SYNTHESIS AND STUDY OF 2-(1-PYRAZOLYL)PURINE DERIVATIVES

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Derivatives of 2-(1-pyrazolyl)-4(3H)-pyrimidinone and 2-(1-pyrazolyl)purine were obtained, and their UV and IR spectra were studied. It is shown that alkyl derivatives of hypoxanthine and 6-chloro- and 6-ethoxypurine exist in the 7H form, which is stabilized by an intramolecular hydrogen bond.

The synthesis and study of new multidentate ligands are of great interest for the solution of the problem of competitive coordination [1]. The possibility of the synthesis of new bidentate ligands that are potentially capable of forming metal chelates stabilized by intramolecular hydrogen bonds formed by the N−H group of the ligand and the ligand anion [2, 3] starting from 6-amino-2-hydrazino-4(3H)-pyrimidinone (II) [4] is worthy of note.

Reaction of II with 5-ethylnonane-4,6-dione in refluxing dimethylformamide (DMF) gives pyrimidinone III, from which hypoxanthine V, 6-chloro- (VI) and 6-ethoxypurine (VII) are obtained by successive reactions (see the scheme below); the reaction of o-diamine IV with 5-ethylnonane-4,6-dione gives hypoxanthine VIII, the structure of which is confirmed by the results of elementary analysis and its UV spectrum, which is very close to the UV spectrum of hypoxanthine V (Table 1).

Synthesized purines V-VIII contain a hydrogen atom capable of prototropic tautomerism, but when there are substituents that are capable of forming hydrogen bonds in the 6 position of these compounds, stabilization due to the formation of intramolecular hydrogen bonds with 7H structures is most likely. The possibility of this sort of stabilization in the hypoxanthine anion has been previously pointed out [5].

The data from the IR spectra of dilute solutions of purines V-VIII in CCl_4 confirm their 7H structure. The IR spectra of hypoxanthines V and VIII contain an "amide I" band at 1690 cm^{-1} and bands of stretching vibrations of a pyrimidine ring N−H bond (3335 cm^{-1}) and an imidazole ring N−H bond (3130 for V and 3150 cm^{-1} for VIII). The latter band is shifted to the long-wave region due to an intramolecular hydrogen bond. As expected, the IR spectra of purines VI and VII contain only bands of stretching vibrations of imidazole ring N−H bonds at 3135 cm^{-1} for VI and 3130 cm^{-1} for VII, which are also shifted to the long-wave region due to intramolecular hydrogen bonds.

EXPERIMENTAL

The IR spectra of V-VIII were recorded with a UR-20 spectrometer; $5 \cdot 10^{-3}$ M solutions of the purines in CCl_4 in NaCl cuvettes (d 1 mm) were investigated over the 1200-1800 cm^{-1} range, and $1 \cdot 10^{-4}$ M solutions of purines V-VIII in CCl_4 in NaCl civettes (d 50 mm) were investigated over the 2800-3600 cm^{-1} range. The UV spectra of $1 \cdot 10^{-4}$ to $5 \cdot 10^{-5}$ M solutions of the synthesized compounds in ethanol and 1 N ethanolic KOH were recorded with a Hitachi EPS-3T spectrophotometer in quartz cuvettes (d 10 mm). The maxima of the absorption bands are presented in Table 1.

6-Amino-2-nitroamino- (I) and 6-Amino-2-hydrazino-4(3H)-pyrimidinone (II). These compounds were obtained by the method in [4].

6-Amino-2-(4-ethyl-3,5-di-n-propyl-1-pyrazolyl)-4(3H)-pyrimidinone (III). A mixture of 19.0 g of II and 19.0 g of 5-ethylnonane-4,6-dione in 150 ml of DMF was refluxed for 8 h, after which 120 ml of DMF was removed by distillation, and 200 ml of water was added. The resulting precipitate was removed by filtration, washed on the filter with water, and dried in a vacuum desiccator to give 25.7 g of III.

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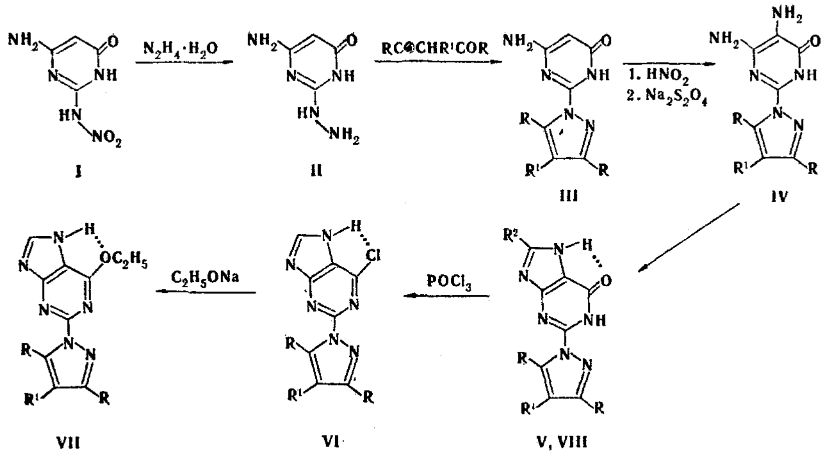
TABLE 1. Results of Analyses and UV Spectra of the Synthesized Compounds

Compound	mp, °C	Found, %			Empirical formula	Calc., %			λ_{max}, nm (lg ε)		Yield, %
		C	H	N		C	H	N	in ethanol	in 1 N ethanolic KOH	
I	270 (dec.)[a]	28,1	3,3	40,9	$C_4H_5N_5O_3$	28,1	3,0	40,9	232 (3,93) 256 (4,07)	262 (3,28) 300 (3,06)	93,6
II	310 (dec.)[a]	34,4	5,2	49,6	$C_4H_7N_5O$	34,0	5,0	49,6	275 (3,51)	265 (3,87)	41,0
III	162,4—163,4[b]	61,9	7,8	24,5	$C_{15}H_{23}N_5O$	62,3	8,0	24,2	246 (3,89) 294 (3,54)	265 (3,63)	90,0
IV	146—148[c]	59,3	7,6	27,7	$C_{15}H_{24}N_6O$	59,2	7,9	27,7	245 (3,93) 286 (3,76) 326 (3,72)	292 (3,53) 350 (3,18)	87,8
V	251—252[b]	61,3	7,0	26,5	$C_{16}H_{22}N_6O$	61,1	7,1	26,7	266 (4,14) 293 (4,20)	269 (4,05)	65,0
VI	192,5—193,2[d]	57,5	6,2	25,4	$C_{16}H_{21}N_6Cl$	57,7	6,3	25,3	245 (4,06) 265 (4,06) 285 (3,78)	250 (4,37) 280 (3,98)	80,5
VII	138,5—139,5[d]	63.2	7,5	24.8	$C_{18}H_{26}N_6O$	63,1	7,7	24,5	265 (4,09)	245 (4,21) 280 (4,25)	65,0
VIII	217,3—218,3[d]	64,3	7,7	23,5	$C_{19}H_{28}N_6O$	64,0	7,9	23,6	265 (4,26) 296 (4,20)	274 (4,16)	42,0

[a] From methanol. [b] From ethanol. [c] From ethanol–heptane. [d] From heptane.



III, IV, VI, VII $R = n\text{-}C_3H_7$, $R^1 = C_2H_5$; V $R = n\text{-}C_3H_7$, $R^1 = C_2H_5$, $R^2 = H$; VIII $R = n\text{-}C_3H_7$, $R^1 = C_2H_5$, $R^2 = n\text{-}C_3H_7$

5,6-Diamino-(4-ethyl-3,5-di-n-propyl-1-pyrazolyl)-4(3H)-pyrimidinone (IV). A solution of 0.7 g of sodium nitrite in 15 ml of water was added with stirring to a solution of 2.5 g of III in 10 ml of acetic acid, and 100 ml of water was added to the resulting green suspension. The solid material was removed by filtration, washed on the filter with water, and suspended in 50 ml of water. Sodium bicarbonate was added to the suspension up to pH 14, 20 ml of ethanol was added, and the mixture was treated with sodium hydrosulfite until it became colorless. It was then acidified to pH 5 with 50% acetic acid, and the precipitate was removed by filtration, washed on the filter with water, and dried in a vacuum desiccator over NaOH to give 2.3 g of IV.

2-(4-Ethyl-3,5-di-n-propyl-1-pyrazolyl)hypoxanthine (V). A 3-g sample of IV was refluxed in 5 ml of formic acid for 2 h, after which the mixture was poured into 100 ml of water, and the precipitate was removed by filtration, washed on the filter with water, and dried in a vacuum desiccator over NaOH to give 2.0 g of V.

6-Chloro-2-(4-ethyl-3,5-di-n-propyl-1-pyrazolyl)purine (VI). A mixture of 0.56 g of V, 3.5 ml of phosphorus oxychloride, and 0.3 ml of triethylamine was refluxed for 2 h, after which it was poured over ice, and the mixture was neutralized to pH 7 with 20% potassium hydroxide solution. The precipitate was removed by filtration, washed on the filter with water, and dried to give 0.48 g of VI.

6-Ethoxy-2-(4-ethyl-3,5-di-n-propyl-1-pyrazolyl)purine (VII). A 0.47-g sample of VI was added to a solution of sodium ethoxide (from 0.5 g of sodium metal in 10 ml of absolute ethanol), and the mixture was refluxed for 1 h. It was then poured into water, and the mixture was neutralized with acetic acid. The precipitate was removed by filtration, washed on the filter with water, and dried to give 0.3 g of VII.

2-(4-Ethyl-3,5-di-n-propyl-1-pyrazolyl)-8-n-propylhypoxanthine (VIII). A mixture of 6.1 g of IV, 3.2 g of 5-ethylnonane-4,6-dione, and 50 ml of DMF was refluxed for 2 h, after which it was poured into 300 ml of water. The precipitate was removed by filtration, washed on the filter with water, and dried to give 3.0 g of VIII.

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α-OXIDES IN REACTION WITH N – H ACIDS OF THE HETEROCYCLIC SERIES

IV.* ALKYLATION OF 1-METHYL-3-NITRO-1,2,4-TRIAZOL-5-ONE WITH OLEFIN OXIDES

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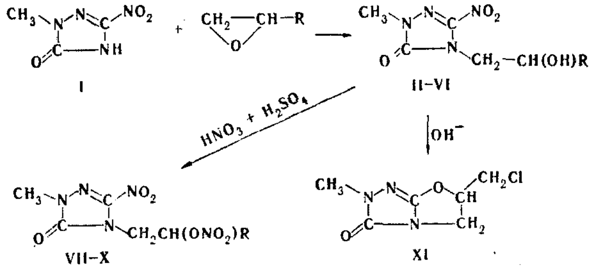
Anumber of 1-methyl-4-(2-hydroxyalkyl)-3-nitro-1,2,4-triazol-5-ones and their derivatives were obtained by reaction of 1-methyl-3-nitro1,2,4-triazol-5-one with α-epoxides. The fact of intramolecular nucleophilic substitution of the nitro group in hydroxy derivatives of 3-nitro-1,2,4-triazol-5-one with cyclization to 2-methyl-3-oxo-5,6-dihydrooxazolo[3,2-b]-1,2,4-triazoline was established.

The available data on the alkylation of 3-nitro-1,2,4-triazol-5-one are extremely contradictory. According to the data in [2], methylation with dimethyl sulfate in alkaline media leads to 1,4-dimethyl-3-nitro-1,2,4-triazol-5-one, whereas it has been reported [3] that exclusively monosubstitution products are formed, which Chipen and Bokaldere [3] explain by rapid hydrolysis of the alkylating agent and the relatively low reactivity of the secondary reaction center.

We have established that 1-methyl-3-nitro-1,2,4-triazol-5-one (I) is alkylated successfully at the second center (N_4) in aqueous media in the presence of bases when α-epoxides, which are relatively stable with respect to hydrolysis, are used. The alkylation conditions are similar to the conditions previously described for 3-nitro-5-bromo-1,2,4-triazole [4], the acidity of which is close to that of triazolone I (pK_a 3.05 and 3.67, respectively, determined potentiometricallv).



II, VII R=H; III, VIII R=CH_3; IV, IX R=CH_2Cl; V, X R=CH_2ONO_2; VI R=CH_2OH

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*See [1] for communication III.

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