SYNTHESIS AND SOME TRANSFORMATIONS OF 4H-PYRANO[3,2-d]PYRAZOLES

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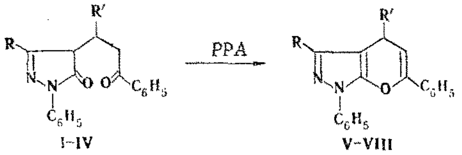
The ability of the amide carbonyl group of the pyrazolone ring to participate in the heterocyclization of oxopropyl-5-pyrazolones under the influence of polyphosphoric acid (PPA) or phosphorus polysulfide in dioxane with the formation of 4H-pyrano[3,2-d]pyrazole derivatives is demonstrated. Ionic hydrogenation of the pyranopyrazoles leads to 5,6-dihydropyrano[3,2-d]pyrazoles, while the action of phosphorus polysulfide in xylene leads to pyrazolo[5,4-b]thiapyrylium salts.

The bulk of the literature data on pyranopyrazoles pertains to the preparation and study of the pharmacological properties of substituted 6H-pyrano[3,2-d]pyrazol-6-ones, which are δ-lactones [1, 2], and 4H-pyrano-[3,2-d]pyrazol-4-ones [3]. The formation of 4H-pyrano[3,2-d]pyrazoles was observed in two cases: In the Diels–Alder reaction of 4-arylidene-4-pyrazolones [4] and in the alkaline cyclization of Michael adducts with 4-arylidene-5-pyrazolones [5, 6].

We have established a new reaction that leads to 4H-pyrano[3,2-d]pyrazole derivatives: We found that 4-(3-oxopropyl)pyrazol-4-ones (I-IV) are capable of undergoing cyclization to pyranopyrazoles V-VIII (Table 1) under conditions of heterogeneous catalysis by means of polyphosphoric acid (PPA):



I, V $R=CH_3$, $R'=C_6H_5$; II, VI $R=CH_3$, $R'=C_6H_4NO_2$-*m*; III, VII $R=R'=C_6H_5$; IV, VIII $R=C_6H_5$, $R'=C_6H_4NO_2$-*m*

The cyclization was accomplished in the absence of a solvent with excess PPA at 60-80°C. It is important to note that the use of alcohol or acetic acid as the solvent slows down the reaction significantly.

The IR spectra of V-VIII contain absorption bands of double bonds of the 4H-pyran ring at 1660 cm^{-1}. The absence of a second high-frequency absorption band at 1700-1730 cm^{-1}, which is characteristic for unsubstituted γ-pyran [7] and sym-octahydroxanthenes [8], can probably be explained by involvement of one double bond of pyran in the conjugation of the aromatic pyrazole ring. Doublets of 5-H vinyl protons at 5.06-5.57 ppm with spin–spin coupling constant (SSCC) 3.5-4.4 Hz and doublets of the adjacent 4-H protons at 4.42-5.12 ppm with SSCC 3.5-4.4 Hz are present in the PMR spectra of V-VIII. Singlets of protons of a methyl group in the spectra of pyranopyrazoles V and VI at 1.86 and 1.46 ppm, respectively, and multiplets of aromatic protons at 6.84-8.0 ppm complete the overall pattern of the PMR spectra of pyranopyrazoles V-VIII (Table 2).

The chief peculiarity of the chemical behavior of the pyranopyrazoles is their stability and inertness in salt-formation reactions with perchloric acid in acetic anhydride and in the Leuckart and Chichibabin reactions. The action of hydrogen sulfide in the presence of protic and aprotic acids, which leads to the corresponding thiopyrans in the case of pyrans that are not condensed with a pyrazole ring [9], has virtually no effect on 4H-pyrano-[3,2-d]pyrazoles V-VIII.

However, ionic hydrogenation, which does not require the participation of the double bond of the pyran ring that is involved in the conjugation of the pyrazole ring, was successful and led, in the case of pyranopyrazoles V and VII, to the formation of the corresponding 5,6-dihydropyrano[3,2-d]pyrazoles (IX, X), which were previously obtained by another method [10].

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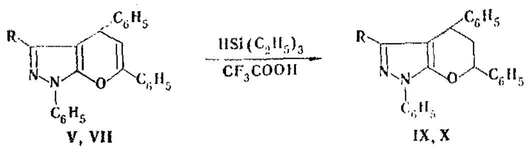
TABLE 1. Yields and Constants of 4H-Pyrano[3,2-d]pyrazoles

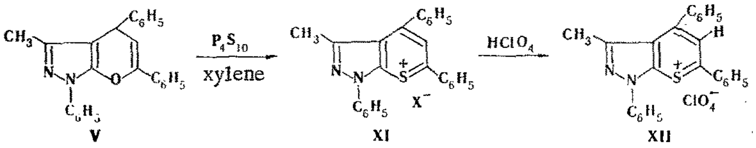
Compound	R	R′	R_f	mp,* °C	IR spectrum, cm⁻¹	Found, %			Empirical formula	Calculated, %			Yield, %
						C	H	N		C	H	N	
V	CH_3	C_6H_5	0,77	124—125	1650	82,5	6,0	7,7	$C_{25}H_{20}N_2O$	82,4	5,5	7,7	82
VI	CH_3	m-$NO_2C_6H_4$	0,57	168—169	1665	73,2	4,6	9,8	$C_{25}H_{19}N_3O_3$	73,3	4,7	10,3	65
VII	C_6H_5	C_6H_5	0,84	167—168	1660	84,5	5,1	6,8	$C_{30}H_{22}N_2O$	84,5	5,2	6,6	70
VIII	C_6H_5	m-$NO_2C_6H_4$	0,73	172—173	1660	75,9	4,4	8,9	$C_{30}H_{21}N_3O_3$	76,4	4,5	8,9	67
XV	CH_3	p-$OCH_3C_6H_4$	0,72	129—130	1665	78,8	5,7	6,8	$C_{26}H_{22}N_2O_2$	79,2	5,6	7,1	40
XVI	C_6H_5	p-$OCH_3C_6H_4$	0,77	176—177	1665	81,3	5,5	6,0	$C_{31}H_{24}N_2O_2$	81,6	5,3	8,9	56

*The compounds were recrystallized: V–VII and XV from ethanol, VIII from acetone, and XVI from ethanol–dioxane (1 :1).



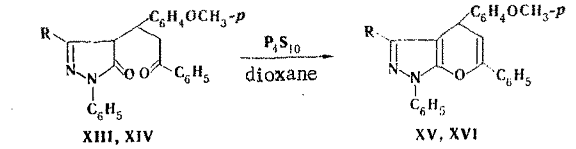
V, IX R=CH_3; VII, X R=C_6H_5

The action of phosphorus polysulfide in xylene on the pyranopyrazoles was studied. We found that a salt with a complex anion, which is a mixture of pyrazolo[5,4-b]thiapyrylium dihydrophosphate, dihydrothiophosphate, and dihydrodithiophosphate (XI), is formed in the case of pyran V. Salt XI was identified through corresponding perchlorate XII.



The PMR spectrum of XII contains, in addition to a singlet of a methyl group and a multiplet of aromatic protons, a singlet of a 3-H proton at weak field at 8.49 ppm. An intense absorption band of a thiapyrylium cation [11] is observed in the IR spectrum of XII at 1575 cm⁻¹. The spectral characteristics of XII, as well as their ability to undergo anion-exchange transformations, constitute evidence for its saltlike nature.

In a study of the action of phosphorus polysulfide in various solvents on oxopropylpyrazolones we noted that the formation of sulfur-containing products takes place through a step involving the formation of the corresponding pyrans. The corresponding 4H-pyrano[3,2-d]pyrazoles can be isolated in 40-60% yields when dioxane is used as the solvent. This method for the formation of pyranopyrazoles is particularly valuable for the preparation of pyrans XV and XVI, the synthesis of which by cyclization with PPA is difficult because of salt formation.



XIII, XV R=CH_3; XIV, XVI R=C_6H_5

It is apparent that the positive inductive effect of the methoxy group increases the hydride lability of the hydrogen atom in the 4 position of pyranopyrazoles XV and XVI, which leads to salt formation.*

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil and hexachlorobutadiene were recorded with a UR-20 spectrometer. The PMR spectra of the compounds were recorded with a Tesla BS-487 spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The purity of the products and the course of the reaction were monitored by thin-layer chromatography (TLC) on Silufol plates in an ethyl acetate – hexane system (12 :27) with development in iodine vapors. The preparation of 3-R-1-phenyl-4-(1-R′-3-phenyl-3-oxopropyl)-2-pyrazolin-5-ones I–IV, XIII, and XIV was described in [12].

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*The salt formation of pyrans XV and XVI will be reported separately.

TABLE 2. PMR Spectra of 4H-Pyrano-[3,2-d]pyrazoles (δ, ppm)

Compound	5-H	4-H	CH_3	Aromatic protons	$J_{4,5}$, Hz	Solvent
V	5,42	4,61	1,86	7,16—7,83	3,6	CCl_4
VI	5,06	4,42	1,46	6,84—7,67	3,5	$CDCl_3$
VII	5,59	4,97	—	7,16—7,95	4,4	$CDCl_3$
VIII	5,57	5,16	—	7,00—8,00	4,4	$CDCl_3$

3-R-1,6-Diphenyl-4-R'-4H-pyrano[3,2-d]pyrazoles (V-VIII) (Table 1). A mixture of 5 mmole of oxopropylpyrazolone I–IV and 20 g of PPA was heated on a water bath at 60-80°C for 1-2 h, after which the excess PPA was decomposed with water, and ether was added. The resulting layers were separated. The aqueous layer was extracted with ether, and the combined ether extracts were washed with water until the wash waters were neutral and dried with $MgSO_4$. The ether was removed by distillation at reduced pressure, and the residue crystallized.

3-R,1,4-5-Triphenyl-5,6-dihydropyrano[3,2-d]pyrazoles (IX, X). A 2.4-mmole sample of triethylsilane and 3 ml of a 3% solution of boron trifluoride etherate in absolute CF_3COOH were added to 2 mmole of starting pyranopyrazole V or VII, and the reaction mixture was heated to 80°C and allowed to remain at this temperature for 1-2 h until the starting pyranopyrazole vanished (monitoring by TLC). The volatile reaction products were evaporated, and the residue was triturated in ethanol and crystallized from ethanol to give 0.33 g (45%) of IX, with mp 178-179°C, and 0.50 g (58%) of X with mp 174.5-175°C [10].

5-Methyl-2,4,7-triphenylpyrazolo[5,4-b]thiapyrylium Perchlorate (XII). Carbon dioxide was bubbled into a solution of 3.64 g (10 mmole) of pyranopyrazole V in 45 ml of absolute xylene at 120°C, and 2.4 g (11 mmole) of phosphorus polysulfide was added with vigorous stirring in the course of an hour. Heating at 140°C was continued for 2.5-3 h, after which the hot xylene solution was separated from the precipitate in the flask by decantation, and the precipitate was triturated in ether and washed with ether to give 3.34 g (70%) of salt XI. A 1.5-ml (25.4 mmole) sample of 70% perchloric acid was added to a suspension of 1 g (2.05 mmole) of salt XI in 10 ml of glacial CH_3COOH. The solution became homogeneous and warmed up spontaneously. The precipitated crystals of perchlorate XII were crystallized from glacial CH_3COOH to give 0.45 g (47%) of a product with mp 216-216.5°C. IR spectrum: 1575 (thiapyrylium cation C=C); 1080-1110, 650 cm^{-1} (ClO_4^-). PMR spectrum (CD_3CN), δ: 8.49 (1H, s, 3-H), 2.31 (3H, s, CH_3), and 7.81 ppm (m). Found: C 62.6; H 4.0; Cl 7.4; N 5.8, S 6.7%. $C_{25}H_{19}ClN_2O_4S$. Calculated: C 62.7; H 4.0; Cl 7.4; N 5.8; S 6.7%.

3-R-1,6-Diphenyl-4-(p-methoxyphenyl)-4H-pyrano[3,2-d]pyrazoles (XV, XVI) (Table 1). A 2-g (9 mmole) sample of phosphorus polysulfide was added with stirring and bubbling in CO_2 at 100°C to a solution of 10 mmole of oxopropylpyrazolone XI or XIV in 100 ml of absolute dioxane. Heating was continued for 1 h until the starting oxopropylpyrazolone vanished (monitoring by TLC). The mixture was then diluted with water and ether, and the layers were separated. The aqueous layer was extracted with ether, and the combined ether extracts were washed with water until the wash waters were neutral and dried with $MgSO_4$. The solvent was removed by distillation at reduced pressure, and the residue was crystallized.

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