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Synthesis and Properties of Acetylene Derivatives Containing Pyrazol, Possessing Anti-Arrhythmic Activity.

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ABSTRACT: Synthesis of valuable from a biological, physiological, pharmacological point of view, nitrogen-containing five-membered heterocyclic compounds with the participation of a triple bond. Development of simple methods for preparing compounds containing various heteroatoms, such as 1,2-pyrozoles, oxazoles, pyrroles, thiophenes, thiazoles, triazoles. The structure of the synthesized compounds of the preparation is confirmed by the data of elemental analysis and IR spectroscopy. 4 [(3-nicotinoyloxypropinyl) -3 - (- nicotinoyloxymethylene)] - pyrazole has a greater breadth of anti-arrhythmic action.

KEY WORDS: Heterocyclic compounds, Acetylene, Triple bond, Urea, Pyrozole, Oxazole, Pyrrole, Thiophene, Thiazole, Triazole, Arrhythmia.

I.INTRODUCTION

The currently intensively developing chemistry of acetylene derivatives of pyrazolyl-urea compounds attracts many researchers, both in Uzbekistan and abroad. [1-7, 16-17]. This is connected, on the one hand, with the rich possibilities of the various chemical transformations that acetyl ethers, pyrozole and urea groups in the molecules of organic compounds provide, and, on the other hand, with the valuable for practical use properties of the organic compounds with the above said groups.

II. SIGNIFICANCE OF THE SYSTEM

The paper mainly focuses on how the chemistry derivatives of pyrazolyl-urea compounds. The study of literature survey is presented in section III, Proposed methodology and discussion is explained in section IV, section V covers the experimental results of the study, and section VI discusses the future study and Conclusion.

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III. LITERATURE SURVEY

There are many examples where the introduction of a triple bond led to the appearance of a gamut of various kinds of physiological, pharmacological and biological activity in cardiology. In 1918, W. Fei first proposed the use of the dextrorotatory quinine isomer, Quinidine, as an antiarrhythmic agent. Thus began the era of the use of drugs that suppress and prevent cardiac arrhythmias. Over the past hundred years, several dozen of these drugs have been created.

Despite the wide selection of antiarrhythmics, when they are used, the clinician often encounters objective factors that cast doubt on the advisability of continuing further therapy. Firstly, the pharmacological suppression of arrhythmia does not eliminate its electrophysiological substrate, which means that discontinuation of the drug most often leads to a relapse of arrhythmia. And secondly, prolonged use of antiarrhythmic drugs reduces the patient's quality of life, due to the constant "attachment" to drug therapy, and increases the risk of neurotization as part of the perception of "chronic patients" (for all ages).

Therefore, the search and synthesis of new antiarrhythmic drugs is an urgent task today. The "framework" of modern therapeutic arrhythmology is composed of the foregoing about antiarrhythmic properties. Skillful "manipulation" of antiarrhythmic drugs, taking into account the "subtleties" of their pharmacodynamics and the vulnerable parameter of arrhythmia, allows not only to significantly alleviate the patient's condition, but also in many cases save lives [8-11].

3,5-di- (hydroxyorganyl) pyrazoles obtained by the reaction of cyclization of diacetylene compounds with hydrazine hydrate are known in the literature [6]. 3 - [(butyloxymethylene) -4-butyryloxy-1-propynyl) pyrozole] having antimicrobial activity is also known [7].

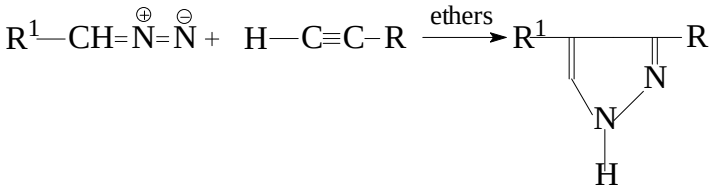
The further development of pyrazolyl-urea acetylene esters, and especially their various derivatives for the search for modern medicinal substances, is an extremely urgent task of the 21st century.

IV. PROPOSED METHODOLOGY AND DISCUSSION

The intermolecular cyclization reactions, where pyrazole derivatives of compounds (I) were obtained, were carried out to clarify the super-reactivity of the —C≡C— -bond. The reactions in fine organic synthesis proceeding with the participation of a triple bond allow developing simple methods for producing nitrogen-containing five-membered heterocyclic compounds, such as 1,2-pyrozoles, oxazoles, pyrroles, thiophenes, thiazoles, triazoles containing various heteroatoms, valuable from biological, physiological , pharmacological point of view.

Based on the foregoing, there were synthesized previously unknown compounds containing various heteroatoms, —C≡C— connection in order to obtain various functional five-membered heterocycles based on them, which have potential very high pharmacological, physiological and biological activity.

The cyclic addition of aliphatic diazo compounds to acetylene-containing compounds with the formation of the 1,2-pyrazole derivative obtained by the Pechmannreaction [1, 12–15].



1,2-pyrazole is obtained by condensation of substituted acetylene with diazomethane by the mechanism of synchronous cyclic addition with the participation of the bipolar structure of diazomethylene.

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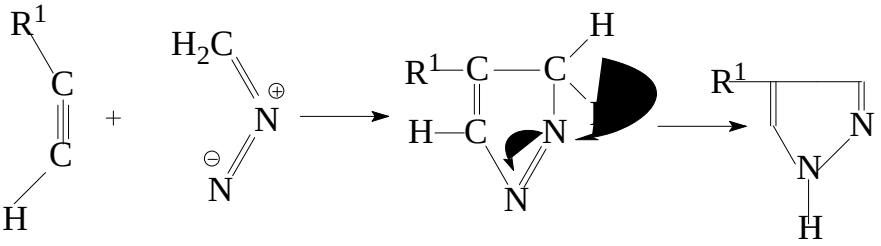
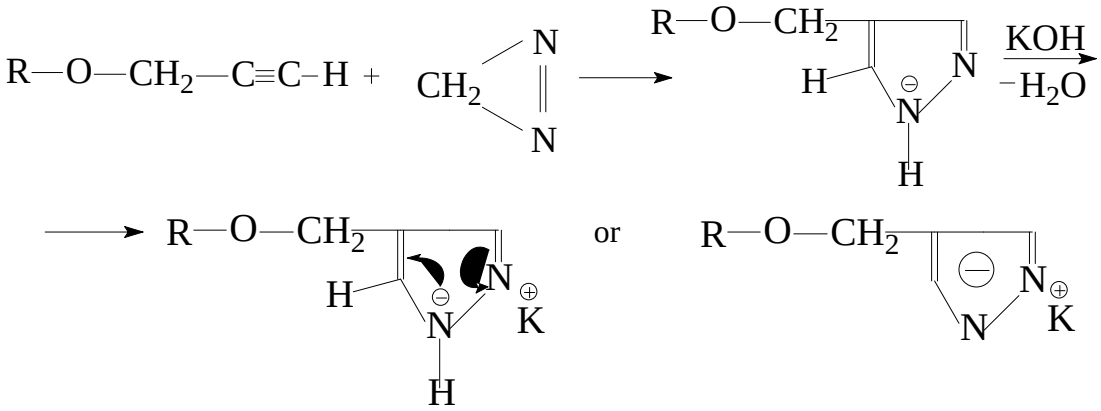
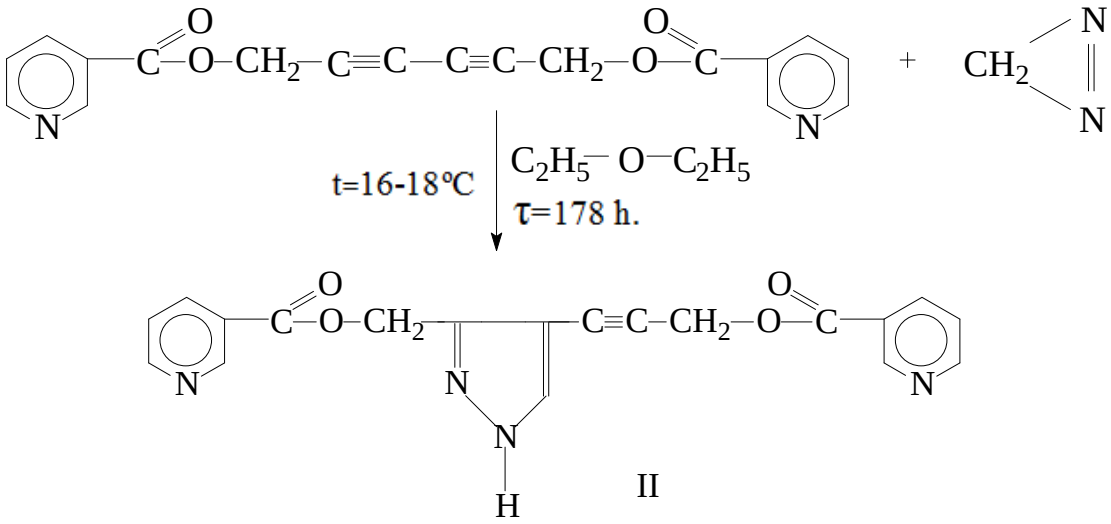


The hydrogen atom at the heteroatom is relatively easily replaced by a metal (Ag, Mg, K, Na, Li, etc.). 1,2-pyrazole forms salts with metals turning into an anion having aromatic properties:



The synthesis of a derivative of 3,4-disubstituted pyrazole (II) was carried out by the interaction of compounds (I) with diazomethane according to the following reaction scheme:



4 - [(3-nicotinoyloxypropynyl-1) -3- (nicotinoyloxymethylene] - pyrazolyl (II)

The structure of the synthesized compound of the drug (II) is confirmed by the data of elemental analysis and IR spectroscopy.

Physico-chemical parameters of the drug (II) are shown in table 1.

In the IR spectra, characteristic absorption bands are observed, in the region of 1542, 1122, 926 cm^{-1} - pulsation oscillations characteristic of the pyrazole ring (table 2).

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In the IR spectrum of the synthesized 4 - [(3-nicotinoyloxypropinyl-1) - 3 - (nicotinoyloxymethylene] - pyrazole in the 3310 cm^{-1} region, there is no absorption band characteristic of the final acetylene bond, which is well manifested in the spectrum of the starting compound. In the 3222 cm^{-1} region there is an absorption band corresponding to stretching vibrations of the pyrazole ring group, vibrations in the region of 1542 cm^{-1} are characteristic of the pyrazole ring itself.

The aromaticity of the cycle is preserved, but the ability to electrophilic substitution at carbon atoms decreases sharply. At the same time, the presence of lone pairs in heteroatoms increases the likelihood of an electrophilic attack on nitrogen, contributing to tautomeric transformations and the formation of quaternary salts. In determining the reactivity of these heterocycles, the mutual influence of the unshared electron pairs of the heteroatoms and the π-electron sextet of the ring becomes even more important, 1,2-pyrazoles exhibit weak acidic properties.

Table 1. Physico-chemical parameters of the drug (II).

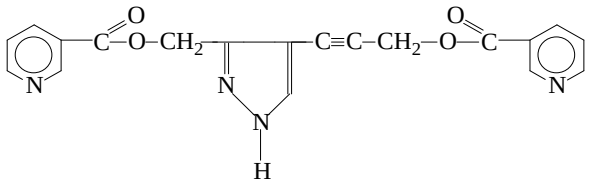
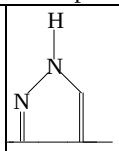
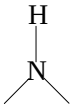
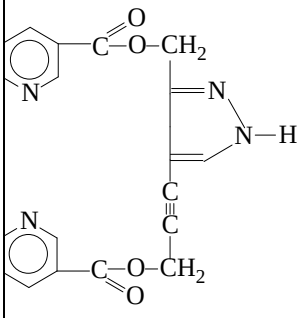
Structural formula	Yield, %	MT., ^0C	R_f	Brutto formula	Elemental analysis, %		M_M
					Calculated	Found	
					N	N	
	90,6	147-148	0,97	$C_{19}H_{14}N_4O_4$	15,46	15,54	362

Table 2. IR spectra of the drug (II)

Structural formula	IR spectra, ν, cm^{-1}							
		—O—CH_2			—C≡C—	—C≡C–CH_2—	—CH_2—	
	1719	1232	772-735	1542, 1122, 926	2231	1133	2870	3222

Thus, the current level of work, reflecting the achievements in the field of chemistry of derivatives of heterocyclic systems, convincingly shows and proves that in studies of recent years, methods for the synthesis of heterocyclic esters of 1,2-pyrazole or 1,2-pyrazoline have been actively developed. The rings of 1,2-pyrazole (or 1,2-pyrazoline) are extremely stable, and many of its derivatives can be distilled without decomposition and melting.

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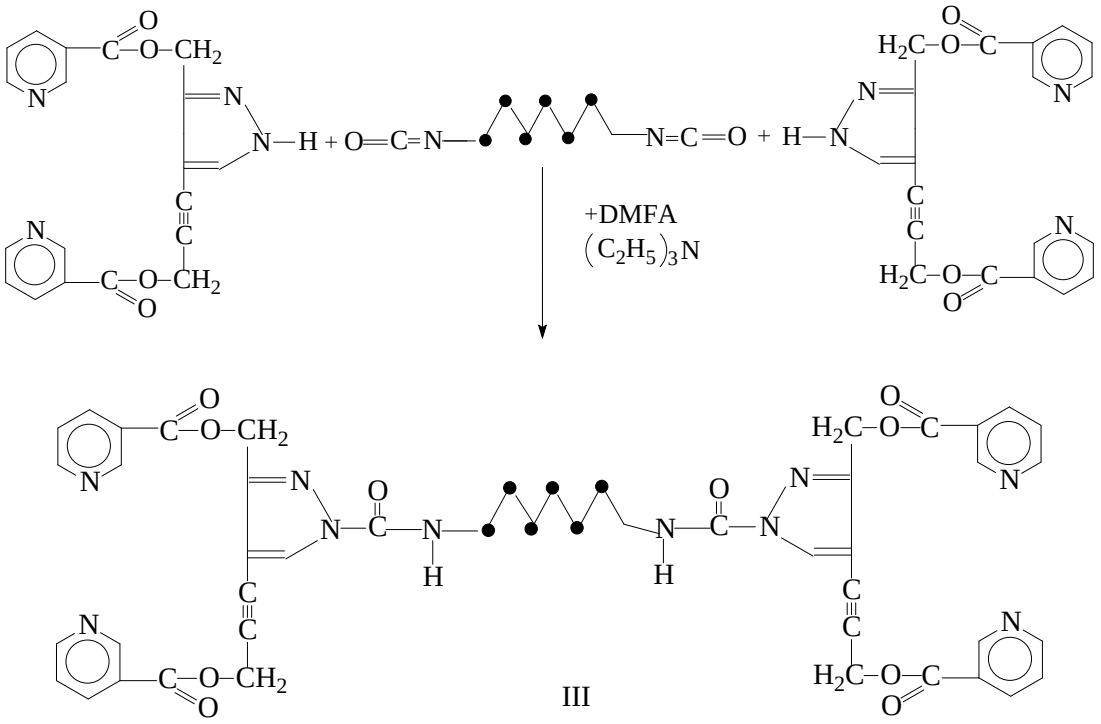
V. EXPERIMENTAL RESULTS

The interaction of the drug (II) with hexamethylenediisocyanate.

Diisocyanates are among the compounds having an extremely super-high reactivity. Secondary amines with heterocyclic compounds containing N-H bonds have the highest reactivity with respect to isocyanate [14].

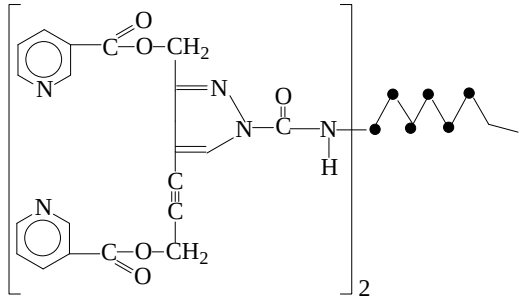
We obtained derivatives of bis-pyrazolyl urea by the interaction of hexamethylenediisocyanate with the drug (II) at a temperature of 30-52 ^{o}C according to the scheme:



III

The synthesis was carried out in a medium of dimethylformamide at a temperature of 30-52 °C for four hours. It should be noted that new environmentally friendly derivatives of bis-pyrazolyl urea are obtained in the form of a snow-white powdery product (III), physicochemical parameters are given in table 3.

Table 3. Physico-chemical characteristics of the drug (III).

Structural formula	Yield, %	MT., ^{0}C	R_f	Brutto formula	Elemental analysis, %		M_M
					Calculated	Found	
					N	N	
	93,4	229-230	0,93	$C_{46}H_{40}N_{10}O_{10}$	15,69	15,43	892

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Compounds were purified by recrystallization from ethyl alcohol. The identity of the drug (III) was established by TLC on the plates.

The following systems were used as eluents:
system I: CH_3Cl_3: CH_3OH: HCOOH = 10: 0,8: 0,2
system II: HCOOH: CH_3COCH_3: CCl_4 = 0,5: 5,0: 0,5

The structure of {N, N^1 –hexamethylene bis [4- (β — nicotinoyloxypropinyl) -3- (β — nicotinoyloxymethylene) pyrazolyl N, N^1 urea]} (III) was confirmed by elemental analysis, as well as IR and H-, ^{13}C-NMR spectroscopy.

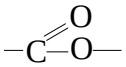
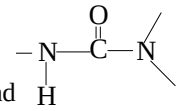
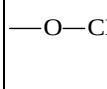
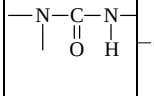
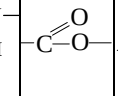
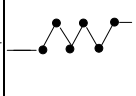
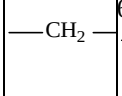
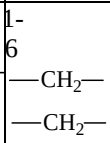
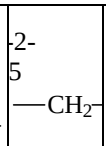
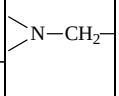
In the IR spectrum of compounds (III), there is a wide absorption band in the region of 1720 cm^{-1}, characteristic of  - groups, and the absorption band in the region of 1623 cm^{-1} corresponds to the absorption of the bond  , a strong absorption band in the region of 3311 cm^{-1} is characteristic of NH groups (table 4).

Table 4. IR and H-, ^{13}C-NMR spectra of the drug (III).

Compounds№	IR spectra, ν, cm^{-1}								H-, ^{13}C-NMR spectra, **δ**, м.д.		
									1-6 	2-5 	
III	3311	1232	772-736	1540;1122; 925	1623	1720	767-733	2872	2,81	1,28-1,06	3,29

Experimental part.

Example 1. Synthesis of 4 [(β-nicotinoyloxypropinyl) -3- (β-nicotinoyloxymethylene)] -pyrazole (II).

3,2 g (0,01 mol) of the starting reagent 1,6- (nicotinate) -hexadiin-2,4 is introduced into a conical flat-bottomed flask, and then gradually add about 1,1 g (0,026 g / mol) of a freshly prepared solution of diisomethane to 35 ml of sulfuric ether. The reaction mixture is kept in the dark at a temperature of up to 16-18 °C until the yellow color is discolored for 178 hours. Then the solvent was evaporated, the product was purified by TLC on Al_2O_3, II degree of activity;
System: CH_3OH: C_6H_{14} = 0,5: 0,5; Rf = 0,97.
Found, %: C 62,88; H 3,51; N 15,54
Calculated for $C_{19}H_{14}N_4O_4$,% : C62,88; H 3,86; N 15,46

The synthesized substance is a yellowish compound with a peculiar, rather mild odor.

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Example 2. N, N^1-Hexamethylene-bis- [4- (β-nicotinoyloxypropynyl) -3- (β-nicotinoyloxymethylene) -pyrazolyl-N, N^1-urea] (III).

7,24 g (0,02 mol) of 4- (β-nicotinoyloxypropinyl) -3- (β-nicotinoyloxymethylene) pyrazole are placed in a three-necked flask equipped with a reflux condenser, thermostat, stirrer, 20 ml of triethylamine, 40 ml of DMF are added, 1,7 g (0,011 mol) of hexamethylene diisocyanate dissolved in 10 ml of DMF are added at a temperature of 30-42 °C with stirring dropwise. The reaction mixture is stirred for 3,0 hours at a temperature of 49-53 °C. After the time, the contents of the flask are transferred to a glass, water is added. The precipitate was washed with TLC. After drying, a slightly colored powder is obtained with a yield of (III) – 93,4 % (of theoretical) %, mp. - 229-230 °C, Rf = 0,93

Found, %:	C 61,69;	H 4,34;	N 15,43
Calculated for $C_{46}H_{40}N_{10}O_{10}$,% :	C62,88;	H4,48;	N 15,69

VI.CONCLUSION AND FUTURE WORK

Antiarrhythmic activity of the drug (II).

It was revealed that the drug (II) has an antiarrhythmic effect.

The antiarrhythmic effect of the drug (II) was studied on white rats weighing 140-250 g of both sexes.
Arrhythmia was caused by the introduction of aconitine (10-15 mkg / kg) and calcium chloride (250-300 mg / kg) into the tail vein.

The well-known antiarrhythmic drug quinidine was taken for comparison.

It was found that it prevents or delays the occurrence of aconitine arrhythmia with the preliminary administration of the test drug (II) in doses of 10, 15, 20, 25, and 50 mg / kg. So, at a dose of 5 mg / kg, the drug prevents arrhythmia in 4 out of 8 rats, and at a dose of 10 mg / kg in 6 of 8 rats (75 %).

This drug also has a therapeutic effect in relation to aconitine arrhythmia. At a dose of 15 mg / kg, it reduces arrhythmia in 6 out of 8 (75 %).

Quinidine, with prophylactic administration, delays (but does not prevent) the occurrence of arrhythmias for 8-10 minutes.

The effect of the study drug compared with quinidine on calcium chloride arrhythmia was also studied.

It was established that this drug, starting with a dose of 15 mg / kg, has an antifibrillatory effect. At the same dose, he prevents fibrillation in two out of 8 rats, at a dose of 25-50 mg / kg - in 3 and 4 out of 8 rats.

At the same time, quinidine at a dose of 15 mg / kg prevents the occurrence of calcium chloride arrhythmias in one out of eight rats. When studying for toxicity, it was revealed that the study drug is low toxic. Its LD_{50} = 150 mg / kg. Quinidine LD_{50} is 56 mg / kg.

Based on the studies, we can conclude that the test substance was less toxic than quinidine and more active in anti-arrhythmic activity compared with it. With prophylactic administration, this drug prevents aconitine arrhythmia in 75% of animals, while quinidine only delays its manifestation. With therapeutic use, the drug (II) reduces aconitine arrhythmia in 75 % of animals, and quinidine in 50 %.

Thus, the drug (II) 4 [(3-nicotinoyloxypropinyl) -3 - (- nicotinoyloxymethylene)] - pyrazole has a greater breadth of anti-arrhythmic action than the well-known drug - quinidine.

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