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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

SYNTHESIS, TRANSFORMATIONS AND BIOLOGICAL ACTIVITY OF PYRAZOLE AND PYRAZOLINES OBTAINED FROM UNSATURATED KETONES

Speciality: 2306.01-Organic chemistry

Field of science: Chemistry

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The work was performed at Institute of Polymer Materials of Azerbaijan National Academy of Sciences at the "Heterocyclic compounds" laboratory

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GENERAL CHARACTERISTICS OF THE WORK

Actuality of the research and degree of elaboration. Rapid development of organic chemistry requires development of efficient methods for the synthesis of organ nitrogen heterocyclic compounds containing special functional groups, significantly important both in medicine and various fields of industry, and the study of the realized reactions. This class of compounds (e.g., nicotinic acid derivatives, pyrroles, isoxazoles, etc.), including their interesting members - pyrazole and pyrazoline derivatives have wide fields of application.

The properties of different functionally-substituted organonitrogen heterocyclic compounds depend on their structure, nature of functional groups in molecule and the state in the cycle. This type of compounds depending on chemical strustures are widely applied for the development of medications in medicine, corrosion inhibitors in industry, special pest control remedies in agriculture, polymer materials production, paint and coating industry.

Pyrazole and pyrazoline derivatives have wide fields of application as interesting members of organonitrogen heterocyclic compounds. Pyrazole and pyrazoline nuclei are found in several natural compounds. For this reason, the recent study of the synthesis and properties of this class of compounds has a significant importance. Pyrazole and pyrazoline derivatives are used in medicine for obtaining medicinal substances. Thus, "Antipyrine", "Analgin", "Amidopyrine" are used in medicine as antipyretics and colds, "Pyramidon" as a painkiller, "Celebrex" as a drug for joint pain, tc.[1] Besides, pyrazole and pyrazoline derivatives are used as insecticides against agriculture pesticides in organic synthesis, ecolorants in polymer chemistry, stabilizers in rubber industry, accelerators for rubber vulcanization and etc. (e.g., 3-methyl-1-phenyl-5-pyrrazolon compound as a dye substance[2], 1-acetyl-4-methyl-3-nitrophenyl-

[1]Kharkevich, D.A. Farmokologiya: (Meditsina) / D.A.Kharkevich. – Moscow: Nauka, − 1987, − p.146-162.

[2]Gorelik, M.V. Proizvodniye 1-fenil-3-aminopirazola v kachestve krasiteley poliakrilnitrilnykh materialov, A.c. 819137 (USSR) / Titov, S.P., Rybinov, V.I. [et al.]: − 1981.

(vinyl)pyrazole compounds as a thermostabilizer[3], 3-difluormethyl-1-methyl-4-carboxamide-1H-pyrazol compound called “Bixafen” as an insecticide[4] against wheat pathogens in agriculture).

In the light of above information, it may be noted, that study of synthesis methods for new functionally-substituted pyrazol and pyrazoline derivatives, determination of their biological efficiency are actual tasks of organic chemistry. From this point of view, the dissertation is devoted to the synthesis of different functionally-substituted pyrazol and pyrazolines, and study of their biological activities.

The object and subject of the research. The main object of the research is the synthesis of pyrazol and pyrazolines on the bases of unsaturated chloroketones and study of the methods for obtaining 1,3,5-substituted pyrazole and pyrazolines by interaction of them with different reagents. But the subject of the research is studying of biological activities of the synthesized different functional groups containing pyrazole and pyrazolines against bacteria and fungi.

The aims and objectives of the research. The aim of the work is the development of efficient synthesis methods for different functionally-substituted new pyrazole and pyrazoline derivatives, determination of the regularities of the realized reactions, compositions, structures, biological activities and possible application fields of the synthesized compounds. For the purpose of achieving the goal:

- The initial substances – unsaturated chloroketones were synthesized by known method and the reactions were studied for obtaining 3-alkyl(aryl)-5-(dialkylaminomethyl)pyrazole and 3-alkyl-5-(dialkylaminomethyl)pyrazolines on the bases of them.
- Reactions of the synthesized 3-alkyl(aryl)-5-(dialkylamino-methyl)pyrazole and 3-alkyl-5-(dialkylaminomethyl)pyrazoli-

[3]Baulin, I.S. Proizvodniye pirazola v kachestve stabilizatorov termookislitelnoy destruktsii polietilena / I.S. Baulin, V.V.Yachenko, S.G.Mikhalenok, et al. Trudy BGTU. Khimiya, tekhnologiya organicheskikh veshestv i biotekhnologiya. – 2012, – №4, – p. 78-81.

[4] http://www.pesticidy.ru/active_substance/bixafen

nes with chloroanhydrides of acetic and monochloroacetic acid and also 1-(2-chloromethylcarbonyl)pyrazols with diamines were studied.

- Synthesis of semicarbazones of unsaturated α, β-dichloroketones and 1-carbamoyl-5-(chloromethyl)pyrazols on the bases of them and also the latters with diamines were studied.
- 3-Alkyl-5-(dialkylaminomethyl)-1-(metoxycarbonylmethyl)pyrazolines were synthesized and new pyrazoline compounds were obtained by carrying out their different conversions.
- Reaction of 3-alkyl-5-(dialkylaminomethyl)pyrazolines was carried out with ethylenechlorohydrine and interaction of the obtained 1-(2-hidroxyethyl)pyrazolines with chloroanhydrides was studied.
- Reaction of 3-alkyl-5-(dialkylaminomethyl)pyrazolines with allylbromide was studied and bis(pyrazolines) were synthesized by their interaction with 1,2-dibromethane.
- Antimicrobial activities of synthesized functionally-substituted pyrazole and pyrazoline derivatives were determined.

Research methods. The research results were determined by standard analysis methods, structures and compositions of obtained compounds were studied by IR, ^{1}H NMR and ^{13}C NMR spectroscopies.

Antimicrobial activities of some synthesized compounds against various bacteria were studied by a serial dilution method.

Basic provisions for defence:

- Development of efficient synthesis methods for new functionally-substituted pyrazole and pyrazoline compounds and study of the occurred reactions.
- Study of biological activities of the synthesized compounds.

Scientific novelty of the research. High yield synthesis of 3-alkyl(aryl)-5-(dialkylaminomethyl)substituted pyrazole and pyrazolines which are unknown in literature, have been realized by an efficient method. 1-acetyl- and 1-(2-chloromethylcarbonyl)pyrazole and pyrazolines have been synthesized by the reaction of the pyrazole and pyrazoline derivatives with acetic and

monochloroacetic acid chloranhydrides in the presence of triethylamine. Interaction of 1-(2-chloromethylcarbonyl)pyrazols with dimethylamine and morpholine has been studied.

Semicarbazones have been obtained by the reaction of unsaturated chloroketones with semicarbazide hydrochloride in the presence of aqueous solution of sodium bicarbonate and it has been determined, that 3-alkyl(aryl)-1-carbamoyl-5-(chloromethyl)pyrazole compounds, containing a reactive chloromethyl group are obtained by cyclization of the synthesized semicarbazones in the presence of pyridine. New 3-alkyl(aryl)-5-(diethylaminomethyl)-1-carbamoyl- and 3-alkyl(aryl)-5-(morpholinomethyl)-1-carbamoylpyrazole compounds have been synthesized by the interaction of them with diamines.

Interaction of 3-alkyl-5-(dialkylaminomethyl)pyrazolines with monochloroacetic acid methyl ester in the presence of potassium carbonate have been resulted in obtaining 3-alkyl-5-(dialkylaminomethyl)-1-(metoxycarbonylmethyl)pyrazolines and new functionally-substituted 3-alkyl-5-(dialkylaminomethyl)pyrazolin-1-yl acetic acid hydrazine and potassium salt derivatives have been synthesized by the reaction of them with hydrazine hydrate and potassium hydroxide in ethyl alcohol medium.

Reaction of 3-alkyl-5-(dialkylaminomethyl)pyrazolines with ethylenechlorohydrine have been carried out in an alkaline medium and resulted in obtaining organonitrogen heterocyclic alcohols. Corresponding ethers have been synthesized by their reaction with chloranhydride of acetic and benzoic acids.

Corresponding 1,2-bis-(3-alkyl-5-(dialkylaminomethyl)pyrazolin-1-yl)ethanes have been synthesized by the interaction of 3-alkyl-5-(dialkylaminomethyl)pyrazolines with 1,2-dibromethane.

As a result of the interaction of allyl bromide and 3-alkyl-5-(dialkylaminomethyl)pyrazolines, a synthesis method have been studied for 3-alkyl-1-allyl-5-(dialkylaminomethyl)pyrazoline compounds containing allyl group of double bonds and having possibility of being suggested as a monomer for bipolymers production in future.

Antimicrobial properties of some synthesized new pyrazole and

pyrazoline compounds have been tested by dilution method on the bases of laboratory experiments. It has been determined, that some of them possess biological activities.

Theoretical and practical significance of the research. An efficient synthesis method was developed for corresponding 3-alkyl(aryl)-5-(dialkylaminomethyl)pyrazole and pyrazoline compounds, semicarbazones on the basis of unsaturated chloroketones and 1-carbamoyl-5-(chloromethyl)pyrazols on the basis of them. New functionally-substituted 1-acetyl- and 1-(chloromethylcarbonyl)pyrazol and pyrazolines, 3-alkyl(aryl)-5-(dialkylaminomethyl)-1-(carbamoyl)pyrazol compounds, 3-alkyl-5-(dialkylaminomethyl)-1-(metoxycarbonylmethyl)-, 1-(2-hydroxyethyl)-, 1(2-methyl(phenyl)-carbonyletoxy)-, 1-(allyl)pyrazoline compounds, as well as (bis)pyrazolines were synthesized on the bases of 3,5-substituted pyrazole and pyrazoline compounds, optimal conditions were determined for occurred reactions and the obtained compounds were characterized.

The synthesized compounds with antimicrobial properties were recommended for use as medications.

Approbation and study of the research. 16 scientific works, including 9 papers, 6 abstracts have been published and 1 patent have been obtained on the materials of the dissertation. The results have been presented and discussed in the following conferences:

Republician scientific conference dedicated to academician A.A. Afandiyev's 75th anniversary of birth (Sumgayit, 2013); the II Republician conference "Organic Reagents in Analytical Chemistry" dedicated to professor A.A. Verdizada's 100th anniversary of birth (Baku, 2014); the III All-Russian scientific conference "Advances in synthesis and Complexing", dedicated to the 55th anniversary of RUDN (Moscow, 2014); Republician scientific conference "Macromolecules chemistry, organic synthesis and composite materials" dedicated to the 50th anniversary of the Institute of Polymer Materials (Sumgayit, 2016); International scientific-practical conference "Innovative perspectives on the development of oil refining and petrochemistry", dedicated to academician V.S. Aliyev's 110th anniversary of birth (Baku, 2018); scientific conference "Naghiyev Readings" dedicated to academician

M.Naghiyev's 110th anniversary of birth (Baku, 2018).

The name of the organization where the dissertation work was performed. The dissertation work was performed at the laboratory of "Heterocyclic compounds" on the research plan of the Institute of Polymer Materials of ANAS (State registration number 0111Az2154).

The applicant's personal presence. The main goals of the research and the ways for solving target issues were revealed, the directions of the researches were determined, the results were discussed by the applicant. Simultaneously, the applicant directly participated in carrying out laboratory experiments and each stage of writing papers, as well as the dissertation.

The scope and structure of the dissertation. The dissertation consists of 165 pages including: introduction – 6 pages (11.298 symbols), four chapters, literature review – 42 pages (44.900 symbols), discussion of the researches (the second chapter) – 43 pages (45.450 symbols), experimental methods (the fourth chapter) – 40 pages (55.536 symbols), results – 2 pages (2.716 symbols), 169 references – 20 pages, 40 figures and 5 tables, and volume – 171950 symbols (with the exception of figures, tables, references and appendicies).

Introduction describes the actuality, objectives, scientific novelty, practical significance, approbation, structure and scope of the topic, publications on it, essense of the chapters briefly.

The first chapter deals with the discussions of literature materials on the researches conducted in the direction of obtaining unsaturated chloroketones and synthesis reactions of corresponding heterocyclic compounds on the bases of them, syntheses, convertions and determination of biological activities of pyrazole and pyrazolines.

The second chapter describes the synthesis of pyrazole and pyrazolines on the bases of unsaturated chloroketones, obtaining their new functional derivatives, study of compositions, structures of the synthesized compounds and directions of experiments.

The third chapter focuses on the results of the experiments carried out on biological, antibacterial and antifungal activities of

some synthesized pyrazole and pyrazoline derivatives.

The fourth chapter is experimental part of the work. Physicochemical properties of the primary substances and synthesized compounds are also set in this chapter.

The Results section reflects the major findings of the research.

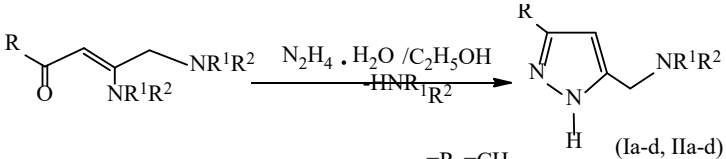
THE MAIN CONTENT OF THE WORK

Currently, synthesis of pyrazole and pyrazolines is a subject of large interest from both theoretical and practical points of view, but extensive study of them is significantly important.

It's evident from literature researches, that pyrazole and pyrazolines possess a very wide-spectrum biological activities, including antimicrobial, antioxidant, anti-cough and anti-tumor effects, and also a number of medications used in medical practice are considered their derivatives. Functional derivatives of these compounds are used for obtaining dyes, luminophores, various fungicidal compositions against agricultural pests and etc. In the light of above information, it may be concluded, that more extensive and purposeful studies are required for the synthesis of new functional derivatives of pyrazole and pyrazolines.

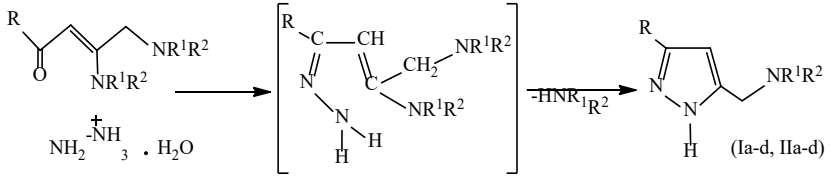
1. Cyclization reaction of 1-alkyl(aryl)-3,4-bis(dialkil-amino)buten-2-on-1 with hydrazine (synthesis of pyrazols)

An efficient method has been developed for obtaining pyrazoles, taking into account their synthetic capabilities and practical significance. It has been determined, that 3-alkyl(aryl)-5-(dialkylaminomethyl)pyrazoles (I a-d, II a-d) are obtained by 5 hour heating of aminoketones at 55÷60ºC with hydrazine hydrate in ethanol medium. The aminoketones contain 1-alkyl(aryl)-3,4-bis(dialkylamino)buten-2-on-1 obtained by the substitution of chlorine atoms with diamines in 1-alkyl(aryl)-3,4-dichlorobuten-2-on-1 molecule. The yield of the synthesized new 3,5-substituted pyrazols is 65-77% [2,4,12]. The synthesized pyrazole compounds are light brown coloured viscous liquids and easily solved in organic solvents.



I R=CH_3(a), C_2H_5(b), Ph(c), 4-ClC_6H_4(d); $R^1=R_2=CH_2$(a-d)
II R=CH_3(a,c), C_2H_5(b,d); $R^1=R_2=C_2H_5$(a,b), $R^1,R_2=(CH_2)_2O(CH_2)_2$(c,d)

A possible mechanism has been developed for the synthesis of pyrazols by this method. Formation of yellow crystals in the reaction period makes a ground to say, that the first step of the reaction is hydrazone formation. The crystals – hidrazones, obtained as intermediates haven't been able to be separated. So, that a heterocyclic anion is formed by intramolecular cyclization of hydrazone in the second step by separation of 1-state nitrogen atom protone. Finally, pyrazol ring is formed by separation of anion, that's to say, one of dialkylamine fragment from heterocyclic anion by vacuum distillation.



I R=CH_3(a), C_2H_5(b), Ph(c), 4-ClC_6H_4(d); $R^1=R_2=CH_2$(a-d)
II R=CH_3(a,c), C_2H_5(b,d); $R^1=R_2=C_2H_5$(a,b), $R^1,R_2=(CH_2)_2O(CH_2)_2$(c,d)

The structure of the synthesized pyrazols (I a-d, II a-d) has been studied by IR, ^1H NMR and ^{13}C NMR spectroscopies, but the purities have been determined by thin layer chromatography (TLC) on the plate of "Silufol UV-254" in the system of corresponding solvents.

Absorption bands in 3290 and 3191 (–NH–), 3085 and 3103 (–CH=), 1648 and 1652 (C=C), 1597 and 1444 cm^{-1} (C=N) have been assigned to the corresponding fragments of pyrazole ring in IR spectrum of 5-(dimethylaminomethyl)-3-phenylpyrazol (Ic) and 5-(diethylaminomethyl)-3-methylpyrazol (II a). As well as, absorption bands were observed in 1548, 1498, 1454 cm^{-1} regions of aromatic ring in the compound of (I c).

2.26 doublet [6H, $N(CH_3)_2$] signals of dimethyl radical protons, 3.49 singlet (2H, CH_2N) signals of aminomethylene and 6.21 singlet

[1H, (CH, H-4)] and 7.62 singlet (1H, NH) signals of pyrazole ring were assigned in ^{1}H NMR spectrum of 5-(dimethylaminomethyl)-3-phenylpyrazol (Ic) compound. But aromatic benzene ring protons were assigned in the range of singlet 7.08-7.41 ppm (5H, -C_6H_5).

^{1}H NMR spectrum of 5-(diethylaminomethyl)-3-methylpyrazole (II a) presents diethyl radical protons in 0.98 ppm triplet [6H, N(-C-CH_3)$_2$] and 2.45÷2.52 quartet [2H, N(-CH_2-)$_2$], and also 2.20 singlet (3H, CH_3), 3.58 singlet (2H, CH_2N), 5.88 singlet [1H, (CH, H-4)] and 6.88 ppm spread singlet (1H, NH) signals (Fig.1).

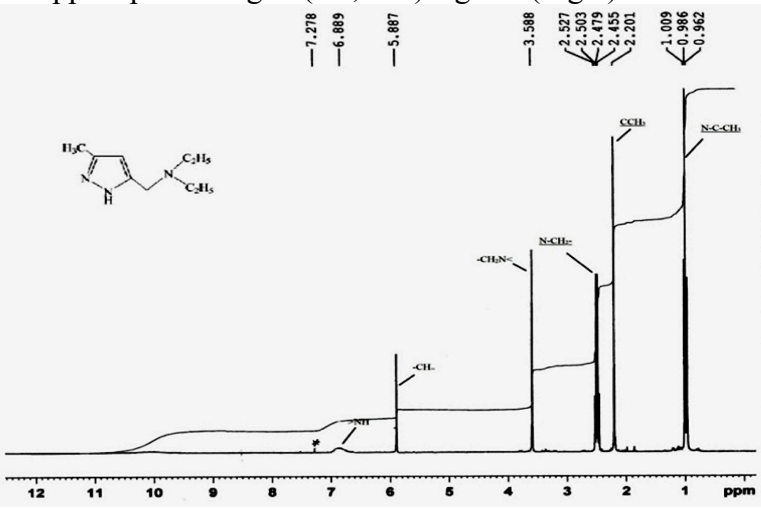


Fig. 1. ^{1}H NMR spectrum of (II a) compound

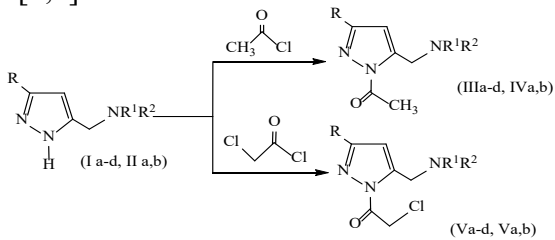
But carbon atoms signals have been observed in the regions of CH_3 (11), CH_2 (53), CH_2 (55), CH_2 (66), CH (104), C (143), C (145) in ^{13}C NMR spectrum of 5-(morpholino)-3-methylpyrazole (IIc) compound.

It has been determined, that 5-(diethylaminomethyl)-3-methylpyrazol (II a) possesses antimicrobial activity and is a biologically active compound.

1.1. Reaction of 3-alkyl(aryl)-5-(dialkylaminomethyl)pyrazols with chloroanhydrides of carbonic acid

The hydrogen atom located in the 1-state in 3,5-substituted pyrazol molecule is more mobile. Its reaction with chloroanhydrides of acetic and monochloroacetic acids has been carried out in the presence of nonaqueous diethyl ether at 15-25ºC for 4-6 h.

Triethylamine has provided removal of HCl from the medium separated during the reaction. Triethylammonium salts - $[(C_2H_5)_3NH]^+Cl^-$ is separated as a by-product as a result of interaction and finally is removed from the medium by washing of the reaction mass with 2% aqueous solution of Na_2CO_3. But the main product in liquid form is separated from the aqueous reaction mass by the extraction with diethyl ether, dried with $MgSO_4$ and distilled under vacuum. Vacuum distillation of complex-structural pyrazole compounds with high boiling points has been carried out in the presence of pyrazole mponds. The yield of the synthesized 1-acetyl- (III a-d, IV a, b) and 1-(2-chloromethylcarbonyl)pyrazoles (V a-d, VI a, b) is 62-75% [2,4].



I, III, V R=CH_3(a), C_2H_5(b), Ph(c), 4-ClC_6H_4(d); R^1=R_2=CH_3(a-d)
II, IV, VI R=CH_3(a), C_2H_5(b); R^1=R_2=C_2H_5(a,b).

Absorption band of –NH– fragment disappears which has been observed in 3190-3290 cm^{-1} in IR spectrum of 3-alkyl(aryl)-1-acetyl-5-(dialkylaminomethyl)pyrazoles and absorption band appears in the region of 1730-1760 cm^{-1} that reveals the presence of carbonyl group characteristic for the synthesized compounds (III a-d, IV a, b). Absorption band belonging to chloromethyl group (CH_2Cl) has been assigned in the region of 710-740 cm^{-1} in addition to carbonyl group absorption band in IR spectra of 3-alkyl(aryl)-5-(dialkylaminomethyl)-1-(2-chloromethylcarbonyl)pyrazoles (V a-d, VI a, b).

But ($CDCl_3$, δ, ppm) 2.08 singlet (3H, CCH_3), 2.26 singlet [6H, $N(CH_3)_2$], 2.46 singlet (3H, CH_3CO), 3.37 singlet (2H, CH_2N), 6.24 singlet (1H, $CH_{pyrazol}$) signals have been assigned in ^1H NMR spectrum of 1-acetyl-5-(dimethylaminomethyl)-3-methylpyrazole (IIIa).

Signals of ($CDCl_3$, δ, ppm) 1.00 triplet [3H, $N(-C-CH_3)_2$], 2.52 multiplet [4H, $N(-CH_2-)_2$] and singlet 2.22 (3H, CCH_3), 3.60 (2H,

CH_2N), 3.85 (2H, CH_2Cl), 5.90 [1H, (CH, H-4)] protons have been assigned in NMR ^1H spectrum of 5-(diethylamino)-1-(2-chloromethylcarbonyl)-3-methylpyrazols (VIa)(Fig. 2).

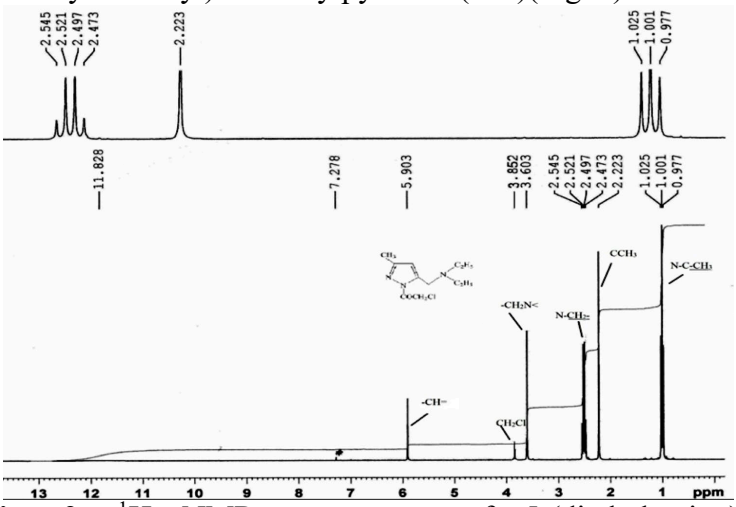


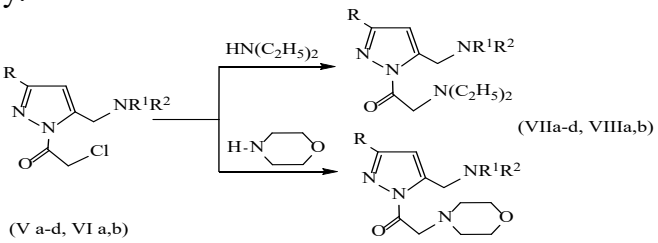
Fig. 2. ^1H NMR spectrum of 5-(diethylamino)-1-(2-chloromethylcarbonyl)-3-methylpyrazols (VI a)

1.2. Interaction of 3-alkyl(aryl)-5(dialkylaminomethyl)-1-(2-chloromethylcarbonyl)pyrazols with diamines

As a continuation of the studies, reactions of 3-alkyl(aryl)-5-(dialkylaminomethyl)-1-(2-chloromethylcarbonyl)pyrazols (V a-d, VI a, b) with diamines have been studied and new pyrazol derivatives have been synthesized [2, 4, 15].

It has been determined, that nucleophil substitution of reactive chlorine atome in pyrazol with dialkylamino group by the interaction of 1-(2-chloromethylcarbonyl)pyrazols (V a-d, VI a, b) with double-dose diethylamine and morpholine results in obtaining 3-alkyl(aryl)-5-(dialkylaminomethyl)-1-(2-dialkylaminomethylcarbonyl)pyrazols (VII a-d, VIII a, b, IX a-c, X a, b) with the yield of 63-72% [2, 4, 15]. The reaction has been carried out in the medium of diethyl ether for 5 h at 30-35 ºC. It has been found out, that the reaction results are unwanted by equimolar ratio of diethylamine and morpholine to pyrazoles (Va-d, VI a, b). But nucleophilic substitution is successful by the double dose use of diamines. So, that the use of excess amount

of amine provides HCl capture separated by the interaction and prevents formation of resin. As a result, high yield of the target product and selected optimal conditions prove this method efficiency.



V, VII, IX R=CH_3(a), C_2H_5(b), Ph(c), 4-ClC_6H_4(d); R_1=R_2=$(CH_3)_2$(a-d)
VI, VIII, X R=CH_3(a), C_2H_5(b); R^1=R_2=C_2H_5(a,b).

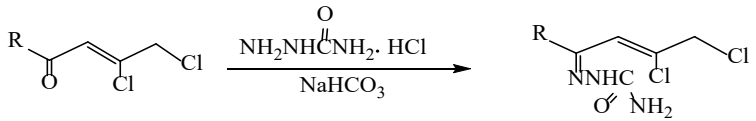
Absorption bands of pyrazole ring in the regions of 3106 (-CH=), 1630 (C=C), 1443 cm^{-1} (C=N) and deformation vibration of (C=O) 1725 and –CH= bond of carbonyl group in the region of 789 cm^{-1} have been assigned in IR spectrum of 5-(diethylaminomethyl)-1-(2-morpholinomethylcarbonyl)-3-methylpyrazol (Xa).

The following signals ($CDCl_3$, δ, ppm) have been assigned in NMR ^1H spectrum of (Xa) compound: 0.98 triplet [6H, N(-C-CH_3)$_2$] and 2.53 quartet [4H, N(-CH_2-)$_2$] fragments, 2.17 singlet (3H, CH_3), 3.21 multiplet (2H, $COCH_2$), 3.59 singlet (2H, CH_2N), 5.89 singlet [1H, (CH, H-4)]. Appearance of triplet forms of 3.46 ppm [4H, N(CH_2)$_2$] and 3.64 ppm [4H, (CH_2)$_2$O] signals via the substitution of chlorine by morpholine in the primary pyrazol (VI) proves positive substitution effect.

1.3. Synthesis of carbomoylpyrazols on the basis of 3,4-dichlorobuten-2-on-1

Test results proved, that semicarbazones have been obtained with the yield of 56-60% by the interaction of 3,4-dichlorobuten-2-on-1 with semicarbazide hydrochloride in the presence of equimolar amount of sodium hydrocarbonate in aqueous medium at 50÷55ºC for 3 h [6,7]. The synthesized compounds are light brown coloured crystalline substances that are easily solved in organic solvents ((XIa) $t_{melt.}$=118-120ºC, (XIb) $t_{melt.}$=154-156ºC). Formation of NaCl salts has also been observed in the reaction time. They have been

removed from the medium by washing of the reaction mass with icy water.



R=CH_3(a), 4-ClC_6H_4(b). (XIa, b)

Structure of the synthesized semicarbazones (XI a, b) have been studied by IR and ^{1}H NMR spectroscopic methods.

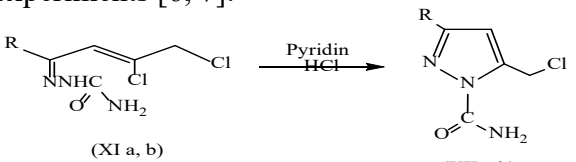
Corresponding absorption bands of semicarbazide amide groups in the regions of 3463, 3385 (NHCO) and 3194 ($CONH_2$), fragments in –CH= (2922, 2853), C=O (1687) have been observed in IR spectrum (ν,cm^{-1}) of 1-methyl-3,4-dichlorobuten-2-on-1 semicarbazone (XI a). Simultaneously, absorption bands have been assigned belonging to valence vibrations of chain-linked bonds of C=N (1578) and C-Cl (721).

1.26 singlet (3H, CH_3), 3.32 singlet (2H, CH_2Cl), 6.32 singlet (2H, NH_2), 8.18 singlet (1H, NH) of mono- and diamine group protons and 6.50 singlet (1H, =CH) group protons signals were determined in ^{1}H NMR spectrum ($CDCl_3$, δ, ppm) of (XI a) compound.

A search of the literature analyses revealed, that synthesis of reactive chloromethyl group containing organonitrogen heterocyclic compounds and study of some chemical properties have great scientific and practical significance. A number of new studies have been carried out in the direction of 3,4-dichlorobuten-2-on-1 semicarbazones cyclization for the purpose of synthesizing this type of compounds [6, 7].

It has been determined, that synthesis of corresponding pyrazols from ketones semicarbazones can be carried out in 2 directions. According to the first method, 3-methyl and 3-(4-chlorophenyl)-5-chloromethyl-1-carbamoylpyrazols (XII a, b) have been synthesized by boiling of semicarbazones (XI a, b) with double dose of pyridine for 8 h with the yield of 63-68%, and on the second method, by heating of them with 2% of aqueous solution of NaOH at 45-50 ºC for 4 h with the yield of 57-60%. But simultaneously with the main

product, resin has also been formed by heating of semicarbazones in an alkaline aqueous solution and the reaction has resulted in low yield. Consequently, the first method has been selected as an efficient one and optimal conditions have been determined by conducting experiments [6, 7].



(XI a, b) (XIIa, b)

R=CH_3(a), 4-ClC_6H_4(b)

N-H group absorption band observed in the regions of 3463-3480 cm^{-1} disappears in IR spectrum of 5-chloromethyl-1-carbamoyl-3-methylpyrazoles (XII a, b) in comparison to IR spectrum of semicarbazones (XI a, b).

Dimethylsulfooxide (DMSO, δ =2.49 ppm) has been used as a solvent for determination of ^{1}H NMR spectrum of 5-chloromethyl-1-carbamoyl-3-methylpyrazole (XII a) and 1.76 singlet (3H, CH_3), 3.39 singlet (2H, CH_2Cl), 6.87 singlet (1H, -CH=) and 6.27 spread singlet (2H, $CONH_2$) signals have been observed in corresponding protons (δ, ppm) (Fig. 3).

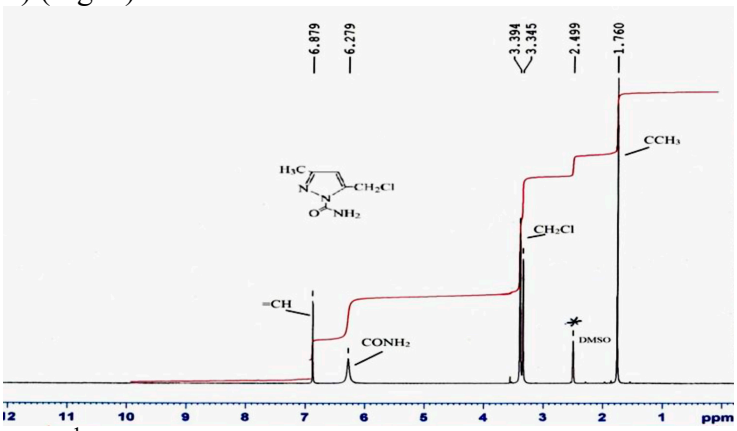


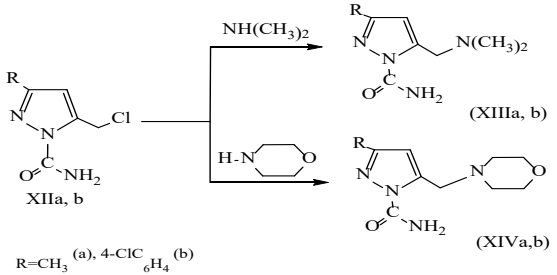
Fig. 3. ^{1}H NMR spectrum of compound (XII a).

7.15 and 7.85 ppm doublet signals of aromatic nucleus have been assigned in ^{1}H NMR spectrum of 3-(4-chlorophenyl)-5-chloromethyl-1-carbamoylpyrazole (XII b) instead of methyl radical

signal, simultaneously with the signals of protons of characteristic groups 3.27 singlet (2H, CH_2Cl), 6.10 singlet (2H, $CONH_2$), 6.65 singlet (1H, $CH_{pyrazole}$) which partially differed from ^1H NMR spectrum of (XIIa) pyrazole compound.

1.4. Interaction of 3-methyl and 3-(4-chlorophenyl)-1-carbamoyl-5-(chloromethyl)pyrazols with diamines

It has been determined, that synthesized 5-chloromethyl-1-carbamoylpyrazoles (XII a, b) have been easily reacted with diamines under optimal conditions. So, that interaction of pyrazoles (XII a, b) with double dose of diethylamine at 25÷30°C and with morpholine at 60÷65°C for 5 h in water-benzene medium resulted in obtaining 5-(dimethylaminomethyl)-1-carbamoylpyrazole (XIII a, b) with the yield of 65-70% by the reaction with dimethylamine and obtaining 5-(morpholinomethyl)-1-carbamoylpyrazol compounds (XIV a, b) with the yield of 64-68% by the reaction with morpholine [6, 7].



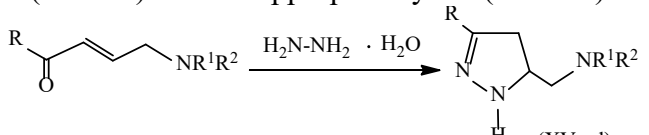
2.05 ppm. (3H, CH_3) and 2.30 ppm. [6H, $N(CH_3)_2$] singlet signals of methyl and dimethyl radicals (DMSO, δ=2.52 ppm), as well as the signals of 3.40 singlet (2H, CH_2N), 6.20 spread singlet (2H, NH_2) and 6.70 singlet (1H, -CH=) protons were observed in ^1H NMR spectrum of 5-(dimethylaminomethyl)-1-carbamoyl-3-methylpyrazol (XIII a) compound.

3.45 ppm [(4H, $N(CH_2)_2$] and 3.60 ppm [4H, $(CH_2)_2O$] triplet signals of characteristic groups of morpholine have been assigned instead of dimethylamine radical signals found in δ=2.30 ppm in NMR ^1H spectrum of 5-(morpholinomethyl)-1-carbamoyl-3-methylpyrazol (XIVa) in differ from the spectrum of (XIIIa) compound.

2. Cyclization reaction of 1-alkyl-4-(dialkylamino)buten-2-on-1 by hydrazine hydrate (synthesis of pyrazolines)

As is known from the literature, differing from pyrazol synthesis method, 1-amino-2-alkylpyrolles have been subjected to heterocyclization[5] by the influence of hydrazine hydrate on 1-alkyl-4-chlorobuten-2-on-1 in ethyl alcohol medium during pyrazolines synthesis. 1-alkyl-4-(dialkylamino)buten-2-on-1 was obtained via the reaction of 1-alkyl-4-chlorobuten-2-on-1 with diamines by a known method for the purpose of preventing the reaction running in the direction of obtaining 1-aminopyrroles [1, 12, 14]. 3-alkyl-5-(dialkylaminomethyl)pyrazolines (XV a-d) have been synthesized by the interaction of hydrazine hydrate with aminoketones in the next stage [1,3,5,12].

The reaction results in obtaining new 3,5-substituted pyrazoline derivatives (XV a-d) with an appropriate yield (68-75%).



R=CH_3(a,c), C_2H_5(b,d); R^1=R_2=C_2H_5(a,b), R^1,R_2=$(CH_2)_2O(CH_2)_2$(c,d). (XVa-d)

^{1}H NMR spectrum ($CDCl_3$, δ, ppm) of (XV a) compound shows 0.86 triplet [6H, N(-C-CH_3)$_2$], 1.83 singlet (3H, CH_3), 2.08 singlet [2H, (CH_2, H-4)], 2.20 multiplet [4H, N(-CH_2-)$_2$], 2.45 multiplet (2H, CH_2N), signals of pyrazoline ring protons in the regions of 3.59 multiplet [1H, (CH, H-5)] and 5.92 ppm. singlet (1H, NH). But carbon atoms signals have been observed in the regions of 11(CH_3), 16(CH_2), 40 (CH), 47 (CH_2), 56 (CH_2), 57 (CH_2), 152 (C).in ^{13}C NMR spectrum of 5-(diethylamino)-3-methylpyrazole (XVa) compound.

Triplet signals of 2.30 ppm. [4H, (CH_2)$_2$ N] and 3.52 ppm. [4H, (CH_2)$_2$O] fragments protons have been assigned in ^{1}H NMR spectrum of 5-(morpholinomethyl)-3-ethylpyrazoline (XV d) simultaneously with corresponding protons signals (Fig. 4).

---

[5] Gadzhily R.A. Geterotsiklizatsiya 1-alkil-4-khlorbut-2-en-2-onov s gidrazin gidratom /R.A. Gadzhily, V.M.Fedoseyev, N.A.Netkacheva // - Riga: Khimiya Geterotsiklicheskikh Soyedineniy, - 1989. № 7, –p. 998-1001

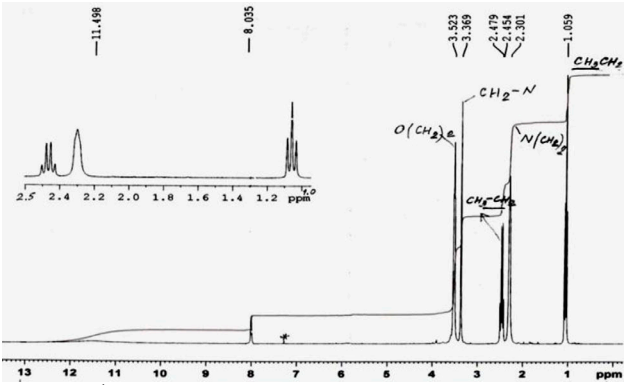
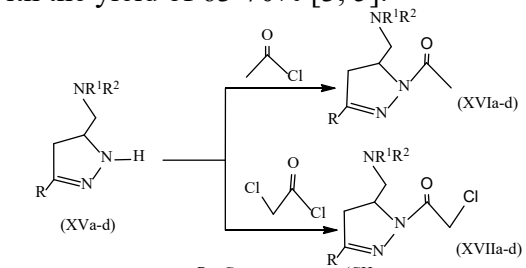


Fig. 4. NMR ^{1}H spectrum of (XV d) compound

2.1. Interaction of 3-alkyl-5-(dialkylaminomethyl)pyrazolines with carbonic acid chloranhydrides

It has been determined, that interaction of 3-alkyl-5-(dialkylaminomethyl)pyrazolines with organic carbonic acid chloranhydrides occurred just as acylation reaction of 3-alkyl(aryl)-5-(dialkylaminomethyl)pyrazols with chloranhydrides. It has been determined, that some amount of resin are formed by the reaction of pyrazolines (XV a-d) with carbonic aciud chloroanhydrides. Optimal conditions have been determined to prevent resin formation. So, that after adding chloroanhydrides into corresponding 3-alkyl-5-(dialkylaminomethyl)pyrazolines (XVa-d) substance in water-free ether at 0÷5ºC, resin formation is prevented by stirring of the reaction mass with an acetic acid chloroanhydride at 15-20 ºC and with a monochloroacetic acid chloroanhydride at 20-25ºC for 4-5 h. It has a positive effect on the main product yield. As a result, 1-acetyl- and 1-(2-chloromethylcarbonyl)pyrazolines (XVI, XVII a-d) are obtained with the yield of 63-70% [3, 5].



R=CH_3(a,c), C_2H_5(b,d); R^1=R_2=C_2H_5(a,b), R^1,R_2=$(CH_2)_2O(CH_2)_2$(c,d).

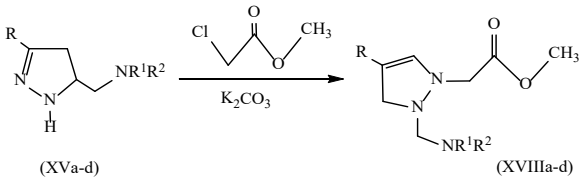
Absorption band assigned in the region 3309 cm^{-1} belonging to –NH– fragment disappears in IR spectrum of 1-acetyl-5-(diethylaminomethyl)-3-methylpyrazolin in comparison to IR spectrum of primary substance (XV a) and corresponding absorption bands appear 2967 (CH), 1743 (C=O), 1434 cm^{-1} (C=N).

Signals of characteristic group protons 0.87 triplet [6H, N(-C-CH_3)$_2$], 1.83 singlet (3H, CCH_3), 2.10 singlet (3H, $COCH_3$), 2.34-2.46 multiplet [8H, (CH_2, H-4), N(-CH_2-)$_2$, CH_2N] and 3.60 ppm. multiplet (1H, CH, H-5) have been observed in ^{1}H NMR spectrum ($CDCl_3$, δ, ppm) of (XVIa) pyrazoline compound. The three protons of the acetyl group form singlet signals 2.10 ppm. (3H, COCH3) were detected instead of the proton of the double amine, also.

It has been determined, that 1-acetyl-5-(diethylaminomethyl)-3-methylpyrazol (XVI a) and 5-(diethylaminomethyl)-3-methyl-1-(2-chloromethylcarbonyl) pyrazol compounds (XVII a) possess antimicrobial activities. It has been found out, that the (XVI a) compound is a biologically active chemical compound and may be also used in medical practice and chemical-pharmaceutical industry as a local antiseptic [8].

2.2. Reaction of 3-alkyl-5-(dialkylaminomethyl)pyrazolines with monochloroacetic acid methyl ether

As it has been previously mentioned, 3-alkyl-5-(diethylaminomethyl)pyrazolines (XV a-d) contain a reactive hydrogen atom in molecule. Reaction of 3-alkyl-5-(diethylaminomethyl)pyrazolines (XV a-d) with monochloroacetic acid methyl ether has been extensively studied for the purpose of obtaining pyrazolines new derivatives and carrying out their conversions [16]. 3-Alkyl-5-(dialkylaminomethyl)-1-(metoxycarbonylmethyl)pyrazolines (XVIII a-d) have been obtained by the influence of monochloroacetic acid methyl ether on aqueous suspension of equimolar amount of potassium carbonate and 3-alkyl-5-(dialkylaminomethyl)pyrazoline (XV a-d) [9, 13, 16]. It has been determined, that new 1-(metoxycarbonylmethyl)-substituted pyrazolines (XVIIIa-d) are synthesized by substitution of a 1-state active hydrogen atom of pyrazole with an ester group during the interaction.



(XVa-d) (XVIIIa-d)

R=CH_3(a,c), C_2H_5(b,d); R^1=R_2=C_2H_5(a,b), R^1,R_2=$(CH_2)_2O(CH_2)_2$(c,d).

Absorption bands of (-CH=) bond of pyrazoline ring in 2967 cm^{-1}, (C=O) of carbonyl group in 1713 and 1744 cm^{-1} and C-O-C bond in the regions of 1151 and 1203 cm^{-1} have been observed in IR spectrum of 5-(diethylaminomethyl)-1-(methoxycarbonylmethyl)-3-methylpyrazol (XVIII a).

3.60 ppm. singlet (3H, OCH_3) and 4.02 ppm. (2H, =N-CH_2) groups singlet signals have been assigned in ^1H NMR spectrum of (XVIII a) compound simultaneously with corresponding signals of pyrazoline ring protons ($CDCl_3$, δ, ppm).

The structure of 5-(diethylaminomethyl)-1-(metoxycarbonyl-methyl)-3-methylpyrazoline (XVIII a) has been also studied by NMR ^{13}C spectroscopy (δ, ppm); 11 (CH_3), 16 (CH_3), 19(CH_3), 32 (CH_3), 47 (CH_2), 51 (CH_2), 55 (CH_2), 57 (CH_2), 63 (CH_2), 152 (CH), 171 (CO).

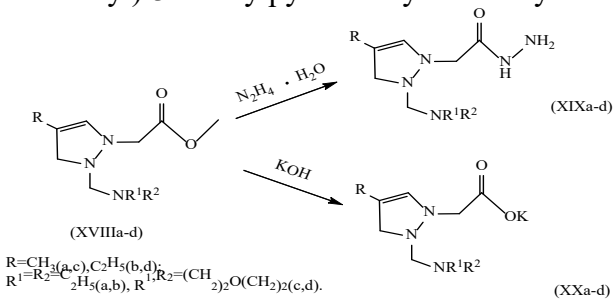
Antimicrobial activity of the synthesized 1-(metoxycarbonyl-methyl)pyrazoline (XVIII a) compound has been found out.

2.3. Interaction of 3-alkyl-1-metoxycarbonylmethyl-5-(dialkylaminomethyl)pyrazolines with hydrazine hydrate and potassium hydroxide

The synthesized pyrazolines molecules contain an active ether group having reactivity that causes formation of new functional group containing pyrazolines by the interaction of them with nucleophilic reagents. Their reactions with hydrazine hydrate and potassium hydroxide have been studied and determined, that 3-alkyl-5-(dialkylaminomethyl)pyrazolin-1-yl acetic acid hydrazines (XIXa-d) and 3-alkyl-5-(dialkylaminomethyl)pyrazolin-1-yl acetic acid potassium salt (XVIIIa-d) derivatives are obtained by boiling of 1-(metoxycarbonylmethyl)pyrazolines (XVIIIa-d) with hydrazine

hydrate in ethyl alcohol medium for 6 h and with potassium hydroxide for 3 h [9, 16]. The yield of the reaction products is 65-75%.

Characteristic absorption bands have been recorded for NH_2 (3395 and 3294) of monoamine, NH (3196) of diamine, CH (2918) and C=N (1601) fragments of pyrazoline ring, C=O (1681 and 1660 cm^{-1}) bond have been assigned in IR spectrum of 5-(diethylaminomethyl)-3-methylpyrazol-1-yl acetic hydrazine (XIXa).



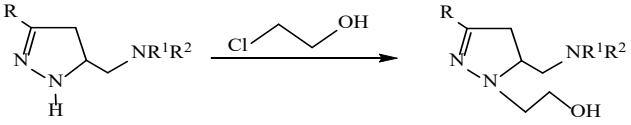
(XVIIIa-d) (XIXa-d) (XXa-d)

R=CH_3(a,c),C_2H_5(b,d); R^1=R_2=C_2H_5(a,b), R^1,R_2=$(CH_2)_2O(CH_2)_2$(c,d).

Absorption bands of CH= (2956) and C=N (1631) fragments, as well as C=O group in the regions of 1698 and 1675 cm^{-1} have been assigned in IR spectrum of 5-(diethylaminomethyl)-3-methylpyrazol-1-yl acetic acid potassium salt (XXa).

2.4. Interaction of 3-alkyl-5-(dialkylaminomethyl)pyrazolines with ethylenechlorohydrine

The experimental studies have revealed, that interaction of equimolar amount of 3-alkyl-5-(dialkylaminomethyl)pyrazolines (XVa-d) with ethylenechlohydrine in KOH aqueous solution has resulted in obtaining 3-alkyl-5-(dialkylaminomethyl)-1-(2-hydroxyethyl)pyrazoline derivatives (XXIa-d) correspondingly by substitution of 1-state hydrogen atom with hydroxyethl group [10, 16].



(XVa-d) (XXIa-d)

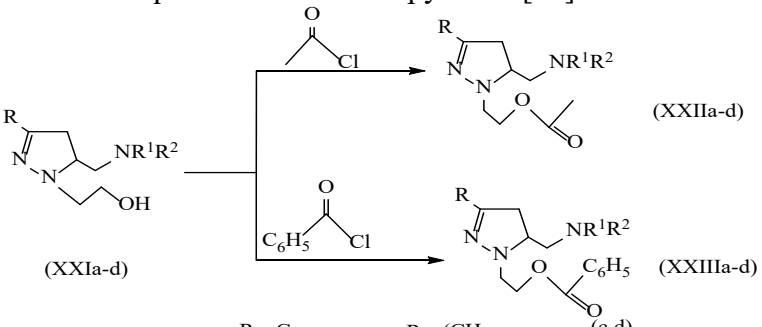
R=CH_3(a,c), C_2H_5(b,d); R^1=R_2=C_2H_5(a,b), R^1,R_2=$(CH_2)_2O(CH_2)_2$(c,d).

The synthesis reaction has been carried out at 30°C for 1 h and new nitrogen-containing heterocyclic alcohols have been obtained with the yield of 69-71%.

The signals of ($CDCl_3$, δ, ppm) 0.93 multiplet [6H, N(-C-CH_3)$_2$], 2.61 multiplet [4H, N(-CH_2-)$_2$], 1.84 singlet (3H, N=C-CH_3), 2.96 multiplet (2H, CH_2N) as well as 3.172 multiplet [2H, N-CH_2], 3.57 singlet (2H, CH_2O) and 3.77 singlet (1H, OH) of hydroxyethyl group protons, 2.44 multiplet (2H, CH_2) and 3.177 multiplet (1H, CH, H-5) of pyrazoline ring protons have been assigned in ^{1}H NMR spectrum of (XXI a) pyrazoline compound.

2.5. Interaction of 3-alkyl-1-(2-hydroxyethyl)-5-(dialkylamino-methyl)pyrazoline with carbonic acid chloranhydrides

Reactions of 1-(2-hydroxyethyl)pyrazolines with acetic and benzoic acid chloranhydrides have been studied and determined, that corresponding 3-alkyl-1-(2-methyl(phenyl)carbonyletoxy)-5-(dialkylaminomethyl)pyrazolines are obtained by acylation of chloranhydrides with 1-(2-hydroxyethyl)pyrazolines (XXIa-d) in the presence of equimolar amount of pyridine [10].



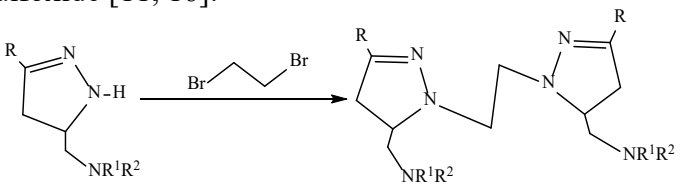
R=CH_3(a,c), C_2H_5(b,d); R^1=R_2=C_2H_5(a,b), R^1,R_2=$(CH_2)_2O(CH_2)_2$ (c,d).

The reaction has been carried out at 20-25°C for 4 h and resulted in obtaining pyrazoline derivatives (XXII a-d, XXIII a-d) with the yield of 63-67%.

Absorption bands of 1738 (C=O), 1230, 1204 and 1174 cm^{-1} (O-C-O) fragments of ester group have been assigned in IR spectrum of 1-(2-methylcarbonyletoxy)-5-(diethylaminomethyl)-3-methyl-pyrazoline (XXIIa).

2.6. Reaction of 3-alkyl-5-(dialkylaminomethyl)pyrazolines with 1,2-dibromethane

It has been studied, that 1,2-bis(3-alkyl-5-(dialkylaminomethyl)pyrazoline-1-yl)ethane compounds have been obtained by the influence of double dose pyrazoline (XVa-d) on 1,2-dibromethane in the medium of potassium hydroxide and dimethylsulfoxide [11, 16].



(XVa-d) (XXIVa-d)

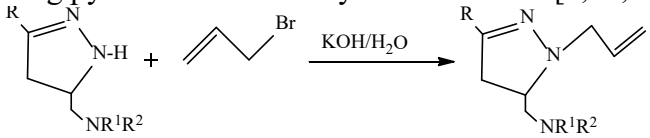
R=CH_3(a,c), C_2H_5(b,d); R^1= (C_2H_5)2(a,b), $(CH_2)_2O(CH_2)_2$ (c,d).

The reaction has been carried out at 30 ºC for 1-2 h and resulted in obtaining bis(pyrazolines) (XXIVa-d) with the yield of 60-66%.

Absorption band of N-N fragment assigned in the region of 3308 cm^{-1} disappears in IR spectrum of 1,2-bis(5-diethylaminomethyl-3-methylpyrazolin-1-yl)ethane (XXIVa) in comparison to IR spectrum of 3-methyl-5-(diethylaminomethyl)pyrazoline (XVa) and absorption bands of 2967, 2934 (CH), 1632, 1577, 1438 cm^{-1} (C=N) fragments belonging to bis(pyrazoline) appears.

2.7. Reaction of 3-alkyl-5-(dialkylaminomethyl)pyrazolines with allyl bromide

3-Alkyl-1-allyl-5-(dialkylaminomethyl)pyrazolines have been obtained by the interaction of equimolar amount of 3-alkyl-5-(dialkylaminomethl)pyrazolines with allyl bromide. The reaction has been carried out at 35-40°C for 2 h and resulted in obtaining corresponding pyrazolines with the yield of 65-70% [1,11,16].



(XVa-d) (XXVa-d)

R=CH_3(a,c), C_2H_5(b,d); R^1=R_2=C_2H_5(a,b), R^1,R_2=(CH_2)$_2$$O(CH_2)_2$ (c,d).

The reaction has been carried out at 35-40°C for 2 h and resulted in obtaining 3-alkyl-1-allyl-5-(dialkylaminomethyl)pyrazolines (XXV a-d) with 65-70% of yield.

Corresponding signals of 1.89 ppm. singlet (3H, CCH_3), 2.41 multiplet [(8H, $N(-C-CH_3)_2$, (CH_2, H-4)] and 2.6 multiplet (2H, CH_2N), 3.26 multiplet [1H, (CH, H-5)], 3.65-3.72 multiplet [4H, $N(-CH_2-)_2$], and also the signals of five protons characteristic for allyl group 3.49 multiplet (2H, $N-CH_2$), 5.21 singlet (2H, $=CH_2$) and 5.91 dublet (1H, =CH-) have been determined in ^1H NMR spectrum (δ, ppm) of (XXVa) pyrazoline compound.

3. Study of biological activities of some synthesized pyrazole and pyrazoline derivatives

Antimicrobial activities of the synthesized 3-methyl-5-(diethylaminomethyl)pyrazole (IIa), 1-acetyl-3-methyl-5-(diethylaminomethyl)pyrazoline (XVIa), 1-chloromethylcarbonyl-3-methyl-5-(diethylaminomethyl)pyrazoline (XVIIa) and 1-metoxycarbonylmethyl-3-methyl-5-(diethylaminomethyl)pyrazoline (XVIIIa) have been tested in "Department of Microbiology and Immunology" of Azerbaijan Medical University. Their antimicrobial activities have been studied by serial dilution method. For this purpose, dilutions of 1% solutions of the substances prepared in ethyl alcohol have been realized in distilled water: 1:100 (1), 1:200 (2), 1:400 (3), 1:800 (4). Golden staph (*St. aureus*) has been tested as a gram-positive organism, intestinal spores (*E. coli*), blue-green pus sticks (*Ps. aeruginosa*) and fungi (*C. Albicans of Candida type*) - as gram-negative bacteria. Meat-peptone agar (MPA) has been used to grow bacteria and Saburo nutrient medium – to grow fungi.

Planting has been carried out every 10, 20, 40, 60 minutes. They have been kept in a thermostate at 37°C for 24 h for the bacteria used in experiments, but for the fungi – at 28°C for 48 h. 1-2 drops of the emulsion having 500 mln of microbial particles in 1 ml have been added into every experimental glass (every dilution).

Antimicrobial activities of the tested substances have been controlly studied in comparison to ethyl alcohol, phenol, chloramine and nitrofungine applied in medical practice. It has been determined,

that only 1% chloramine among controlled substances has a low antimicrobial activity against test-cultures.

As a result of experimental researches, it has been determined, that the tested 5-(diethylaminomethyl)-3-methylpyrazol (IIa), 5-(diethylaminomethyl)-3-methyl-1-(chloromethylcarbonyl)pyrazol (XVIIa), 5-(diethylaminomethyl)-3-methyl-1-(metoxycarbonylmethyl)pyrazoline (XVIIIa) have high antimicrobial activities against golden staph and Candida fungus, but 1-acetyl-5-(diethylaminomethyl)-3-methylpyrazoline (XVIa) – against intestinal spores and blue-green pus sticks (Table).

Table. Antimicrobial activities of the synthesized compounds

Test cultures	**Exposition duration (min)**	Concentrations of substances (IIa, XVIa, XVIIa, XVIIIa)															
		Substance (IIa)				Substance (XVIa)				Substance (XVIIa)				Substance (XVIIIa)			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
St. aureus	10	-	-	+	+	-	+	+	+	-	-	+	+	-	+	+	+
	20	-	-	+	+	-	+	+	+	-	-	-	+	-	+	+	+
	40	-	-	-	+	-	+	+	+	-	-	-	+	-	-	+	+
	60	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-
Ps.aeruginoza	10	-	+	+	+	-	+	+	+	-	+	+	+	-	+	+	+
	20	-	-	+	+	-	-	-	+	-	-	-	+	-	-	+	+
	40	-	-	-	+	-	-	-	+	-	-	-	+	-	-	-	+
	60	-	-	-	+	-	-	-	-	-	-	-	+	-	-	-	+
E. coli	10	-	+	+	+	-	+	+	+	-	+	+	+	-	+	+	+
	20	-	+	+	+	-	+	+	+	-	-	+	+	-	+	+	+
	40	-	-	+	+	-	-	-	-	-	-	-	+	-	-	+	+
	60	-	-	-	+	-	-	-	-	-	-	-	+	-	-	-	+
Cand. albicans	10	-	-	-	+	-	+	+	+	-	-	-	+	-	-	-	+
	20	-	-	-	+	-	+	+	+	-	-	-	+	-	-	-	-
	40	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-
	60	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-

"+" – indicates a full completion, "-" – indicates no completion

Conclusions

1. An efficient method was developed for obtaining 3-alkyl(aryl)-5-(dialkylaminomethyl)substituted pyrazoles on the basis of heterocyclization of 1-alkyl(aryl)-3,4-bis(dialkylamino)buten-2-on-1 with hydrazine hydrate in ethyl alcohol medium, new 1-acetyl- and 1-(2-chloromethylcarbonyl)pyrazole compounds with high yield (62-75%) were synthesized by the interaction of them with chloroanhydrides of acetic and monochloroacetic acids. New 3-alkyl-(aryl)-5-(dialkylaminomethyl)-1-(2-dialkilaminomethylcarbonyl)pyrazole derivatives were obtained by nucleophilic substitution of chlorine atoms with amine groups remaining ester group by the interaction of 3-alkyl(aryl)-5-(dialkylaminomethyl)-1-(2-chloromethylcarbonyl)pyrazoles with diamines [4, 14, 15].
2. Semicarbazones with 56-60% of yield were synthesized by the interaction of 3,4-dichlorobuten-2-on-1 with semicarbazide hydrochloride in the presence of equimolar amount of $NaHCO_3$ in aqueous medium at 50-55 ºC. But cyclization of them in the presence of double dose amount of pyridine resulted in obtaining new 1-carbamoyl-5-(chloromethyl)substituted pyrazoles, and conversion reactions were occurred [7].
3. An efficient method was developed for obtaining 3-alkyl-5-(dialkylaminomethyl)pyrazolines by the interaction of 1-alkyl-4-(dialkylamino)buten-2-on-1 with hydrazine hydrate in ethyl alcohol medium at 55-60ºC, new pyrazolines possessing bactericidal and fungicidal efficacies were synthesized by acylation reaction of the obtained 3,5-substituted pyrazolines with chloroanhydrides of acetic and monochloroacetic acids at a low temperature (15-20 ºC) [5, 8].
4. It was determined, that a reactive hydrogen atom in 1-state was substituted by an ester group as a result of monochloroacetic acid methyl ether effect on 3-alkyl-5-(dialkylaminomethyl)pyrazolines. As a result, 3-alkyl-5-(dialkylaminomethyl)-1-(2-methoxycarbonylmethyl)pyrazolines were obtained and their reactions with hydrazine hydrate and potassium hydroxide were studied [13, 16].

5. Nitrogen-containing heterocyclic alcohols were obtained by the interaction of 3,5-substituted pyrazolines with ethylenechlorohydrine in alkaline medium and new 1-(2-acetoxy)pyrazolines - by the effect of carbonic acid chloroanhydrides on the latters [10, 16].
6. Bis- and 1-(allyl)pyrazolines were synthesized by the interaction of 3-alkyl-5-(dialkylaminomethyl)pyrazolines with 1,2-dibromethane and allyl bromide separately (65-70% of yield) [11, 16].
7. Antibacterial and antifungal efficacies of some synthesized pyrazole and pyrazoline derivatives were studied and their higher bactericidal efficacy was determined in comparison to ethanol, phenol, chloramine, nitrofungin used in medical practice as controlled substances. It was found out, that differing from controlled substances, these substances had higher antimicrobial efficacy against all of the test-cultures even after dilution in distilled water in a 1:800 ratio.

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