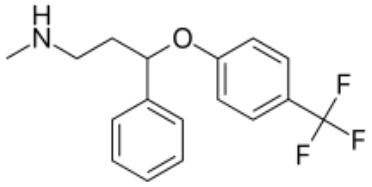
2. Write structures of following compounds. Give IUPAC names (substitutive approach). Identify which of compounds are primary, secondary or tertiary halides. Indicate reaction centers.

Allyl chloride	Isoamyl chloride
Tert.-butyl bromide	Chloroprene
Benzyl chloride	Methylene chloride
Chloroform	Vinyl chloride

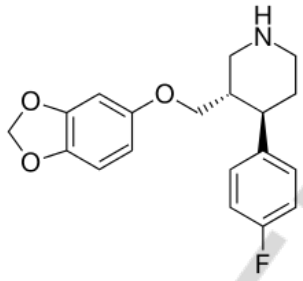
3. Give IUPAC names to following natural compounds:

 It was isolated from the digestive gland of the bearded seal	 *Halomon* is halogenated monoterpene which was first isolated from the marine red algae and being potential anticancer drug
 Violacene (isolated from algae)	 It was isolated from fungi

4. The relatively small size of fluorine is convenient as fluorine acts as an approximate bioisostere of the hydroxyl group. Chemists using organofluorine strategy try to introduce carbon-fluorine bond to increases the probability of having a successful drug. An estimated 20 % of pharmaceuticals, and 30–40 % of agrichemicals are organofluorines, including several of the top drugs. *Fluoxetine* and *Paroxetine* are selective serotonin re-uptake inhibitors and used as antidepressants.
Find reactivity centers in both substances. Show graphically the influence of functional groups on distribution of charge in benzene ring. Predict solubility of both substances in physiological pH.



Fluoxetine



Paroxetine

5. Write structural formulas of substances and rank the set of compounds in terms of relative reactivity in S_N2 reactions.

Methyliodide, bromoethane, 2-bromobuthane, *tert.*-butyl chloride

Benzyl chloride, bromobenzene, chloromethane, chlorodiphenylmethane

6. Write structural formulas of substances and rank the set of compounds in terms of relative reactivity in S_N1 reactions

Bromoethane, 2-chlorobuthane, 1-chloro-1-methylcyclohexane

Benzyl chloride, bromobenzene, chloromethane, chlorodiphenylmethane

7. Complete reaction schemes. Give systematic names to products. Identify reaction type.

Halide	Reagent	Product and type of reaction
Chlorocyclohexane	$\xrightarrow{NaI}$	
3-Bromohexane	$\xrightarrow{NaOH/H_2O}$	
3-Bromo-2,4-dimethylpentane	$\xrightarrow{NaOH/C_2H_5OH}$	
1-Bromo-2-methylcyclopentane	$\xrightarrow{KOH/C_2H_5OH}$	
2-Methyl-3-chlorobutane	$\xrightarrow{C_6H_5ONa}$	
Benzyl chloride	$\xrightarrow{NH(CH_3)_2}$	
3-Bromo-2-methylpentane	$\xrightarrow{KCN}$	
2-Bromo-3-methylbutane	$\xrightarrow{HC\equiv CNa}$	

8. Write the reactions of (S-) iodo-1-phenylpropane with potassium cyanide in methanol and acetone respectively. Explain the stereochemistry of both reactions and why is allyl and benzyl chlorides exhibit increased activity in the nucleophilic substitution.

9. Write schemes and discuss the mechanisms of the reactions between:

tert.-Butyl bromide and water (t=100^{0}C)

Isoamyl bromide and aq. sodium hydroxide

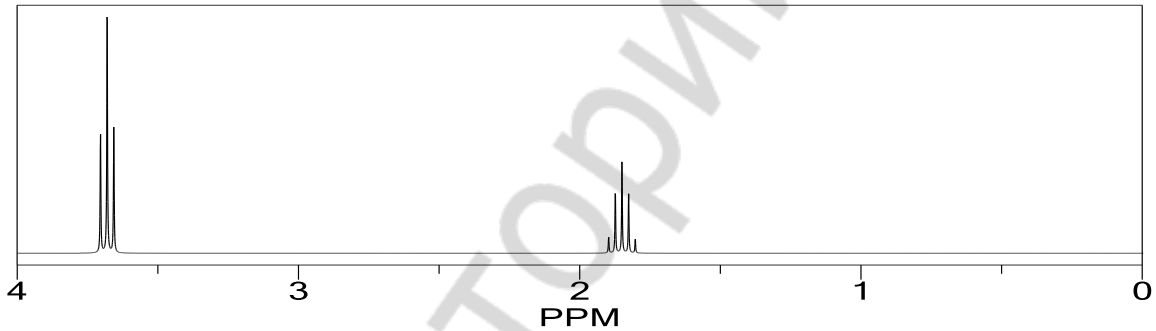
Chlorocyclopentane and alcoholic sodium hydroxide

10. Write alkylation reaction of biologically active compounds: *Norepinephrine* (R)-4-(2-amino-1-hydroxyethyl)benzene-1,2-diol), ethanolamine and *Nicotinamide* with methyl iodide. Name the products (including trivial biochemical names). Explain why alkylation with alkylhalides is impossible in living cell and name the group of substances that generate methylation *in vivo.*

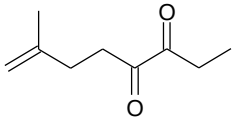
11. Design regioselective synthesis of less (*Hofmann*) and more substituted (*Zaitsev*) alkenes starting from 2-methyl-1-chloro-cyclohexane and using elimination reactions.

12. Hydrolysis of compound ($C_5H_{11}Br$) gives tertiary alcohol and its dehydrobromination leads to 2-methylbut-2-ene. Find the structure of substrate and write the corresponding reactions.

13. Correlate the NMR ^1H spectrum with the structure of dibromopropane.



14. Predict for substance shown below frequency bands in IR spectrum as well as chemical shifts, J-coupling and integrity in the ^1H NMR spectrum.



EXPERIMENTAL SECTION

All tests presented below can be used for detecting of chloroform, benzyl chloride, bromobenzene, bromobutanes, and any other halogenated hydrocarbons.

Experiment 1. *Beilstein* test.

Any halogenated compound as a positive standard, such as, 1-bromobutane, and any non-halogenated compound, such as butan-1-ol, as a negative standard.

Heat the tip of a copper wire* in a burner flame until there is no further coloration of the flame. Let the wire cool slightly, then dip it into the unknown (solid or liquid, e.g. chloroform*) and again, heat it in the flame. A green flash is indicative of chlorine, bromine, and iodine; fluorine is not detected because copper fluoride is not volatile. The *Beilstein* test is very sensitive, thus halogen-containing impurities may give false results.

A green flash is indicative of chlorine, bromine, and iodine, but NOT fluorine

Do the same procedure with butan-1-ol*. Fix the false test result for assay.

Whether Beilstein test is applicable for detecting chlorine in nitrogen mustard derivatives of the general formula $RN(CH_2CH_2CI)_2$, which are used as antitumor agents?

Experiment 2. Silver nitrate test on chloroform.

Place in tube 3 drops of chloroform* and 5 drops of 10 % NaOH (21). Heat the reaction mixture to start boiling. Cool to room temperature. Acidify (indicator) with concentrated Nitric acid*. Add 2 drops of 1 % silver nitrate*. Record the time required for precipitate to form. If no precipitates are seen after 5 minutes, heat the solution on the steam bath for approximately 5 minutes. Note whether a precipitate forms in the test tube.

Experiment 3. Silver nitrate test on benzyl and aryl halides.

Place in two tubes 2 drops of chlorobenzene* and 2 drops of benzyl chloride* and add to each y 6–8 drops of water. Heat to boiling and add to both tubes 1–2 drops of 1 % silver nitrate solution*. Observe the formation of precipitate only in one tube. Which reagent was hydrolyzed?
Write the reaction scheme of hydrolysis.

Explain the reason for the ease of hydrolysis of one of the reagents and resistance to hydrolysis of the other.

Signature of teacher:

LABWORK №14
ALCOHOLS, PHENOLS, THIOLS, ETHERS, SULFIDES

Objective: to study the structure and properties of alcohols, phenols, thiols, ethers and sulfides.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.

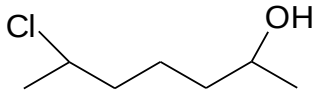
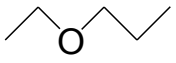
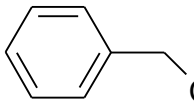
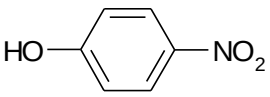
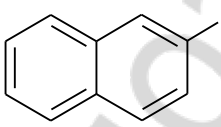
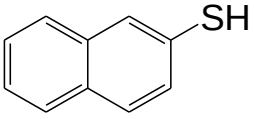
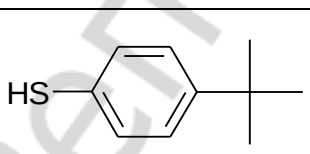
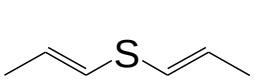
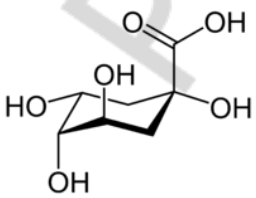
2. *Машковский, М. Д.* Лекарственные средства / М. Д. Машковский. 16-е изд., перераб., испр. и доп. Москва : Новая волна, 2012.

Problems for discussion:

1. Structure and nomenclature of alcohols, phenols, thiols, ethers and sulfides.
2. Acidic/basic and nucleophilic properties of alcohols, phenols, thiols and their conjugated bases.
3. Reactivity of alcohols and phenols.
4. Alcohols as substrates in nucleophilic substitution and elimination reactions.
5. Oxidation of alcohols, phenols and thiols *in vitro* and *in vivo.*
6. Special properties of polyols as polyfunctional compounds.
7. Ethers and esters in synthesis and life processes. Ethers as solvents.
8. Chemical and instrumental detection of amines and azo compounds.

PRACTICE PROBLEMS

1. Give IUPAC names to following compounds.

	
	
	
	
 Quinic acid	This acid is a versatile chiral starting material for the synthesis of new pharmaceuticals. A medication for the treatment of influenza A and B strains called *Tamiflu* has been successfully developed and launched into the market.

2. Write structures of following compounds. Give IUPAC names (substitutive approach). Indicate reaction centers.

Phenetole (phenyl ethyl ether)	*p*-Cresol
Divinyl ether	Benzyl mercaptane
Anisole	Hydroquinone
Benzyl-2,4-dinitrophenyl sulfide	Butan-1-thiol

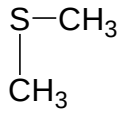
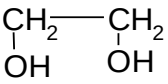
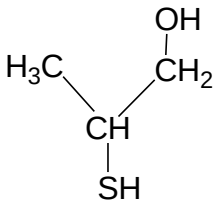
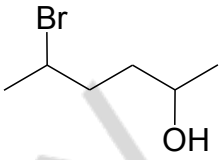
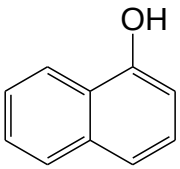
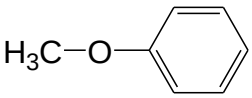
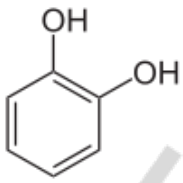
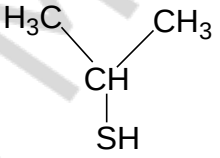
3. Write constitutional formulas of substance and rank the set of compounds in terms of relative acidity.

Methanol, phenol, glycerol, methanthiol

Methanol, 2-methylpropan-2-ol, trifluoromethanol

2,4,6-Trinitrophenol, 1-amino-3-hydroxybenzene, hydroquinone, catechol

4. Indicate reaction centers:

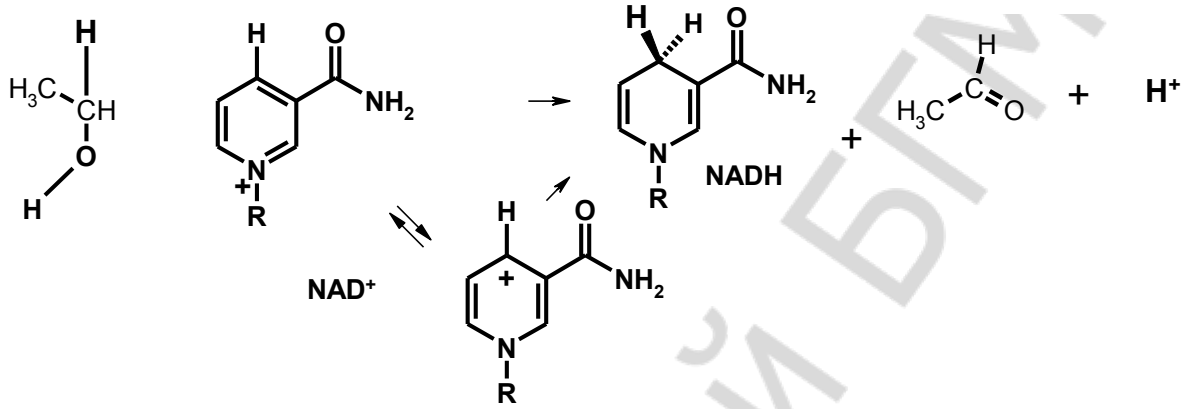
5. Write the scheme of multi-step reaction between 2-methylbutan-2-ol and 15 % H_2SO_4 (draw arrows for each step to show electron-movement. Indicate the mechanism of the reaction).

6. Write the scheme of multi-step reaction between cyclohexylmethanol and concentrated phosphoric acid (draw arrows for each step to show electron-movement and indicate the type of each step-reaction).

7. Write the scheme of multi-step reaction between (R,R-) 2-methylcyclohexanole and hydrogen bromide (draw arrows for each step to show electron-movement). Explain the stereoselectivity.

8. Nicotinamide adenine dinucleotide (NAD^+) is a coenzyme found in all living cells. In metabolism NAD^+ is involved in redox reactions, carrying hydride anion (electrons) from one substance to another. The coenzyme is, therefore, found in two forms in cells: NAD^+ is an oxidizing agent — it accepts hydride anion from other molecules and becomes reduced. This reaction forms NADH, which is a reducing agent to donate hydride anion. It is also used in other cellular processes. Because of the importance of these functions, the enzymes involved in NAD metabolism are targets for drug discovery.

Draw arrows to show electron-movement in oxidation of ethanol *in vivo*. Draw a circle around the atom that functions as nucleophile, and a square around the electrophilic center.

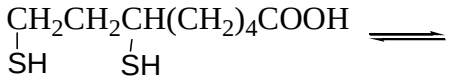


9. Write reaction scheme for oxidation of methanol with NAD^+. Draw arrows to show electron movement. Explain why methanol is much more toxic than ethanol.

10. Write reaction schemes that can be used to distinguish *n*-butyl and *tert.*-butyl alcohols.

11. Write reaction schemes that can be used to distinguish propan-2-ol and propan-1,2,3-triol.

12. Write reaction scheme for *in vivo* oxidation of dihydrolipoic acid, which participate in a variety of biochemical transformations, in particular in redox processes.



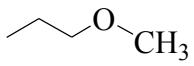
Dihydrolipoic acid is optically and only the R-enantiomer is biochemically significant. Write it's Newman projection for C_6-C_7 bond.

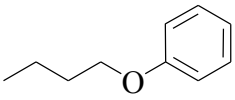
Antioxidants are _____

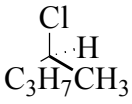
_____

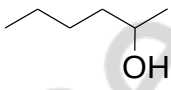
13. Write the scheme of reversible two-electron, two-proton redox system for cathechol/*ortho*-benzoquinone pair.

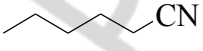
14. Based on nucleophilic substitution design synthetic schemes for substances shown below:

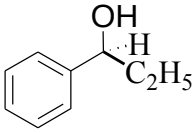
а) 

б) 

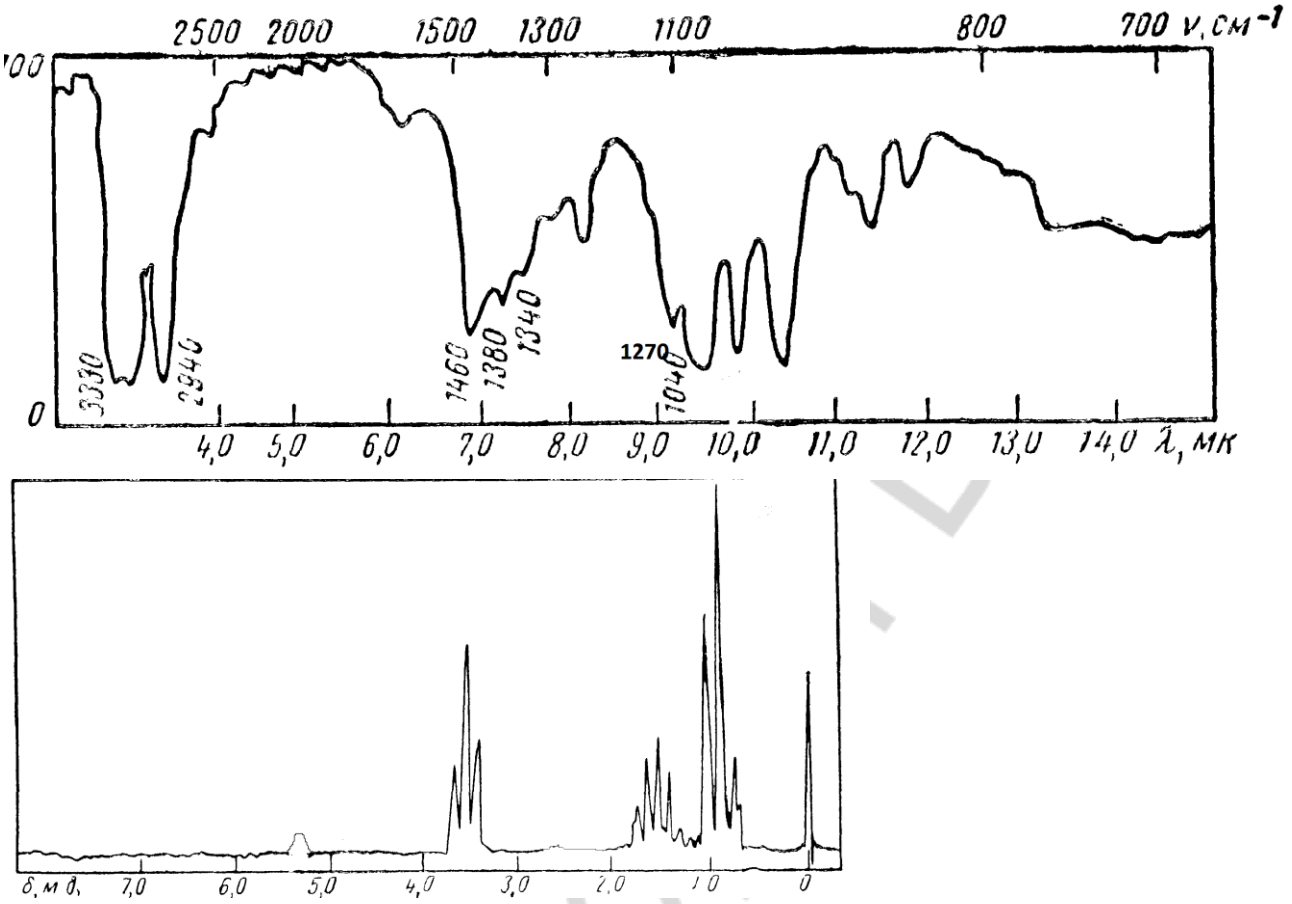
в) 

г) 

д) 

е) 

15. The compound C_3H_8O has now absorbtion in UV absorption in the UV region. By using IR and NMR spectra identify its structure. NMR ^1H: 0.92 ppm. – t, 1.57 ppm. – m, 3.8 ppm. – t, 5.2 ppm. – broad s.



16. Find drugs which contain in their structure two or more hydroxyl groups [2]. Indicate reaction centers and structural fragments.

EXPERIMENTAL SECTION

Experiment 1. Detection of primary, secondary and tertiary alcohols (*Lucas* test).

To 3–4 drops of unknown alcohol (primary, secondary and tertiary alcohols, e.g. butan-1-ol*, butan-2-ol*, *t-butyl* alcohol*) in a test tubes add 6 drops of the *Lucas* reagent (18) at room temperature. Stopper the tube and shake vigorously, then allow the mixture to stand. Note the time required for the formation of the alkyl chloride, which appears as an insoluble layer or emulsion.

Positive test is an appearance of a cloudy second layer or emulsion:
tertiary alcohols: immediate to 2–3 minutes;
secondary alcohols: 5–10 minutes;
primary alcohols: no reaction.

Explain the role of zinc chloride in the reaction.

Explain why alcohols with more than six carbon atoms cannot be tested in Lucas test.

Experiment 2. *Jones* oxidation for primary and secondary alcohols.

To 2 drops of the unknown (primary, secondary or tertiary alcohols, e.g. ethanol*) in tube add *Jones* reagent: 1 drop of 10 % sulfuric acid (23) and 2 drops of 10 % potassium dichromate (24). Heat the tube. A positive test is marked by the formation of a green color within 15 seconds upon addition of the orange-yellow reagent to a primary or secondary alcohol. Ethanol oxidation gives ethanol with apple scent.

Add 1 drop of the resulting solution to a second tube containing 3 drops of fuchsine sulfurous acid (33). It appears pink-violet color (*Shiff* test on the aldehyde group).

Aldehydes also give a positive test, but tertiary alcohols do not. A positive test for aldehydes and primary or secondary alcohols consists in the production of an opaque suspension with a green to blue color. Tertiary alcohols give no visible reaction within 2 seconds, the solution remaining orange in color. Disregard any changes after 15 seconds.

Explain why phenols and enols can give positive test.

Experiment 3. Iodoform test on ethanol

To 4 drops of ethanol* in two test tubes add 5 drops of the iodine solution, I_2 in KI solution (47), and 3 drops of 10 % sodium hydroxide (21). Stopper the test tube and shake vigorously. A positive test will result in the brown color of the reagent disappearing and the yellow iodoform solid precipitating out of solution.

Which alcohols do form iodoform?

Iron (III) Chloride test for phenols

Place 3 drops of phenol emulsion* in the tube. Add 1 drop of 1 % aqueous iron (III) chloride solution (8). Observe the pink coloring.

Proceed analogously with 1 % solutions of catechol (19), resorcinol (17), hydroquinone (22). For α-naphthol we need % alcoholic solution.

A red, blue, green, or purple coloring is a positive test.

Explain why we needed alcoholic solution of α-naphthol.

Signature of teacher:

LABWORK № 15
TEST № 2. STRUCTURE, REACTIVITY AND IDENTIFICATION OF HALIDES, ALCOHOLS, PHENOLS, THIOLS, ETHERS, SULFIDES. ACADEMIC RESEARCH № 2

Objective: to systematize the knowledge of the structure, reactivity and identification of halides, alcohols, phenols, thiols, ethers and sulfides.

Remind the program material from the theme 13, 14.

Recommended literature: study the literature from the 13, 14.

EXPERIMENTAL SECTION

An example for experimental problem:
1. Propose and carry out chemical tests, which allow us to distinguish catechol and ethylene glycol.
2. Identify chemically the proposed substance.
3. Predict spectral characteristics (UV, IR, NMR-spectra) of the proposed substance.

ACADEMIC RESEARCH № 2

Signature of teacher:

LABWORK № 16
AMINES, AZO AND DIAZO COMPOUNDS

Objective: to study the structure and properties of amines, azo and diazo compounds.

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.

2. *Машковский, М. Д.* Лекарственные средства / М. Д. Машковский. 16-е изд., перераб., испр. и доп. Москва : Новая волна, 2012.

Problems for discussion:

1. Structure and nomenclature of amines, azo and diazo compounds.
2. Basic and nucleophilic properties of amines.
3. Reactivity of amines.
4. Alkylation and acylation of amines.
5. Nitrosation and diazotization of amines.
6. Formation of diazonium salts and their substitution and coupling reactions.
7. Chemical and instrumental detection of amines and azo compounds.
8. Diazomethane in organic synthesis and analysis.

PRACTICE PROBLEMS

1. Write the structures. Identify which of them are primary, secondary or tertiary amines. Indicate reaction centers. Give substitutive IUPAC nomenclature names.

Ethylamine	Methylethylamine
Dimethylamine	Triethylamine
Isoamylamine	Ethanolamine
2,4,6-Tribromaniline	N,N-Dimethylaniline
Phenylenediamine	*p*-Aminosalicylic acid
Triethylbenzylammonium chloride	(R-) Amylmethylphenylbenzylammonium chloride

2. Write constitutional formulas of substances and rank the set of compounds in terms of relative basicity.

Aniline, *p*-nitroaniline, *p*-methoxyaniline, *p*-toluidine.

Dimethylamine, trimethylamine, benzylamine, phenylethylamine.

Acetanilide, diphenylamine, aniline.

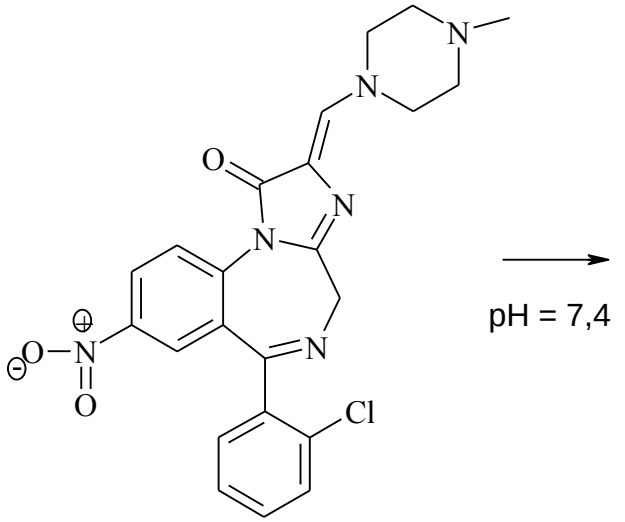
3. Give the structural formulas of local anesthetics [2]. Detect the basic centers and indicate the strongest. Write reaction with hydrochloric acid.

Procaine

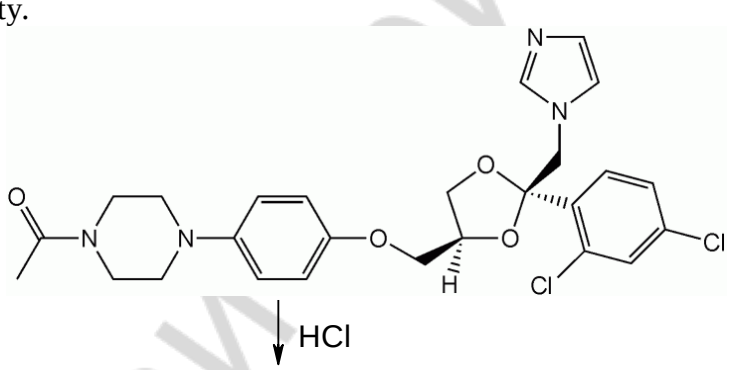
Lidocaine

Articaine

4. *Loprazolam* is a short-acting benzodiazepine possessing anxiolytic, sedative, anticonvulsant and skeletal muscle relaxant properties. Show the structure of the predominate form of the following molecules at physiological pH 7.4.



5. The systemic antifungal agent *Ketoconazole* is administered orally as the free base. The oral bioavialability of this drug is dependent upon solubility in the gastric contents and solubility is promoted by the acidic pH of the digestive tract. Using structures show how acidity enhances ketoconazole solubility.



6. Write schemes and name of the products of the following reactions of aniline and benzyl ethyl amine.

Acylation with propionyl chloride

Acylation with acetic anhydride

Alkylation with 2-bromopropane

7. Write the scheme of multi-step diazotization reaction between *p*-methoxyaniline and nitric acid (draw arrows for each step to show electron-movement).

8. Write and name the products of the reaction between the resulting diazonium salt from previous problem and with compounds listed below. Indicate mechanism and specify conditions of each reaction.

Water

Sodium iodide

Sodium bromide

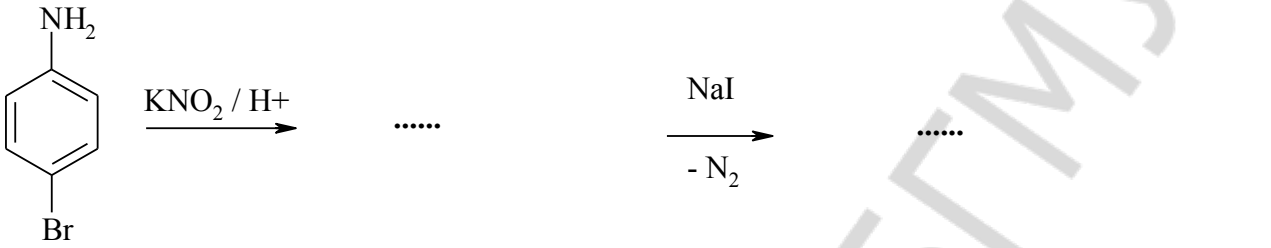
Potassium cyanide

Tetrafluoroboric acid

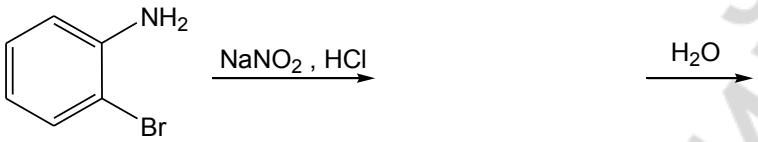
Metaphosphoric acid

β-Naphthol

9. Write reaction schemes and name the products:



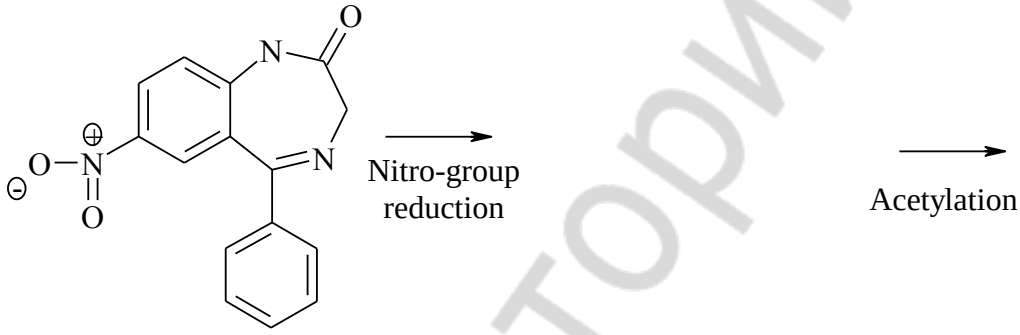
10. Complete the scheme and name the products.



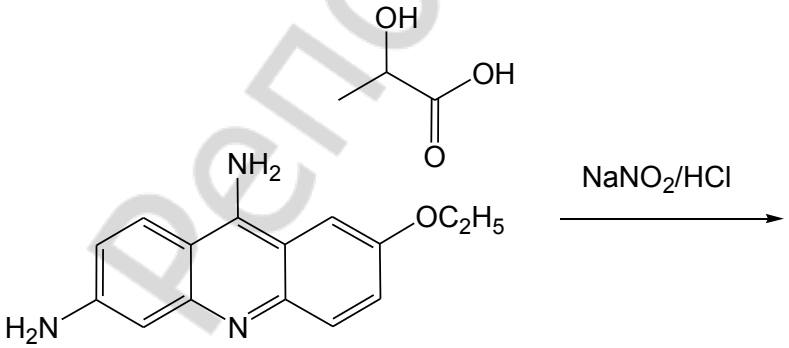
11. Design the synthesis of 1,3,5-tribromoamiline from benzene using the nitration/diazotization strategy.

12. Write reactions of diazomethane with hydrogen bromide, resorcinol, isoamyl alcohol, isobutyric acid, *p*-toluenesulfonic acid, pent-2-ene.

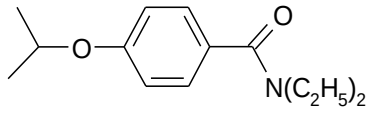
13. *Nitrazepam* is psychoactive drug possessing mostly hypnotic and sedative action. Show the end product of *Nitrazepam* metabolism resulting from nitro group reduction followed by conjugation of the intermediate aniline derivative by acetylation.

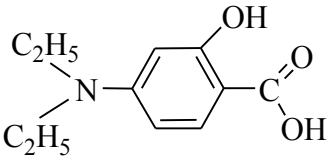


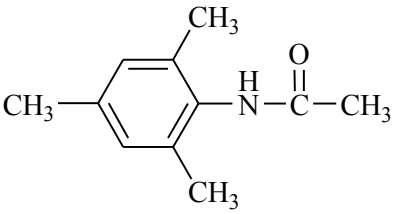
14. Explain the color change from yellow to crimson for *Ethacridine Lactate* (antiseptic medication) reacting with sodium nitrite in an acidic conditions. Discuss the possibility of spectral detection of the compound.

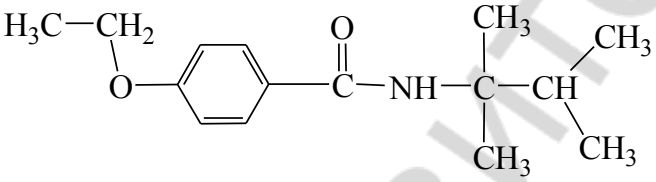


15. Predict frequency bands in IR spectrum as well as chemical shifts, J-coupling and intensity in the ^{1}H NMR spectrum. Explain the answer.









EXPERIMENTAL SECTION

Experiment 1. Aniline synthesis.

Add 5 drops of concentrated hydrochloric acid* and a small granule of zinc metal* to a tube with 2 drops nitrobenzene*. Shake the tube vigorously and carry out the reaction till zinc will be dissolved completely (you may need to heat the tube and/or to add few more drops of hydrochloric acid*). As the result you will see the upper layer of nitrobenzene will disappear to give the aniline hydrochloride which is well soluble in water. The solution obtained you should use exp. 2.

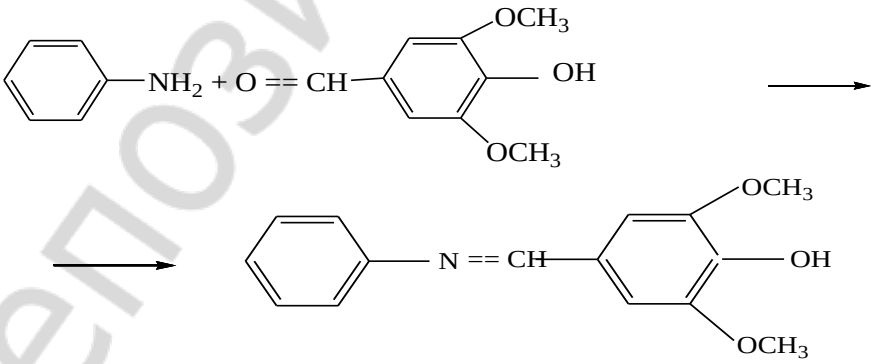
Add sodium hydroxide solution and fix the changes.

Write the reaction of aniline formation.

Write the reaction which is taking place after addition of sodium hydroxide to aniline hydrochloride *solution. On what grounds can be judged on the formation of free aniline?*

Experiment 2. Aniline detection.

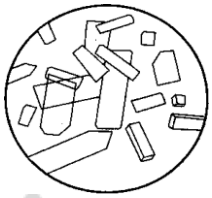
Webster has proposed a very simple test for primary and secondary aryl amines. The test depends on the action of lignin in newsprint paper. Ethanolic solution of amines applied on newsprint paper and treated with hydrochloric acid (approx. 6M HCl,). Primary and secondary aryl amines produce immediate yellow or orange color, while alkyl and alicyclic amine require hot solution for color development. The test is based on the reaction of the substances containing amino-group with aromatic aldehydes forming under acidic hydrolysis of lignin, e.g. syringaldehyde (4-hydroxy-3,5-dimethoxybenzaldehyde).



Place few drops of hydrochloric solution from previous experiment on newsprint and filter paper. It will produce on newsprint paper immediate yellow or orange coloring in contrary to filter paper.

Explain the difference in lignin probe for newsprint and filter paper.

Experiment 3. Aniline acetylation.



Many of the acetylated derivatives of aromatic amines (or anilines) are pharmacologically important compounds. Some of these exhibit distinct analgesic activity (e.g. N-acetyl-4-hydroxyaniline, or acetaminophen).

Place 2 drops of aniline* in the test tube and add 4 drops of acetic anhydride* (you can observe warming of the tube). Heat the mixture over the burner flame. After cooling add 10 drops of water and shake vigorously the tube. The well-shaped crystals are formed. With a glass rod place a few crystals on a microscope slide. Examine crystals under the microscope. They have the form of prismatic plates.

Write the reaction of aniline acetylation. Discuss the mechanism of the reaction.

Which functional derivatives of acetic acid are better to use for aniline acetylation*?*

Experiment 4. Basic properties of aliphatic and aromatic amines.

Place one drop of diethylamine* and aniline* in two different tubes followed by addition of 3 drops of water in each. Shake vigorously. With a glass rod place a bit of both mixtures to pH indicator and determine the approximate value of pH. Compare the solubility in water and the basic properties of both amines.

Divide aniline emulsion into two portions followed by adding 1 drops of 10 % hydrochloric (9) and 10% sulfuric (23) acids.

Explain the higher solubility of diethylamine?

Explain the higher basisity of diethylamine.

Experiment 5. Amine nitrosation.

Place 6–7 drops of glycine (6) (analogue of primary amine), N,N-dimethylaniline* and aniline* in three different tubes and cool tubes in ice water bath. Add dropwise (aprox. 5 drops) add successively concentrated HCl* and 5 % aq. sodium nitrite (34)

Fix the changes in both tubes.

Write reaction schemes and show the mechanisms of the reactions.

Experiment 6. Diazotization of aniline and diazo coupling.

Place in the first tube5 drops of aniline*, 5 drops of concentrated HCl* and a piece of ice* followed by addition of 5 drops of 5 % aq. sodium nitrite (34). Shake the tube vigorously after adding of each drop. To check the end of reaction place a bit of mixture onto strip of iodine-starch paper — the blue coloring indicates the end of the reaction.

Place in the second tube a few crystals of β-naphthol* followed by addition of 10 % aq. NaOH (21) till the solid come to solution. Add the drop of the solution from the second tube into the first tube.

Divide azo dye into two tubes followed by addition of 10 % aq. HCl (9) 10% aq. NaOH (21) in different tubes.

Write the schemes and mechanisms of reactions.

Design schemes of detection (using azo-coupling reactions) for
α-naphthol *para-phenetidine*

Signature of teacher:

LABWORK № 17
OXO COMPOUNDS

Objective: to study the structure and properties of oxo compounds (aldehydes and ketones).

Recommended literature

1. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.

2. *Машковский, М. Д.* Лекарственные средства / М. Д. Машковский. 16-е изд., перераб., испр. и доп. Москва : Новая волна, 2012.

Problems for discussion:

1. Structure and nomenclature of aldehydes and ketones.
2. Structure of carbonyl group. Reaction sites and reactivity of oxo conpounds.
3. Reactions of nucleophilic addition at the carbonyl group: the general scheme, the role catalysis.
4. Reactions with O-, C-, S-, N-nucleophiles: the general scheme, examples.
5. Reactions with C-nucleophiles: mechanism and application.
6. Hydrogenation: mechanism of hydrogen and hydride addition, and application.
7. Condensation reactions: the general scheme, the role catalysis.
8. Reactions with alcohols and thiols: mechanism and application.
9. Reactions with nitrogen nucleophiles: mechanism and application.
10. Keto-enol balance and formation of an enolate anion.
11. α-Substitution in aldehydes and ketones.
12. Oxidation/reduction of aldehydes and ketones *in vitro* and *in vivo*.
13. Some representatives of aldehydes and ketones (formaldehyde, acetaldehyde, acryl aldehyde, benzaldehyde, acetone, cyclohexanone, and etc.), their application in medicine and pharmacy.
14. Chemical and instrumental detection of oxo compounds.

PRACTICE PROBLEMS

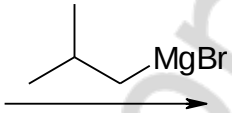
1. Write structures, convert trivial names. Determine electronic effects and indicate reaction sites.

2,3-Dimethylpentanal	4-Ethylhex-1-en-3-one
Butyraldehyde	Vanillin

2. Show graphically the distribution of charge in the molecules of formaldehyde, ethanal, benzaldehyde and butanone. Indicate reaction centers and discuss the influence of substituents on electrophility of carbon in carbonyl group.

3. Rank formaldehyde, acetaldehyde, acetone and chloroacetic aldehyde according to their ability to nucleophilic addition.

4. Write the structural formulas and addition reactions of oxo compounds. Give the name of the reaction products.

Oxo compound	**Reagent**	**Product**
1,3-Dimethylcyclohexanone	H_2/Pd →	
2-Methylhexanal	$NaCN/H^+$ →	
2-Methylpentan-3-one		
Methyl ethyl ketone		
Cyclopentanone	$HC\equiv CNa$ →	
Benzaldehyde	CH_3OH / H^+ → (Equimolar)	
Trihloroethanal	H_2O →	

5. Write the scheme of multi-step condensation reaction between cyclohexanone and excess of methanol in acidic conditions. Draw arrows for each step to show electron-movement.

6. Write the scheme of multi-step intermolecular cyclization of γ-hydroxybutyraldehyde in ether as a solvent. Draw arrows for each step to show electron-movement.

7. Write the scheme of multi-step intermolecular cyclization of 5-hydroxy hexan-2-one in methanol solution under acid catalysis with the formation of mixed acetal. Draw arrows for each step to show electron-movement.

8. Write the scheme of multi-step condensation reaction between cyclopentanone and benzylamine: imine formation. Draw arrows for each step to show electron-movement.

9. Write the scheme of multi-step condensation reaction between cyclopentanone and diethylamine: enamine formation. Draw arrows for each step to show electron-movement.

10. Hexamethylenetetramine (*Urotropine*) was discovered by *Alexander Butlerov* in 1859 and widely used in organic synthesis. As the mandelic salt (*Methenamine mandelate*) it has being used from the end of 19^{th} century for treatment of urinary tract infection. It decomposes at an acidic pH to form formaldehyde and ammonia, and the formaldehyde is bactericidal; the mandelic acid adds to this effect, along with aspirin *Urotropine* being one of the first pro-drug. Though its use had temporarily been reduced in the late 1990s, due to adverse effects, now its application been reapproved because of the prevalence of antibiotic resistance to more commonly used drugs.
Write the scheme of multi-step formation of hexamethylenetetramine. Draw arrows for each step to show electron-movement.

11. Write reaction scheme (draw arrows for each step to show electron-movement) for syringaldehyde (4-hydroxy-3,5-dimethoxybenzaldehyde) reduction in interaction with:

Hydrogen (Pt-catalyzed)

Lithium aluminum hydride (followed by alcoholate hydrolysis)

Formaldehyde (*Cannizzaro* dismutation in presence of KOH)

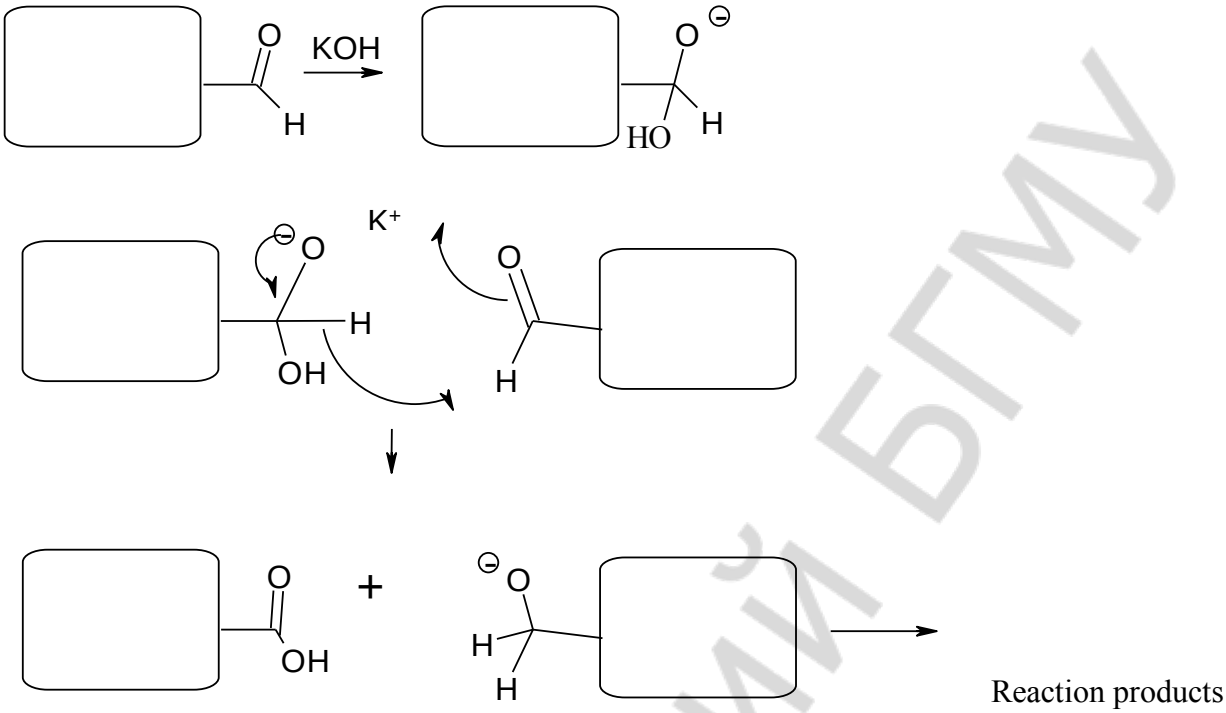
NADH *in vivo*

Zinc amalgam and HCl (*Clemmensen* reduction)

in *Wolff-Kishner* reduction (hydrazone denitrogenation)

12. Write the scheme of benzaldehyde dismutation (*Cannizzaro* reaction).

13. Complete the scheme of cross *Cannizzaro* reaction between formaldehyde and 1-acetylcyclohexene by adding the missing elements (taking in account the electrophility of carbonyl carbon).



Reaction products

Explain why the transition state is energetically stable.

14. Write reaction scheme for aldol condensation of hexan-3-one with equimolar formaldehyde in acidic conditions (aldol formation).

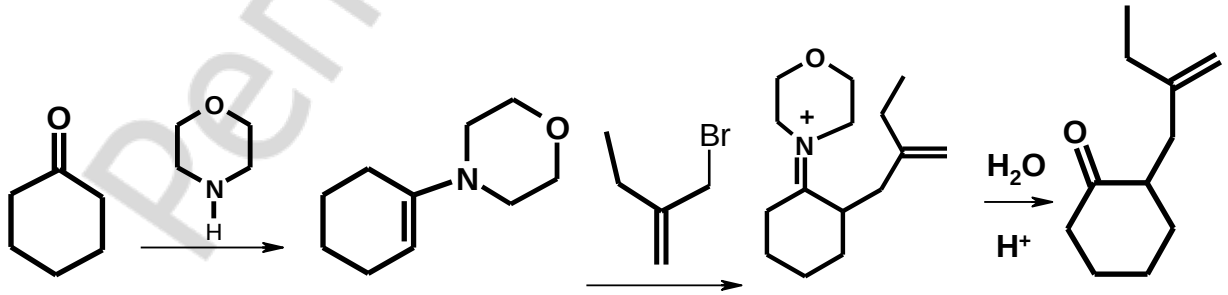
15. Write reaction scheme for aldol condensation of nicotinic aldehyde with acetophenone in basic conditions (unsaturated ketone formation). Draw arrows for each step to show electron-movement.

16. Write reaction schemes of acetaldehyde and cyclohexanone oxidations in mild and drastic conditions (CrO_3, $KMnO_4$/40ºC, $KMnO_4$/120ºC, C_6H_5COOOH)

17. Write reaction schemes of cyclohexane alkylation with ethylbromide in presence of LDA (lithium diisopropylamide).

Based on *Brønsted* concept explain why LDA behaves as one of the strongest bases and widely used in synthesis for deprotonation.

18. *Storch* enamine strategy is used for alkylation of oxo compounds in mild conditions. Draw arrows to show electron-movement in the following multi-step reaction (draw arrows for each step).

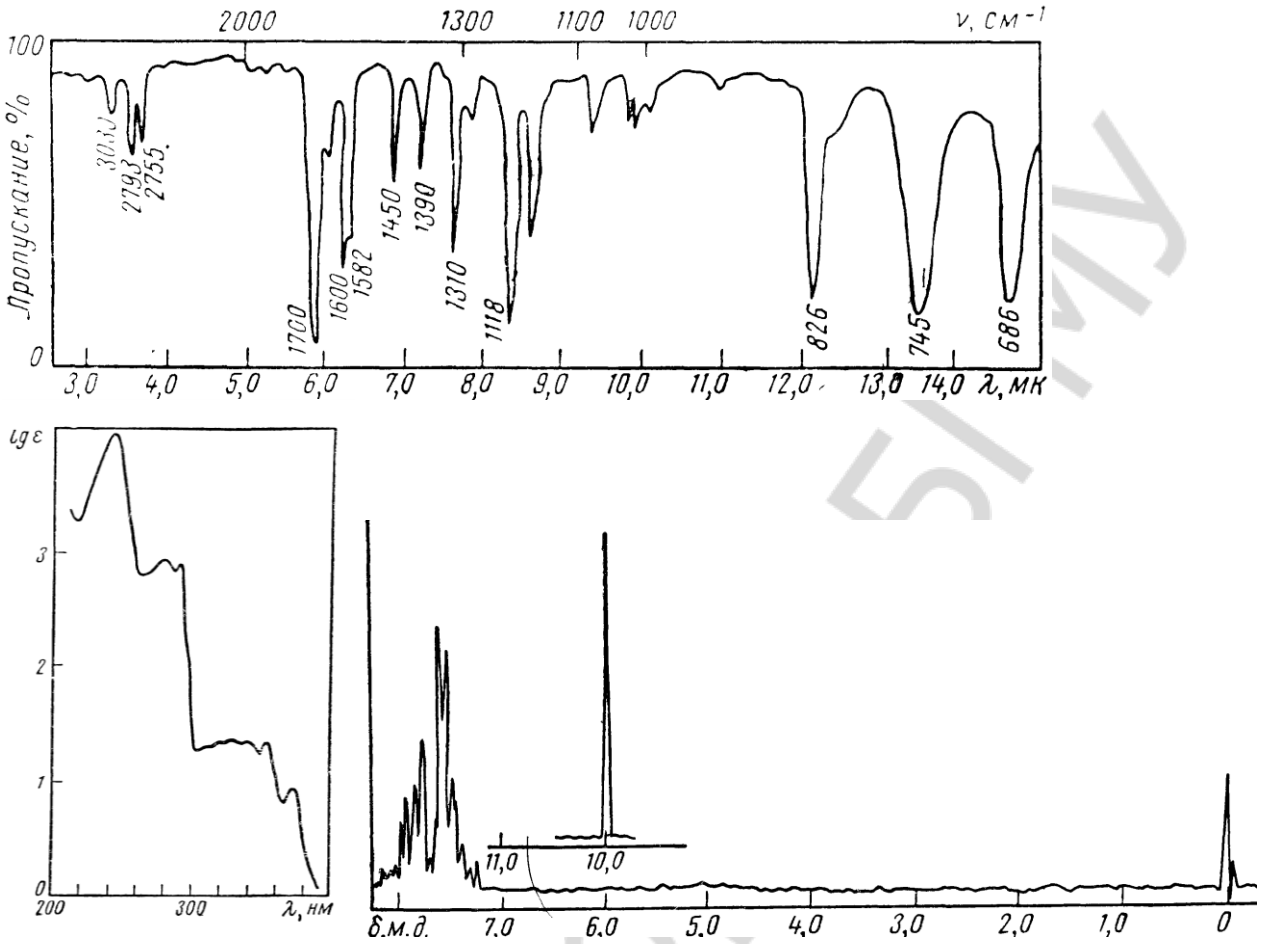


19. Design the synthesis of *Nylon* 6, or polycaprolactam, (which is widely used in polymer industry, in particular for surgical sutures production) based on benzene structure and acid catalyzed *Beckmann* rearrangement of cyclohexanone oxime).

20. Design the synthesis of N-methyldihydroxyphenylalanine based on 3,4-dihydroxyphenylacetic aldehyde structure and aminocyanation strategy (hydrocyanation of imino group).

21. Design the synthesis of acetylcyclohexane from acetylbenzene, using the procedure of the carbonyl group acetal protection in the reduction reaction.

22. Compound (C_7H_6O) has an absorption in the UV region. By using IR and NMR spectra identify its structure.



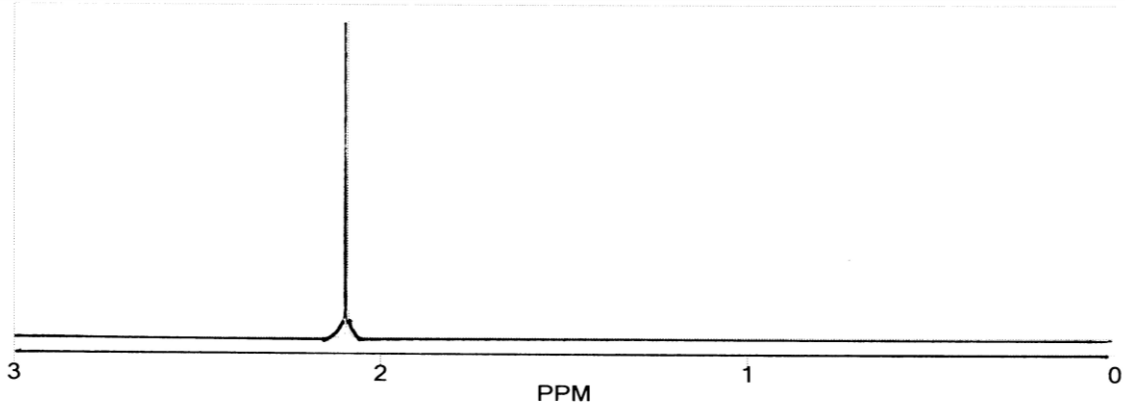
23. Detect substances based on chemical shifts and spin coupling in NMR ^1H spectra:

Dimethyl ketone and diethyl ketone

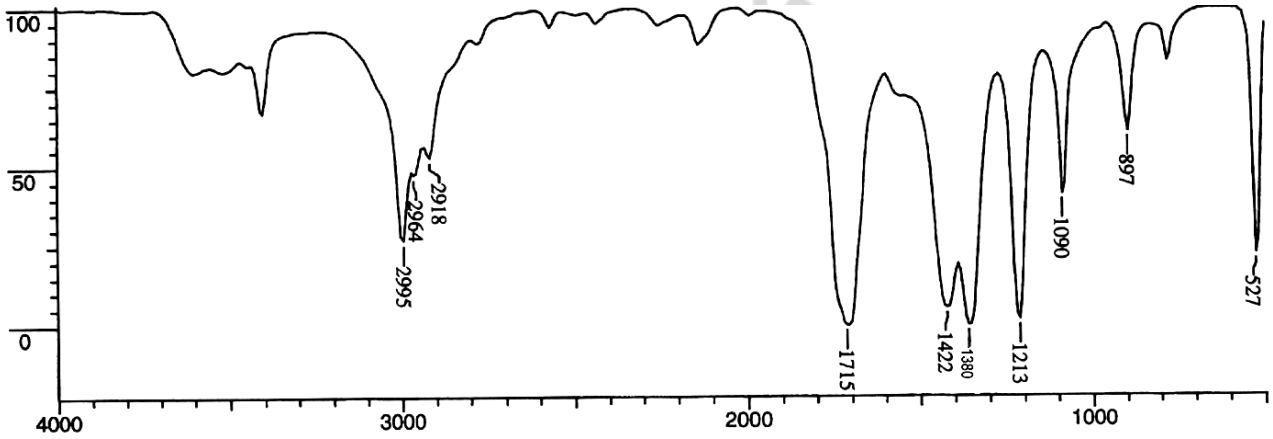
para-Methoxybenzaldehyde and acetophenone

Methyl isobutirate and 2,2-dimethylpropanal

24. The oxidation of hydrocarbon C_6H_{12} with potassium dichromate gives compound which ^1H NMR spectrum has the only singlet at 2.04 ppm. Detect substrate and product of the oxidation.



25. Define the structure based on IR spectrum of compound (C_3H_6O).



EXPERIMENTAL SECTION

Experiment 1. Synthesis of acetone oxime.

200 mg of hydroxylamine hydrochloride (13) and 200 mg of sodium carbonate (15) is dissolved in 2.5 ml of water. After the end of carbon dioxide formation, cool the mixture (ice water bath) and add dropwise (so that the temperature does not rise above 15 °C). Add to the mixture 1 mL of acetone with stirring (or shaking). The acetone oxime usually starts to crystallize when about half the acetone has been added. When the addition is complete, the mixture is allowed to stand in ice-water for additional 15 minutes. The solution is filtered and the crude acetone oxime is collected, yielding approximately 1 g of crystalline product. The acetone oxime so obtained contains the small amount of sodium chloride, but is otherwise almost pure for the most synthesis purposes. Crude acetone oxime is purified by crystallization from petroleum ether (with boiling point 60-80 °C) or other hydrocarbons. The acetone oxime is freely soluble in water and in most organic liquids.

Write step-by-step reaction scheme for acetone oxime *formation.*

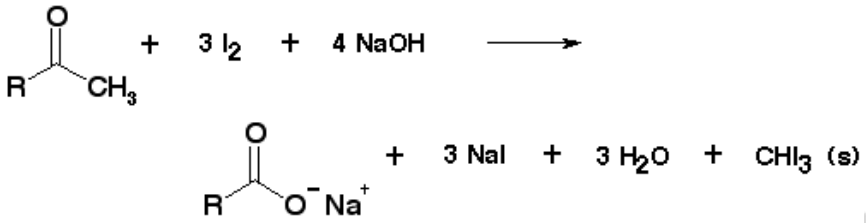
Explain why the reaction depends much on pH of solution.

Experiment 2. 2,4-DNP test for benzaldehyde (cyclohexanone, benzophenone).

Add a solution of 1 or 2 drops of benzaldehyde* in 2 mL of 95 % ethanol* to 3 mL of 2,4-dinitrophenylhydrazine reagent*. Shake vigorously, and, if no precipitate forms immediately, allow the solution to stand for 15 minutes.
Formation of a precipitate is a positive test.
Write the scheme of the reaction showing all arrow drawings for multistep mechanism.

Why some allylic alcohols give a positive 2,-4-DNP test?

Experiment 3. Iodoform test for acetone



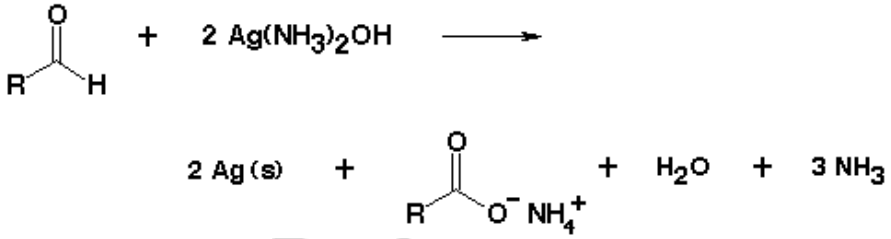
Place in a tube 3 drops of the iodine solution, I_2 in KI solution, (47). Add dropwise 10 % sodium hydroxide (21) till the solution come colorless. Add to the obtained mixture 1 drop of acetone. Stopper the test tube and shake vigorously. A positive test will result in the brown color of the reagent disappearing and the yellow iodoform solid precipitating out of solution.

Formation of solid iodoform (yellow) is a positive test. Iodoform can be recognized by its odor and yellow color and, more securely, from the melting point 119–123 °C.

Write the scheme of the reaction showing all arrow drawings for multi-step mechanism.

Which oxo compounds do not work in iodoform test?

Experiment 4. Tollen's test for aldehydes.



To prepare *Tollens* reagent place into each of three test tubes 2 drops of 1 % silver nitrate and 2 drops of 10 % sodium hydroxide (21). Then add 10 % ammonia solution, drop by drop, with constant shaking, until almost all of the precipitate of silver oxide dissolves.

Add in three test tubes with freshly prepared *Tollens* reagent 1–2 drops of formalin (32), benzaldehyde* and acetone* to 1 mL of the. Gentle heating can be employed if no reaction is immediately observed.

Formation of silver mirror or a black precipitate is a positive test.

Why aromatic amine and some phenols give positive Tollen's Test?

Experiment 5. Formaldehyde dismutation.

Place the tube in 2–3 drops of 40 % formaldehyde (32) solution. Add 1 drop of methyl red indicator* (the range of color change which is within pH of 4.8–6.0).

Explain the change of color observed.

Signature of teacher:

LABWORK № 18
TEST №3 STRUCTURE, REACTIVITY AND IDENTIFICATION OF AMINES, ALDEHYDES AND KETONES. ACADEMIC RESEARCH № 3

Objective: to systematize the knowledge of the structure, reactivity and identification of oxo compounds.

Remind the program material from the theme 16, 17.

Recommended literature: study the literature from the 16, 17.

EXPERIMENTAL SECTION

An example for experimental problem:
1. Propose and proceed chemical tests which allow us to distinguish formaldehyde, acetone, phenol (solutions).
2. Identify chemically the proposed substance.
3. Predict spectral characteristics (UV, IR, NMR-spectra) of the proposed substance.

ACADEMIC RESEARCH № 3

Signature of teacher:

RECOMMENDED LITERATURE

Basic

1. *Lakhvich, T. T.* Organic chemistry : handbook. Part I / T. T. Lakhvich, O. N. Ryneyskaya, G. P. Fando. Minsk : BSMU, 2017. 132 p.
2. *Lakhvich, T. T.* Organic chemistry : handbook. Part II / T. T. Lakhvich, O. N. Ryneyskaya, G. P. Fando. Minsk : BSMU, 2017. 152 p.
3. *Chernykh, V. P.* Organic chemistry. Basic lecture course : the study guide for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. 4 ed., rev. and enl. Kharkiv : NUPh, Original, 2011. 440 p.
4. *Chernykh, V. P.* A. Applied infrared spectroscopy : a manual for students of higher schools / V. P. Chernykh, L. A. Shemchuk ; ed. by V. P. Chernykh. Kharkiv : NUPh, 2014. 152 p.
5. *Zurabian, S.* Fundamentals of bioorganic chemistry: textbook for medical students / S. Zurabian. Москва : Гэотар, 2012. 304 p.

Additional

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7. *Loudon, M.* Organic Chemistry / M. Loudon, J. Parise. 6th ed. New York : W. H. Freeman and Company, 2015. 1648 p.
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Table of IR absorptions

Groups	Vibration type	Frequency range (cm^{-1})	Intensity*
Alyl, cycloalkyl	Stretching C–H:		
	Asymmetric	2999–2926	s – m
	Symmetric	2872–2853	s – m
	Bending C–H:		
	Asymmetric	1485–1430	m
	Symmetric	1380–1340	s
Double bond	Stretching C=C	1680–1600	m
	Stretching =C – H	3100–3000	m
	Terminal vinyl group $=CH_2$:		
	Asymmetric	3100	m
	Symmetric	3000	m
	Bending =C–H	1000–800	s
***Z*-diastereomers**	Bending =C–H	730–650	s
***E*- diastereomers**	Bending =C–H	980–900	s
Triple bond	Stretching C≡C	2300–2100	m
	Stretching ≡C–H	3333–3267	s
	Bending ≡C–H	700–610	
Benzene fragment	Stretching C_{ar}⋯C_{ar}	~ 1600	
		~ 1580	m
		~ 1500	
		~ 1450	
	Stretching C_{ar}–H	3100–3000	m
	Bending C_{ar}–H	900–675	m
monosubstituted	Bending C_{ar}–H	710–690; 770–730	m; m
***o*-disubstituted**	Bending C_{ar}–H	770–735	m
***м*-disubstituted**	Bending C_{ar}–H	710–690	m
		810–750	m
***n*-disubstituted**	Bending C_{ar}–H	840–810	m
Hydroxyl group	Stretching O–H	3650–3200	s, board
primary	Stretching C–O	~ 1050	s
	Bending O–H	1350–1260	s
secondary	Stretching C–O	~ 1100	s
	Bending O–H	1350–1260	s
tertiary	Stretching C–O	~ 1150	s
	Bending O–H	1410–1310	s
Hydroxyl group (phenols)	Stretching O–H	3650–3200	s
	Stretching C–O	1200	s
	Bending O–H	1410–1310	s

* s — strong; m — medium; w — weak.

Groups	Vibration type	Frequency range (cm^{-1})	Intensity*
Etheric	Stretching C–O–C:		
alkyl	Asymmetric	1150–1085	s
aryl	Asymmetric	1275–1200	s
	Symmetric	1075–1020	s
vinyl	Asymmetric	1225–1200	s
	Symmetric	1075–1020	s
Mercapto group	Stretching S–H	2600–2550	w
Sulfoxides	Stretching S=O	1070–1030	s
Sulfones	Stretching SO_2		
	Asymmetric	1350–1300	s
	Symmetric	1160–1140	s
Sulfonic acids	Stretching SO_2		
	Asymmetric	1260–1150	s
	Symmetric	1080–1010	s
Amines	Free stretching N–H:		
primary	Asymmetric	~ 3500	m
	Symmetric	~ 3400	m
	Bonded	3400–3250	s
secondary	Free stretching N–H	3450–3300	m
	bonded	3350–3200	s
	Bending N–H	1650–1550	m
aliphatic	Stretching C–N	1220–1020	w
aromatic	Stretching C–N	1360–1280	s
Amine salts	$^{+}$		
	Stretching NH in RNH_3	~ 3000	s
	$^{+}$		
	Stretching NH		s
	in R_2NH_2	2700–2250	
	in R_3NH		s
		2700–2250	
Azo compounds	Stretching N=N	1630–1575	m
Diazo compounds	$^{+}$		
	Stretching –N≡N	2300–2000	m
Nitro compounds	Stretching NO_2:		
aromatic	asymmetric	1570–1500	s
	symmetric	1370–1300	s
aliphatic	asymmetric	1570–1550	s
	symmetric	1380–1370	s
***C*-Nitro compounds**	Stretching NO	1600–1500	s
***N*-Nitro compounds**	Stretching NO	1500–1430	s

Groups	Vibration type	Frequency range (cm^{-1})	Intensity*
***O*-Nitro compounds**			
trance	Stretching NO	1680–1650	s
cis	Stretching NO	1625–1610	s
Nitriles	Stretching C≡N	2260–2220	m
Imines, oximes	Stretching C=N	1690–1630	m
Aldehydes	Stretching C=O		
aliphatic		1740–1720	s
α, β-unsaturated		1705–1680	s
aromatic		1715–1695	s
Ketones	Stretching C=O		
aliphatic		1725–1705	s
alkyl aryl		1700–1680	s
diaryl		1670–1660	s
1,4-quinones		1690–1660	s
	Bending C=O	~1100	s
Carboxylic acids	Stretching OH	2700–2500	w
	Stretching C=O		
aliphatic		1725–1700	s
α, β- unsaturated		1715–1690	s
aromatic		1700–1680	s
Carboxylates	Stretching C=O		
	Asymmetric	1650–1610	s
	Symmetric	1450–1400	s
Esters			
aliphatic	Stretching C=O	1750–1735	s
α, β-unsaturated, aromatic	Stretching C=O	1730–1717	s
Amides	Stretching C=O		
	(I amide band)	1700–1630	c
	Free stretching N–H	3500–3400	m
	Bonded stretching N–H	3350–3140	m
	Bending N–H (II amide band)	1620–1510	s
Anhydrides	Stretching C=O:		
	asymmetric	1870–1800	s
	symmetric	1790–1740	s
	Stretching C–O	1130–900	s
Acyl halides	Stretching C=O	1810–1750	s
Halides	Stretching: C–F	1400–1000	s
	C–CI	800–600	s
	C–Br	600–500	s
	C–I	~ 500	s

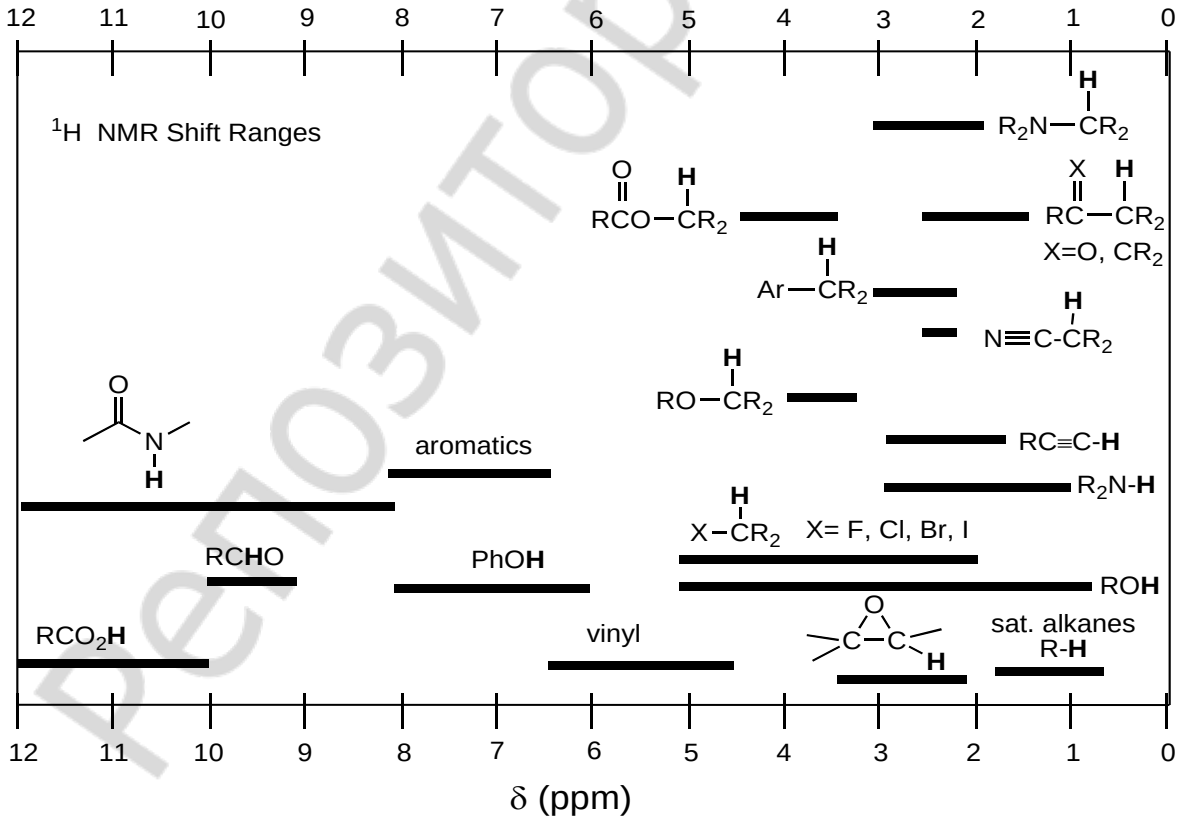
Suppliment 2

Typical vibrational frequencies of functional groups

Bond	Molecule	Wavenumber (cm^{-1})
C–O	Alcohols, ethers, esters, carboxylic acids, etc.	1300 – 1000
C=O	Aldehydes, ketones, esters, carboxylic acids	1750 – 1680
C=O	Amides	1680 – 1630
N–H (Stretching)	Amines and amides	3500 – 3100
–N–H (Bending)	Amines and amides	1640 – 1550
O–H	Alcohols	3650 – 3200
C–N	Amines	1350 – 1000
S–H	Mercaptans	2550

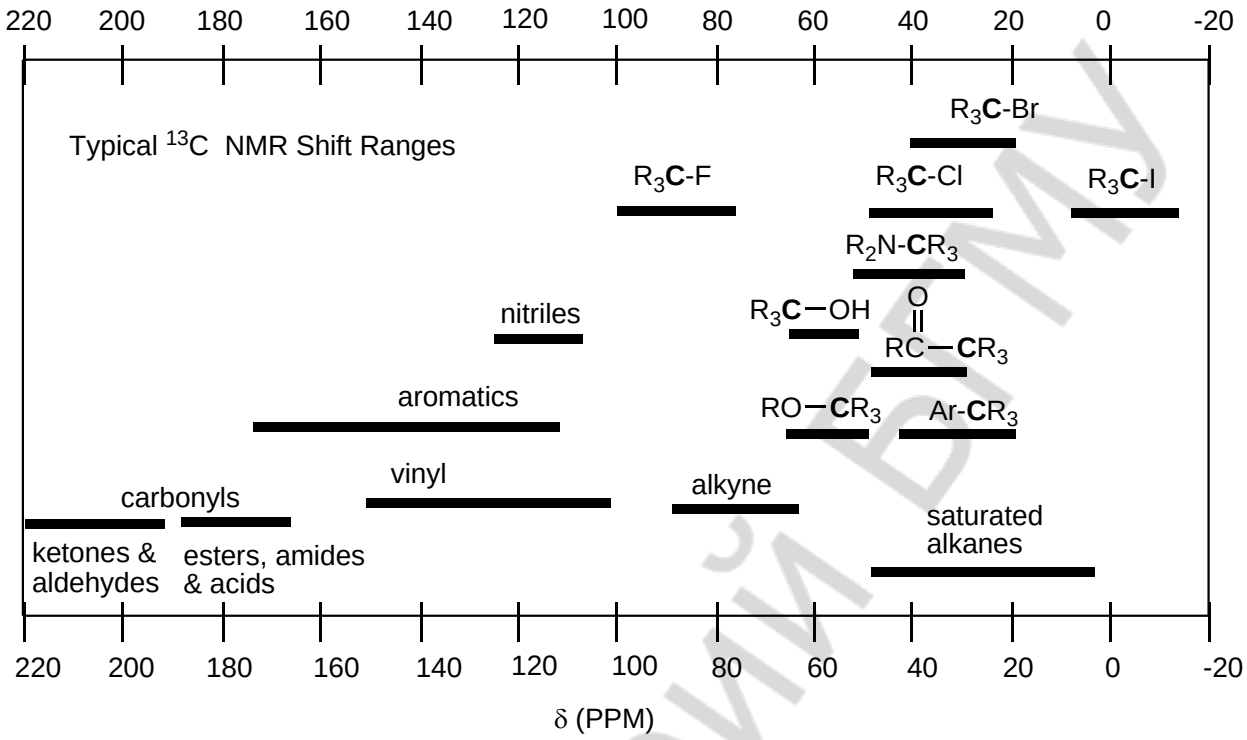
Suppliment 3

Typical ^{1}H NMR chemical shifts ranges; additional substitution*



* Can move the resonances out of the range.

Typical ^{13}C NMR chemical shifts ranges



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Лабораторный практикум

На английском языке

В двух частях

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