SYNTHESIS OF SOME AMINOPROPYNYLPYRAZOLES

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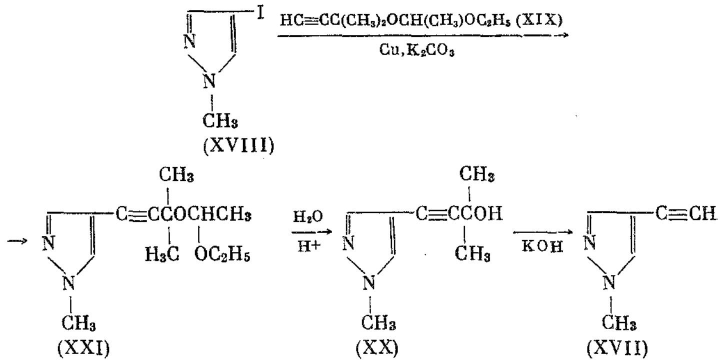
As a continuation of our research on the synthesis and study of the biological activity of acetylenic amines [1-4] we synthesized a number of aminoacetylenic derivatives of pyrazole, containing a structure that varied in a regular manner, and investigated their acute toxicity and antiarrhythmic action.

Amines (I)-(XI) (Table 1) were obtained by the Mannich reaction from the corresponding ethynylpyrazoles

$$\mathrm{PzC{\equiv}CH} \xrightarrow{\mathrm{HCHO,\ HNR_2}} \mathrm{PzC{\equiv}CCH_2NR_2}$$

The starting 4-ethynyl-1,3,5-trimethyl-(XII), 4-butadiynyl-1,3,5-trimethyl-(XIII), 3,5-diethynyl-1-methyl-(XIV), 3,4-diethynyl-1-methyl-(XV), and 4,5-diethynyl-1-methylpyrazole (XVI) were described previously [5, 6]. 4-Ethynyl-1-methylpyrazole (XVII) was synthesized in an overall yield of 70% by the condensation of 4-iodo-1-methylpyrazole (XVIII) with acetaldehyde ethyl 2-methyl-3-butyn-2-yl acetal (XIX) [6, 7], with the subsequent removal of the acetal protection of the hydroxyl and cleavage of the pyrazolylacetylenic alcohol (XX) by the reverse Favorskii reaction

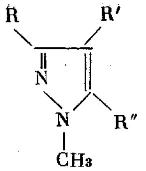


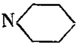
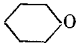
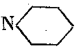
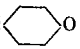
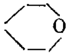
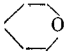
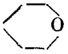
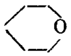
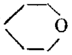
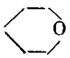
The aminomethylation of ethynylpyrazoles (XII)-(XVII) was run in dioxane in the presence of CuCl. With diethylamine and piperidine the reaction was ended in 7-9 h at 35°C, while 2-3 h at 80° was sufficient for its total completion with any of the employed amines. The differences in the reactivity of the acetylenic groups, occupying different positions in the pyrazole ring, are slight. In the case of 4,5-diethynyl-(XVI) and 3,5-diethynyl-1-methylpyrazole (XIV), respectively, the relative condensation rates (piperidine, 35°) at $5\text{-C}{\equiv}\text{CH}$ are ~4 times higher than at $4\text{-C}{\equiv}\text{CH}$, and ~1.6 times higher than at $3\text{-C}{\equiv}\text{CH}$.

Together with the Mannich reaction, in order to obtain diamines (X) and (XI), and also 3,4,5-tri-(N-morpholino-2'-propyn-1'-yl)-1-methylpyrazole (XXII), we employed the method of directly inserting the acetylenic substituents into the pyrazole ring. As the acetylenic component we used 1-N-morpholino-2-propyne (XXIII) [8]

Institute of Chemical Kinetics and Combustion, Siberian Branch of the Academy of Sciences of the USSR. The Novosibirsk Medical Institute. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 11, pp. 2524-2529, November, 1972. Original article submitted July 6, 1971.

TABLE 1. Aminoacetylenic Derivatives of Pyrazole



Compound	R	R′	R″	Synthesis method	Yield, %	mp, °C (from petroleum ether)	Found/Calculated, %	Empirical formula
I	H	$C\equiv CCH_2N$ 	H	A	64,5	47—48	$\frac{20,90}{20,67}$	$C_{12}H_{17}N_3$
II	CH_3	$C\equiv CCH_2N$ 	CH_3	A	82,0	44—45	$\frac{18,07}{18,17}$	$C_{14}H_{21}N_3$
III	CH_3	$C\equiv CCH_2N(C_2H_5)_2$	CH_3	A	86,5	T. bp, 136—137° (1,5 mm), n_D^{20} 1,5135	$\frac{19,42}{19,16}$	$C_{13}H_{21}N_3$
IV	CH_3	$C\equiv CCH_2N$ 	CH_3	A	82,5	T. bp, 137—138° (2 mm); n_D^{20} 1,5345	$\frac{19,10}{19,34}$	$C_{13}H_{19}N_3$
V	CH_3	$C\equiv CCH_2N$ 	CH_3	A	85,2	72,5—73	$\frac{18,02}{18,01}$	$C_{13}H_{19}N_3O$
VI	CH_3	$C\equiv CC\equiv CCH_2N$ 	CH_3	A	63,5	94—95 (decomp.)	$\frac{16,68}{16,33}$	$C_{15}H_{19}N_3O$
VII	$C\equiv CCH_2N$ 	H	$C\equiv CCH_2N$ 	A	66,7	82—83	$\frac{16,91}{17,27}$	$C_{20}H_{28}N_4$
VIII	$C\equiv CCH_2N$ 	H	$C\equiv CCH_2N$ 	A	65,0	94,5—95,5	$\frac{17,21}{17,06}$	$C_{18}H_{24}N_4O_2$
IX	$C\equiv CCH_2N$ 	$C\equiv CCH_2N$ 	H	A	90,0 *	77—78	$\frac{17,01}{17,27}$	$C_{20}H_{28}N_4$
X	$C\equiv CCH_2N$ 	$C\equiv CCH_2N$ 	H	A B	66,0 71,8	79—80	$\frac{17,09}{17,06}$	$C_{18}H_{24}N_4O_2$
XI	H	$C\equiv CCH_2N$ 	$C\equiv CCH_2N$ 	A B	58,5 75,0	—†	$\frac{17,04}{17,06}$	$C_{18}H_{24}N_4O_2$
XXII	$C\equiv CCH_2N$ 	$C\equiv CCH_2N$ 	$C\equiv CCH_2N$ 	B	80,0	90—91 (from petroleum ether-benzene)	$\frac{15,69}{15,51}$	$C_{25}H_{33}N_5O_3$

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*Yield of crude amine.

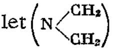
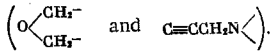
†Viscous liquid; NMR spectrum (CCl_4, δ, ppm): 3.80 (NCH_3); 7.27 (3-H); 2.39-2.52 multiplet  $\left(N\begin{smallmatrix}CH_2\\CH_2\end{smallmatrix}\right)$; 3.38-3.60 multiplet  $\left(O\begin{smallmatrix}CH_2-\\CH_2-\end{smallmatrix}\right.$ and $\left.C\equiv CCH_2N<\right)$.

TABLE 2. Physiological Activity of Aminopropynylpyrazoles

Compound No.	Hydrochloride				LD_{50}	Antiarrhythmic action		
	mp, °C	found, Cl, %	empirical formula	calc. Cl, %		effective concentration, g/ml	Duration of effect, min	
						Model I	Model II	Model III
I	-	-	$C_{12}H_{19}N_3Cl_2$	-	25.6 ±1.9	$1 \cdot 10^{-4}$	0*	-
II	110-110.5 (from dioxane)	23.47	$C_{14}H_{19}N_3Cl_2$	23.31	77 ±6.2	$2 \cdot 10^{-4}$	0.5-3	10-11
III	139-140 (from dioxane)	24.20	$C_{13}H_{23}N_3Cl_2$	24.26	54 ±1.2	$1 \cdot 10^{-4}$	2-5	0-11
IV	119-120 (decompn.)	24.73	$C_{13}H_{21}N_3Cl_2$	24.48	62 ±3.1	$2 \cdot 10^{-4}$	1-3	-
V	195-19.5 (decompn.; from dioxane)	23.24	$C_{13}H_{21}N_3OCl_2$	23.16	~350	$2 \cdot 10^{-4}$	-	†
VI	197-198 (decompn.; from dioxane)	21.52	$C_{15}H_{21}N_3OCl_2$	21.48	185 ±13.6	$2 \cdot 10^{-4}$	1-4	0
VII	Decomposes	18.00	$C_{20}H_{30}N_4Cl_2$	17.84	30.6 ±2.7	Not effective	-	†
VIII	199-200 (decompn.; from isobutanol)	17.62	$C_{18}H_{26}N_4O_2Cl_2$	17.67	122.5 ±3.6	"	0	0
IX	Decomposes	24.22	$C_{20}H_{31}N_4Cl_3$	24.52	61.7 ±5.4	$4 \cdot 10^{-5}$	0.5-5*	1.5-20
X	"	-	‡	-	463 ±23.7	$1 \cdot 10^{-4}$	-	-
XI	"	-	‡	-	~375	$2 \cdot 10^{-4}$	1-20	1.5-5
XXII	"	18.81	$C_{25}H_{36}N_5O_3Cl_3$	18.97	~500	$4 \cdot 10^{-4}$	-	-
XXVII	201-202 (decompn.; from petroleum ether–isopropanol)	23.22	$C_{14}H_{27}N_3Cl_2$	23.00	172 ±8.0	$2 \cdot 10^{-4}$	0-1.5*	
Novocaine amide	-	-	-	-	100 [10]	$4 \cdot 10^{-5}$	0.3-**	8-10**

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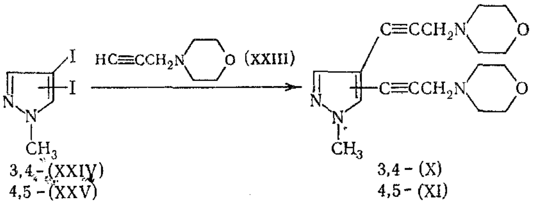
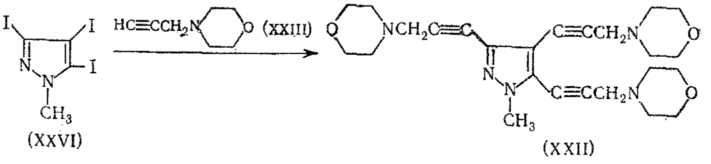
*Dose 10 mg/kg; in the other cases 20 mg/kg.

†Increases the arrhythmia.

‡Hygroscopic, could not be analyzed.

**Increases the arrhythmia in some cases.





Despite the lower activity of propargylamine (XXIII) in this reaction when compared with acetal (XIX), and the long condensation time (75-95 h), the yields of the di- and triaminoacetylenic pyrazole derivatives (X), (XI), and (XXII) reached 70-80%. The starting iodides (XXIV)-(XXVI) were synthesized either by the methylation of the 3,4-diiodo- and 3,4,5-triiodopyrazoles [6] or by the iodination of N-methylpyrazole (XXVII) in the presence of HIO_3. With stoichiometric amounts of the reactants the diiodination proceeds in 4 h at 80° and leads to a mixture of the 3,4-(XXIV) and 4,5-isomers (XXV) in an ~1 : 1 ratio. The triiodination under the same conditions requires at least 20 h.

The pharmacological properties of the hydrochlorides of the synthesized amines were studied. Their toxicity varies in a wide range and decreases with increase in the number of substituents in the ring, in which connection the decrease is sharpest when the hydrogen in the 4 position is replaced (Table 2). The morpholine derivatives are the least toxic. Some of the compounds [(IX), (II)] have a well-defined antiarrhythmic action in the case of experimental arrhythmia in animals, induced by the internal injection of a solution of $BaCl_2$ [9] (Model II) or strophanthin K [10] (Model III). The antiarrhythmic activity of the hydrochloride of amine (IX) on the isolated frog heart [11] (Model I) is equal to the activity of novocaine amide. In all cases the presence of an unsubstituted hydrogen atom in the 4 position of the heterocycle removes the antiarrhythmic activity. Its dependence on the other traits of the structure is less distinct. It is important that a parallelism is absent in the change of the antiarrhythmic action and the toxicity.

EXPERIMENTAL METHOD

Oxidative Iodination of 1-Methylpyrazole (XXVII). To a solution of 3 g of (XXVII) in 20 ml of glacial CH_3COOH at 80° were added ~5 ml of water (until turbid), 3.7 g of I_2, 1.5 g of HIO_3, 1 ml of conc. H_2SO_4, and 3 ml of CCl_4. The reaction mass decolorized within 15 min. After cooling and making alkaline with aqueous NaOH solution the product was extracted with $CHCl_3$, dried over K_2CO_3, and distilled. The yield of 4-iodo-1-methylpyrazole (XVIII) was 5.9 g (77.5%), bp 101-105° (15 mm); mp 62-63° [12].

The iodination of 1 g of (XVIII) by the same procedure gave 1.4 g (88%) of a mixture of diiodopyrazoles (XXIV) and (XXV) [6] in a 1 : 1 ratio (based on the GLC data). The reaction time was 4 h.

Under analogous conditions (80-85°, 20 h), 1 g of the obtained mixture of (XXIV) and (XXV) was iodinated to the triiodide (XXVI); yield 1.3 g (95%), mp 152-153° (from petroleum ether–benzene, 10 : 1) [6].

Condensation of Iodopyrazole (XVIII) with Acetal (XIX). A mixture of 4.2 g of (XVIII), 9.4 g of (XIX), 4 g of K_2CO_3, and 1.3 g of Cu powder in 50 ml of pyridine was refluxed, with stirring, in a N_2 atmosphere for 75 h, cooled, diluted with 500 ml of ether, the precipitate was filtered, and the ether–pyridine solution was washed with 25% aqueous NH_3 solution and then dried over K_2CO_3. Distillation gave 4 g (83.5%) of (XXI), bp 120-123° (1 mm); n_D^{20} 1.4905. Infrared spectrum (ν, cm^{-1}): 2240 ($C \equiv C$), 1056, 1083, 1125, 1160 ($C-O-C-O-C$). Found: N 11.76%. $C_{13}H_{20}N_2O_2$. Calculated: N 11.86%.

1-(1'-Methyl-4'-pyrazolyl)-3-methyl-1-butyn-3-ol (XX). Compound (XXI) (0.7 g) was hydrolyzed with 1 ml of 2.5% HCl solution in 2 ml of dioxane at 20°. We obtained 0.5 g (99%) of (XX), mp 85-86° (from petroleum ether–benzene, 8 : 1). Infrared spectrum (ν, cm^{-1}): 2237 ($C \equiv C$), 3615 (OH; broad band of the hydrogen bond with a maximum at 3385). NMR spectrum (CCl_4, δ, ppm): 3.77 (NCH_3), 1.47 (CH_3), 7.32 and 7.25 (5- and 3-H), 2.55 (OH). Found: N 16.90%. $C_9H_{12}N_2O$. Calculated: N 17.06%.

4-Ethynyl-1-methylpyrazole (XVII). Compound (XX) (0.9 g) was ground well with 0.1 g of fused KOH and heated at 90-100° (1 mm). Here 0.5 g (84.5%) of (XVII) distilled; n_D^{20} 1.5285 [after molecular distillation at 30° (1 mm)]. Infrared spectrum (ν, cm^{-1}): 3320 ($C \equiv C-H$), 2128 ($C \equiv C$). NMR spectrum (CCl_4, δ, ppm): 2.88 ($4C \equiv C-H$), 3.75 (NCH_3), 7.38 and 7.36 (5- and 3-H). Found: N 26.15%. $C_6H_6N_2$. Calculated: N 26.40%.

4-(3'-N-Piperidino-1'-propynyl)-1,3,5-trimethylpyrazole (II). A mixture of 2 g of (XII), 1.7 g of piperidine, 0.6 g of paraform, and 0.01 g of CuCl in 20 ml of dioxane was stirred at 35° for 8 h. The condensation time was shortened to 30 min when the temperature was raised to 80°. After filtration through a small layer of Al_2O_3 and distilling off the solvent the product was vacuum-distilled. We obtained 2.8 g (82%) of (II), bp 170-171° (3 mm); mp 44-45°. Infrared spectrum (ν, cm^{-1}): 2220 ($C \equiv C$).

Amines (I) and (III)-(XI) were synthesized in a similar manner (method A). Their constants and yields are given in Table 1, while the melting points of the hydrochlorides are given in Table 2.

Dihydrochloride of 4-(3'-N-Piperidinopropyl)-1,3,5-trimethylpyrazole (XXVII). A solution of 0.6 g of (II) in 20 ml of CH_3OH was hydrogenated at 20° and atmospheric pressure in the presence of $Pd/CaCO_3$. Then the catalyst was removed, the methanol was distilled off, and the residue was chromatographed on Al_2O_3 (V activity) in a 7 : 1 mixture of $CHCl_3$ and ether. A solution of the free base in ether was saturated with HCl. The yield of (XXVII) was 0.4 g (53.5%), mp 201-202° (decompn., from a 3 : 1 petroleum ether – isopropanol mixture). The compound is hygroscopic.

Relative Aminomethylation Rates of Ethynyl Groups in Different Positions of Pyrazole Ring. To a mixture of 0.35 g of piperidine, 0.2 g of paraform and 0.01 g of CuCl in 25 ml of freshly distilled dioxane at 35°, in a N_2 atmosphere was added 2.6 g of (XIV) and the mixture was stirred for 3 h, in which connection the reaction was followed by TLC on Al_2O_3 (V activity). After dilution with ether the reaction mass was filtered through Al_2O_3, the solvent was distilled off, and the excess (XIV) was removed by vacuum-distillation. The obtained mixture of 3-ethynyl-5-piperidinopropynyl- (XXVIII) and 5-ethynyl-3-piperidinopropynyl-1-methylpyrazole (XXIX) was additionally freed of (XIV) by preparative TLC in the system: $CHCl_3$–benzene, 5 : 1; yield 0.9 g (99%). Based on the data of the NMR spectra and GLC, the ratio of the (XXVIII) and (XXIX) isomers is 1.6 : 1.

In a similar manner, from 2.6 g of (XVI) was obtained in quantitative yield a mixture of 4-ethynyl-5-piperidinopropynyl- (XXX) and 5-ethynyl-4-piperidinopropynyl-1-methylpyrazole (XXXI) in a 4 : 1 ratio.

3,4,5-Tri-(3'-N-morpholinopropyn-1'-yl)-1-methylpyrazole (XXII). A stirred mixture of 4.6 g of (XXVI), 11.3 g of (XXIII), 7.1 g of K_2CO_3, and 0.6 g of Cu in 25 ml of pyridine was heated at 113-115° for 95 h. Then the mixture was cooled, diluted with ether, filtered through a small bed of Al_2O_3, and the solvent was removed. We isolated (XXII) by preparative TLC on Al_2O_3 (V activity) in the system: $CHCl_3$ – ether, 1 : 1. The yield of (XXII) was 3.6 g (80%), mp 90-91° (from petroleum ether–benzene, 8 : 1). Infrared spectrum (ν, cm^{-1}): 2250 ($C{\equiv}C$).

Diamines (X) and (XI) were obtained in a similar manner (method B). The yields and constants are given in Table 1.

CONCLUSIONS

A number of mono-, di-, and tri(aminopropynyl)pyrazoles was synthesized by the Mannich condensation from pyrazolylacetylenes, and by the condensation of N-substituted propargylamines with iodopyrazoles.

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