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NEW TYPE OF CONDENSATION OF 5-PYRAZOLONES UNSUBSTITUTED AT THE NITROGEN

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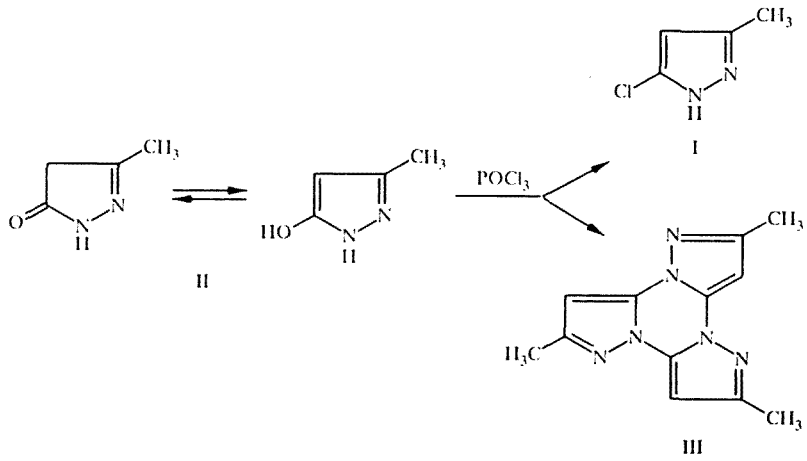
1,5-Tripyrazolylenes were prepared with satisfactory yields by the reaction of 5-pyrazolones unsubstituted at the nitrogen atom with an equimolar amount of $POCl_3$ in open vessels together with 5-chloro derivatives (Michaelis reaction).

In an attempt to simplify the method of preparation of 3-methyl-5-chloropyrazole (I) by the reaction of $POCl_3$ and 3-methyl-5-pyrazolone (II) [1], we conducted the reaction in an open vessel instead of a sealed tube at a bath temperature of 160°C. Instead of predicted compound I, we obtained substance III, significantly less soluble in benzene—hexane mixture, as a result. According to the data from elemental analysis, compound III only contained C, H, and N and corresponded to the empirical formula $(C_4H_4N_2)_x$. The mass spectrometric determination of the molecular weight gave a value of 240; thus x = 3, and the empirical formula is $C_{12}H_{12}N_6$. The PMR spectrum recorded in CF_3COOH contained two signals with an integral intensity ratio of 3:1 and chemical shifts of 2.56 and 6.60 ppm, respectively, indicating the symmetric structure of the trimer. In comparison to 3-methylpyrazole (2.14 and 6.05 ppm [2]), there is an abnormally strong shift of the signal of both the proton in position 4 (0.55) and the protons of the CH_3 group (0.42 ppm) to weak fields, which cannot be explained simply by protonation of the molecule in the conditions of recording of the PMR spectrum; this indicates a higher degree of aromaticity of compound III in comparison to pyrazole. The pKa_1 and pKa_2 obtained, respectively equal to -2.48 ± 0.16 and -4.88 ± 0.30 (determined spectrophotometrically), demonstrate the weakly basic properties of compound III. All available information thus suggested the following structure of compound III.



By analogy with the trivial name "triphenylene," we propose the name of "1,5-tripyrazolylene" for the nucleus of compound III. Retaining its numbering in pyrazole nuclei, compound II should be called: tri(3-methyl-1,5-pyrazolylene). The

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TABLE 1. Yields and Constants of 5-Pyrazolones

5-Pyrazolone	Initial β-ketoester	Mp,* °C	Yield, %	Literature
3-Methyl	Acetoacetic	214*	85	[7]
3,4-Dimethyl	Methylacetoacetic	267	64	[8]
3-Methyl-4-ethyl	Ethylacetoacetic	226*[2]	67	[9]
3-Methyl-4-isopropyl	Isopropylacetoacetic	183	71	
3,4-Tetramethylene	o-Carbethoxycyclohexanone	285	82	[10]
3-Phenyl	Benzoylacetic	235	75	[11]

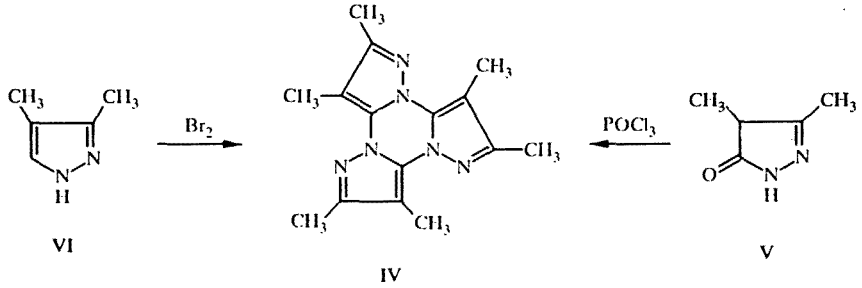
*In a sealed capillary.

*2Published data mp = 195°C [9].

IR spectrum of compound III contains an intense band in the region of 1625 cm^{-1} characterizing vibration of the total conjugated system of four rings: triazine and three pyrazole (3-methylpyrazole in the 1595 cm^{-1} region is distinguished by low absorption intensity [3]). The lower basicity of compound III in comparison to the basicity of 3-methylpyrazole (by 4.5 orders of magnitude) indicates that a significant portion of the π-electron density is shifted to the triazine ring. The UV spectrum contains an intense absorption maximum at 239 nm (log ε 4.69), indicative of a total conjugated system, since pyrazole itself has a K absorption band at 210 nm (log ε 3.5) [4]. Each C and N atom in the triazine ring has one π electron in common with the pyrazole nucleus, each belonging to pyrazole. Due to combination of the electron density of the pyrazole nuclei, the *p* pair of electrons of the $N_{(2)}$ nitrogen atom of the pyrazole nucleus is shifted to the pyrazole ring, which sharply decreases the basicity.

Since the yield of compound III in the experiment described above was only 10%, while the yield of compound I was 6%, attempts were made to improve the yield of trimer III by changing the reaction conditions. Using $SOCl_2$, PCl_5, $C_6H_5SO_2Cl$, and polyphosphoric acid instead of $POCl_3$ did not cause the formation of compound III at all. The use of solvents (Tetralin, chlorobenzene) caused strong contamination of the reaction mixture. P_2O_5 and KCl additives reduced the yield, and decreasing the amount of $POCl_3$ from equimolar to half-molar or increasing it to 2 moles, led to the same result. The yield was much better when technical-grade instead of freshly distilled $POCl_3$ was used. The optimum conditions of the reaction were: equimolar ratio of pyrazolone and $POCl_3$ and heating at 200°C for 5 h.

A structure of this type — tri(3,4-dimethyl-1,5-pyrazolylene) (IV) was obtained previously in [5] in oxidation of 3,4-dimethylpyrazole (VI) with bromine, but without rigorous demonstration of the structure.



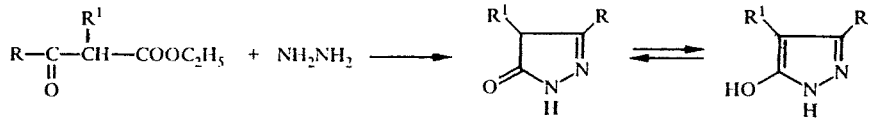
VI IV V

The tri(3,4-dimethyl-1,5-pyrazolylene) obtained here in the reaction of $POCl_3$ and 3,4-dimethyl-5-pyrazolone (V) was totally identical to compound IV synthesized with the method in [5] (IR spectra and melting point of the mixed sample). Our attempts to oxidize the structural analog of compound VI — 3,4-tetramethylpyrazole — with bromine were unsuccessful: the corresponding tripyrazolylene was not separated. In the reaction of $POCl_3$ and 3,4-tetramethylene-5-pyrazolone, tri(3,4-tetramethylene-1,5-pyrazolylene) was formed with a good yield (see Table 2). No difficulties caused by incorporation of new substituents arose in synthesis of other substituted tripyrazolylenes (a total of six compounds was obtained), although the yields varied significantly (Table 2). All of the starting pyrazolones were synthesized from β-ketoesters by the reaction with hydrazine hydrate (see Table 1).

TABLE 2. Yields and Constants of 1,5-Tripyrazolylenes

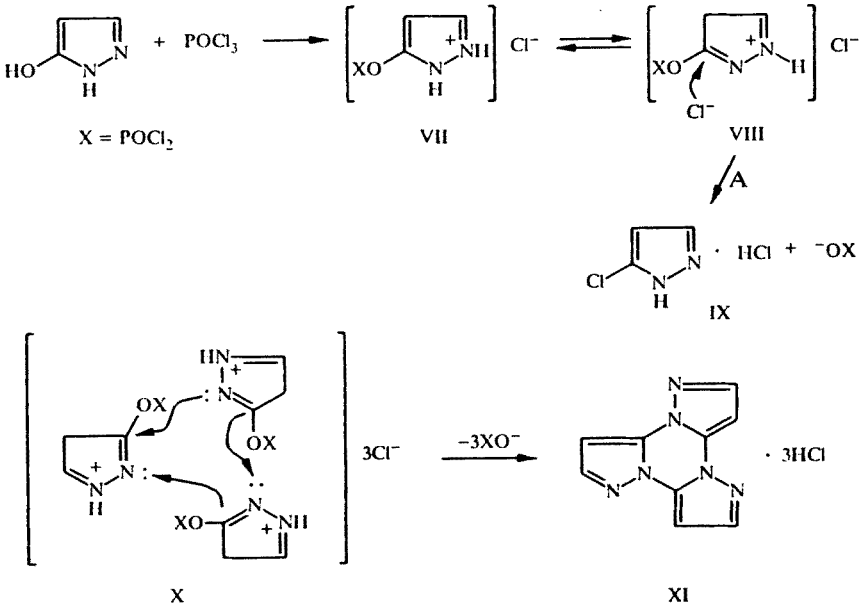
Substituents in pyrazole nucleus of 1,5-tripyrazolylenes	Empirical formula	Mp,* °C (solvent)	IR spectrum ν , cm^{-1}	UV spectrum, λ_{max} (log ε)	Yield, %
3-Methyl	$C_{12}H_{12}N_6$	194...196 (benzene–hexane, 1 : 6)	1625, 3060	214 (3,84) 239 (4,69)	29
3,4-Dimethyl	$C_{15}H_{18}N_6$	210...212 (acetic acid)	1638, 2990	244 (4,34)	26
3-Methyl-4-ethyl	$C_{18}H_{24}N_6$	148...150 (acetic acid)	1635, 2980	244 (4,67) 256 (4,58)	41
3-Methyl-4-isopropyl	$C_{21}H_{30}N_6$	168...170 (acetic acid)	1630, 2940	244 (4,90) 256 (4,81)	36
3-Phenyl	$C_{27}H_{18}N_6$	250...252 (toluene)	1625	276 (4,58) 282 (4,54)	25
3,4-Tetramethylene	$C_{21}H_{24}N_6$	304...306 (toluene)	1647, 2980	239 (4,39) 263 (3,96)	66

*In sealed capillary.



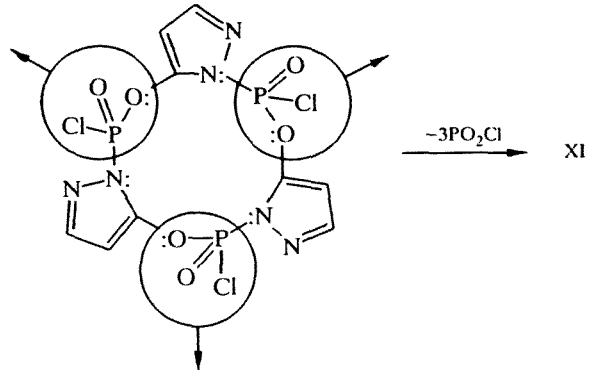
An excess of hydrazine should be avoided in the reaction, since pyrazolones yield salts readily soluble in water with hydrazine.

In our opinion, cyclization takes place according to the following scheme: pyrazolone in the hydroxy form reacts with $POCl_3$ at the oxygen atom, forming salt VII; salt VII in the form of VIII undergoes nucleophilic attack, either by Cl^- in the case of an excess (sealed tube), yielding the usual product of the Michaelis reaction — chloropyrazole IX [6], or when the reaction takes place in an open vessel and when excess chlorine anion departs in the form of HCl, salt VIII undergoes nucleophilic attach by a nitrogen atom from another identical molecule with displacement of XO^- anion (see intermediate X).



When three molecules are involved, the closed, stable, aromatic system of 1,5-tripyrazolylene XI is formed. The process could pass through formation of cyclic phosphoric amido ester XII, containing three $POCl_3$ residues and three molecules

of 5-hydroxypyrazole (pyrazole can also act in the protonated form), which decomposes with separation of three molecules of PO_2Cl and formation of compound XI.



EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer 577 in KCl pellets, and the UV spectra were recorded on a Specord M-40 in alcohol. The PMR spectra were recorded on a Tesla BS-497 (100 MHz) in CF_3COOH. The mass spectra were obtained on a MAT HS Q 30 in conditions of direct introduction of the sample in the ion source.

Overall Method of Synthesis of 5-Pyrazolones Unsubstituted at the Nitrogen. A 50-85% solution of hydrazine hydrate containing 0.5 mole of hydrazine was added by parts to a mixture of 0.5 mole of freshly distilled β-ketoester, 50 ml of methanol, and 6 ml of acetic acid. After the turbulent reaction ended, the mixture was heated (~100°C) for 1 h and cooled. The crystals of pyrazolone were filtered off and boiled for 30 min with 50 ml of methanol, cooled, and the pyrazolone crystals were filtered off. After drying, the preparation was pure enough for subsequent cyclization. The yields and properties of the synthesized compounds are reported in Table 1. All of the pyrazolones from Table 1 are known except for 3-methyl-4-isopropyl-5-pyrazolone, and elemental analysis for C, H, and N gave good results. IR spectrum: 1598 cm^{-1}; UV spectrum: λ_{max} 230, 250 (log ε 3.56, 3.66).

General Method of Synthesis of 1,5-Tripyrazolylenes. Here 0.11 mole (16.9 g, 10.1 ml) of technical-grade $POCl_3$ was added to 0.1 mole of dry pyrazolone. Energetic liberation of HCl and weak heating immediately began. The reaction mixture was heated for 5 h at a bath temperature of 200°C. During heating, liberation of HCl slowed and crystals of tripyrazolylene began to distill. After cooling to 60-70°C, 50 ml of water was added to the reaction mixture by parts, and after the turbulent reaction ended, 20% NaOH solution was added to pH 8-9. The contents of the flask were then heated to boiling and cooled. The crystalline mass was separated and boiled for 30 min with 30 ml of water, cooled, and the crystalline mass of wet tripyrazolylene was filtered off and washed with water. It was then boiled with 20 ml of hexane, cooled, the crystals were filtered off and purified by crystallization, and the yields and constants are reported in Table 2.

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