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PROTROPIC TAUTOMERISM AND CONFORMATIONAL ISOMERISM OF 4-(N-ARYLAMINO)-2-(1H-PYRAZOL-1-YL)PYRIMIDINES

A. V. Ivashchenko, O. N. Garicheva, L. V. Shmelev, and Yu. S. Ryabokobylko

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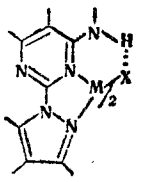
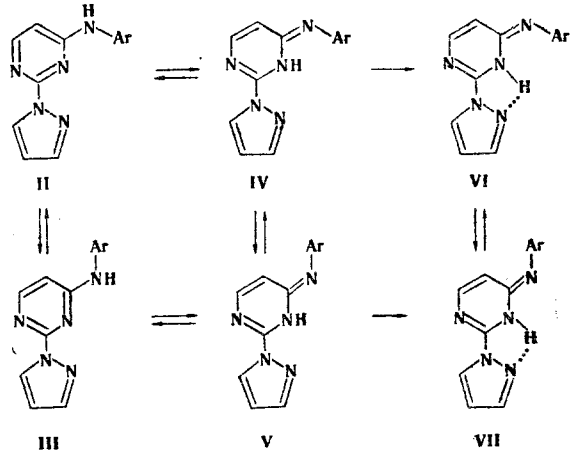
New 4-(N-arylamino)-2-(1H-pyrazol-1-yl)pyrimidine derivatives were synthesized, and the UV, IR, and PMR spectra of solutions of them in $CHCl_3$, CCl_4, and d_6-DMSO were studied. The questions of intermolecular association and conformational isomerism are discussed.

4-(N-Arylamino)-2-(1H-pyrazol-1-yl)pyrimidines are of interest as bidentate ligands that are potentially capable of reacting with transition metal salts to give complexes that are stabilized by metal chelates that include an intramolecular hydrogen bond (I) [1].



I

However, the structure of this series of compounds and their behavior in solutions have not been discussed. In addition, conformational isomerism and prototropic tautomerism (II-



II IV VI

III V VII

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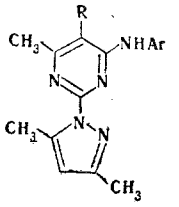
TABLE 1. Results of Analysis of the Synthesized 4-Arylamino-2-(1H-pyrazol-1-yl)pyrimidines

Compound	R	Ar	mp, °C (from ethanol)	Found, %			Empirical formula	Calc., %			% Calc.,
				C	H	N		C	H	N	
VIII	H	C_6H_5	146.3—147.3	68.9	6.3	24.9	$C_{16}H_{17}N_5$	68.8	6.1	25.1	62
IX	C_2H_5	C_6H_5	183.0—184.0	70.1	6.8	23.0	$C_{18}H_{21}N_5$	70.3	6.9	22.8	60
X	H	p-$C_6H_4C_4H_9$	128.5—129.5	71.8	7.3	20.9	$C_{20}H_{25}N_5$	71.6	7.5	20.9	58
XI	C_2H_5	p-$C_6H_4C_4H_9$	176.5—177.5	72.5	8.2	19.5	$C_{22}H_{29}N_5$	72.7	8.0	19.3	70

VII) are possible for 4-(N-arylamino)-2-(1H-pyrazol-1-yl)pyrimidines; stabilization of the imino form by an intramolecular hydrogen bond (VI, VII) is possible in the case of prototropic tautomerism.

We selected 4-(N-anilino)- (VIII, IX) and 4-[N-[p-(n-butyl)anilino]]-2-(3,5-dimethyl-1H-pyrazol-1-yl)-5-R-6-methylpyrimidines (X, XI) (Table 1), which were obtained by the method



VIII–XI

in [2, 3], as the subjects of this study. We described the synthesis of 4-[N-[p-(n-butyl)anilino]]-5-ethyl-2-(4-ethyl-3,5-dipropyl-1H-pyrazol-1-yl)-6-methylpyrimidine (XII) in [3].

In the case of an equilibrium between conformational isomers II and III, one should have expected, as in [4-8], the presence of two absorption bands in the IR spectra in the region of the stretching vibrations of the N—H bond, whereas one band should have been expected in the case of the existence of one of the conformers (II or III) or stabilization of the imino form (IV, V); with allowance for the data in [8, 9], one may assume *a priori* that the frequency of the NH stretching vibrations will increase in the II-VII series.

According to the data from the IR spectra of dilute solutions in tetrachloromethane, VIII-XII exist in the free state and in the form of associates. Thus, e.g., the spectrum of a $5 \cdot 10^{-3}$ M solution of 4-[N-[p-(n-butyl)anilino]]-6-methyl-2-(3,5-dimethyl-1H-pyrazol-1-yl)-pyrimidine (X) in the region of the stretching vibrations of N—H bonds contains broad low-intensity bands at 3300 and 3360 cm^{-1} due to intermolecular associates and two bands at 3410 and 3441 cm^{-1} of stretching vibrations of free N—H bonds (Fig. 1).

The data obtained (Fig. 1 and Table 1) constitute evidence that in dilute solutions in trichloromethane and tetrachloromethane VIII and X exist primarily in the form of two conformers (II and III) or two tautomers (II and IV or III and V). However, considering the fact that the UV spectra of VIII and X are very similar to the UV spectra of 2-(3,5-dimethyl-1H-pyrazol-1-yl)-6-methyl-4-(N-piperidyl)pyrimidine (XIII), for which tautomerism is impossible (Fig. 2), and are similar to the spectra of 2-(N-anilino)pyridines, which also exist in the amino form [8], it may be concluded that VIII and X exist in solution in the form of two conformers II and III [4, 9].

The band at the lower frequency is due to conformer III, and its shift to the low-frequency region as compared with the ν(2NH) band of conformer II is due to the formation of a weak intramolecular hydrogen bond between the NH group and, according to [4], the nitrogen atom of the pyrimidine ring. Within the limits of a change in the concentration from $5 \cdot 10^{-4}$ to $5 \cdot 10^{-3}$ M (CCl_4) the ratios of the molar extinction coefficients of the bands of the stretching vibrations of the NH bonds of conformers II and III remain virtually unchanged, and this indicates a constant conformational composition and predominance of conformer III.

In the same region of the IR spectrum IX, XI, and XII have only one band of stretching vibrations of a free NH group at 3461-3463 cm^{-1} (Fig. 1 and Table 2), and this constitutes evidence for the existence of these compounds in solution only in the form of conformer II.

TABLE 2. IR Spectra of Solutions of the Synthesized 4-(N-Arylamino)-2-(1H-pyrazol-1-yl)pyrimidines

Compound	Solvent	Concn., M	ν (ε), cm^{-1}		
			1NH (ε_1)	2NH (ε_2)	$\varepsilon_1/\varepsilon_2$
VIII	$CHCl_3$	$5 \cdot 10^{-3}$	3403 (164)	3432 (56)	2.92
VIII	CCl_4	$5 \cdot 10^{-3}$	3408 (96)	3441 (38)	2,52
IX	CCl_4	$7 \cdot 10^{-4}$		3463 (160)	
X	$CHCl_3$	$5 \cdot 10^{-3}$	3405 (124)	3432 (42)	2.95
X	CCl_4	$5 \cdot 10^{-3}$	3410 (96)	3441 (38)	2.52
X	CCl_4	$5 \cdot 10^{-4}$	3410 (180)	3441 (72)	2,44
XI	CCl_4	$7 \cdot 10^{-4}$		3461 (142)	
XII	CCl_4	$7 \cdot 10^{-5}$		3462 (165)	

The stabilization of conformer II in this case is evidently explained by the steric factor, i.e., the ethyl substituent in the 5 position of the pyrimidine ring of IX, XI, and XII hinders the formation of conformer III. The higher frequency (3462 cm^{-1}) of the band of the stretching vibrations of the N–H bond in the IR spectra of IX, XI, and XII as compared with the spectra of VIII and X (3441 cm^{-1}) is evidently associated with the steric effect of this substituent, since its electronic effect would, on the contrary, lead to a decrease in the frequency [10].

The IR spectra of more concentrated solutions offer little information for the determination of the conformational composition because of the formation of intermolecular associates. We therefore used PMR spectroscopy for the study of the conformational isomerism and association of VII-XII in more concentrated solutions.

Data on the concentration dependence of the chemical shift of the proton of the amino group show that the formation of intermolecular associates in the case of VIII and X occurs at concentrations of up to 10^{-3} M, whereas IX and XI are virtually completely dissociated at a concentration of $2.5 \cdot 10^{-3}$ M, which indicates weakening of the intermolecular hydrogen bond. The weakening of the intermolecular hydrogen bond when an ethyl substituent is introduced in the 5 position is apparently due to steric factors, which confirms the existence of IX and XI in the form of conformer II, since such steric hindrance to the formation of an intermolecular hydrogen bond would be absent in conformer III.

Judging from the change in the chemical shifts of the methyl groups upon dilution, the formation of an N–H...N intermolecular hydrogen bond has the greatest effect on the 6-CH_3 group of pyrimidine and the 3-CH_3 group of the pyrazole ring. This may indicate participation of the N_1 or N_3 atom of the pyrimidine ring and the N_2 atom of the pyrazole ring in the intermolecular hydrogen bond. The pronounced decrease in the stability of the associates when an n-propyl group (which is bulkier than the methyl group) is introduced in the 3 position of the pyrazole ring in XII, which, according to the PMR data (Fig. 3), dissociates virtually completely at a concentration of $7 \cdot 10^{-3}$ M, evidently indicates the primary participation of the N_2 atom of the pyrazole ring in the intermolecular hydrogen bond. The difference in the strength of the association and in the effect on the chemical shift of the 6-CH_3 group in the spectra of VIII-XI, on the one hand, and in the spectrum of 2,4-bis[N-[p-(n-butyl)anilino]]-6-methylpyrimidine (XIV) [11], on the other, is in agreement with this conclusion. In the case of XIV, in which the basicity of the pyrimidine nitrogen atoms is close to that for the investigated VIII-XI, over the same concentration range (10^{-3}–10^{-1} M) the range of change in the chemical shifts of the NH protons is $\leqslant$0.9 ppm, and virtually complete dissociation is observed at a concentration of $5 \cdot 10^{-3}$ M, while the chemical shift of the 6-CH_3 group remains virtually unchanged.

The ortho and meta protons (with respect to the amino group) of the phenyl ring of IX and XI are identically weakly deshielded as the concentration decreases (Fig. 4), whereas in the case of VIII and X one observes appreciable shielding of the ortho protons and deshielding of the meta protons of the phenyl ring (Fig. 4). This difference is evidently associated with a change in the conformational composition of VIII and X when the intermolecular hydrogen bond is cleaved, since in the case of IX and XI in the free and associated states the conformational composition is constant because of steric hindrance to the formation of conformer III.

Steric hindrance in the associates of conformer II is evidently the reason for the significant (0.3-0.4 ppm) changes in the chemical shift of the 6-CH_3 group in the case of cleavage

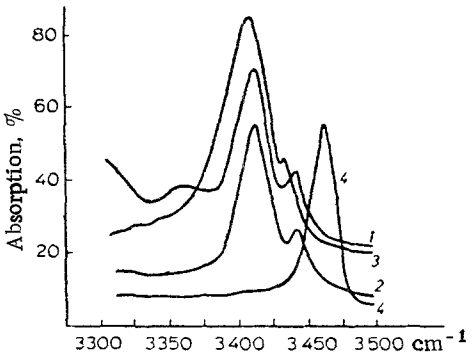


Fig. 1

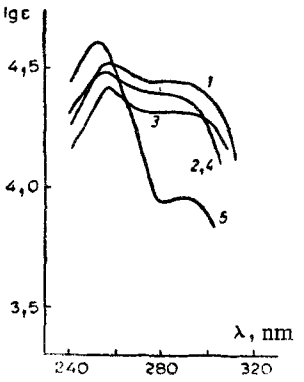


Fig. 2

Fig. 1. Bands of the stretching vibrations of the N—H bonds of X in CCl_4: 1) $5 \cdot 10^{-3}$ M; 2) $5 \cdot 10^{-4}$ M; in $CHCl_3$: 3) $5 \cdot 10^{-3}$ M; of XI in CCl_4: 4) $7 \cdot 10^{-4}$ M.

Fig. 2. UV spectra of $(1.5\text{-}2.2) \cdot 10^{-5}$ M solutions of 2-(1H-pyrazol-1-yl)pyrimidines in ethanol: 1) VIII; 2) IX; 3) X; 4) XI; 5) XIII.

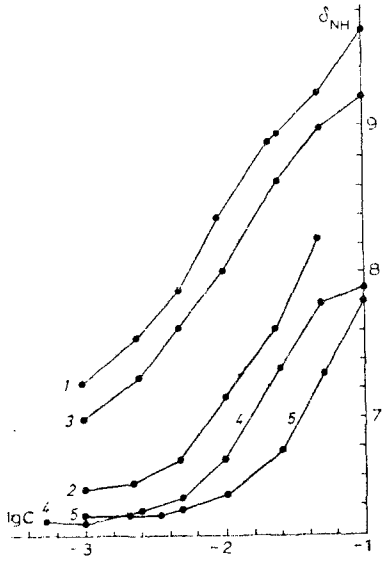


Fig. 3

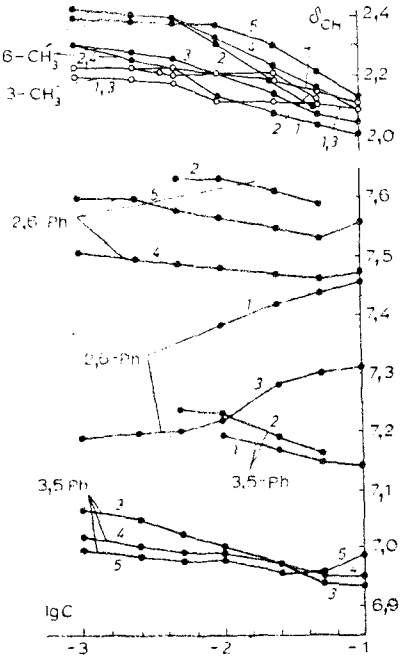


Fig. 4

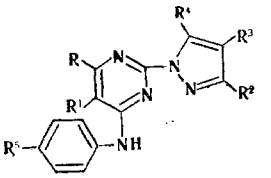
Fig. 3. Dependence of the chemical shift of the proton of the NH group of 4-(N-arylamino)-2-(1H-pyrazol-1-yl)pyrimidines in CCl_4 on the concentration: 1) VIII; 2) IX; 3) X; 4) XI; 5) XII.

Fig. 4. Dependence of the chemical shifts of the protons of the methyl groups and the phenyl protons of 4-(N-arylamino)-2-(1H-pyrazol-1-yl)pyrimidines in CCl_4 on the concentration: 1) VIII; 2) IX; 3) X; 4) XI; 5) XII.

of the intermolecular hydrogen bonds for both IX, XI, and XII, which exist exclusively in the form of conformer II, and for VIII and X, the associates of which exist primarily in the form of conformer II.

The spectral characteristics of VIII-XII in the associated state in concentrated solutions of low-polarity organic solvents, as expected, differ little (Table 3) from their characteristics in solutions in dimethyl sulfoxide (DMSO) (strong intermolecular interaction of VIII-XII with the solvent occurs in the latter case).

TABLE 3. Chemical Shifts of the Protons in the PMR Spectra of 4-(N-Arylamino)-2-(1H-pyrazol-1-yl)pyrimidines (VIII-XII)



Compound	Solvent	Concn., M	CH_3, s	R^1			R^2, CH_3, s	R^3, H, s	R^4, CH_3, s	NH, s	m	m	R^5				
				H, s	1-CH_3, t	2-CH_2, q					2,6-H_2,	3,5-H_2,	H, m	1-CH_3, t	2-CH_2, m	3-CH_2, m	4-CH_2, t
VIII	CCl_4	0,1	1,99	6.20			2,10	5,83	2,59	9,66	7,49	7,14	6.88				
	CCl_4	0,001	2,32	6.31			2.21	5,80	2,57	7.25							
	DMSO d_6	0,16	2,33	6,51			2,18	6,01	2.48	9,63	7,62	7,30	7.00				
IX	CCl_4	0,05	2.09		1,01	2.47	2.11	5,76	2,42	8.23	7,59	7,16	6,90				
	CCl_4	0,001	2,45		1.29	2,65	2,24	5,79	2,50	6.52							
	DMSO d_6	0,15	2,31		1,13	2,72	2,14	5,94	2,38	8,58	7,61	7.29	7,03				
X	CCl_4	0,1	2,05	6,17			2,12	5.81	2,58	9.21	7,31	6.93		0,92	1,32	1,48	2,51
	CCl_4	0,001	2,32	6,26			2,22	5,80	2,58	7,00	7,19	7,08					
	DMSO d_6	0,1	2,31	6,47			2,17	6,01	2,47	9,53	7,48	7,11		0,89	1,15	1,60	2,53
XI	CCl_4	0,1	2,09		0,99	2,49	2,12	5,75	2,41	8,05	7,47	6,95		0,92	1,33	1,55	2,54
	CCl_4	0,001	2,40		1,25	2,60	2,33	5,74	2,44	6,30	7,51	7,02					
	DMSO d_6	0,10	2,25		1,10	2,69	2,11	5,91	2,36	8,49	7,45	7,07		0,87	1,15	1,60	2,53
XII	CCl_4	0,1	2,13							7,86	7,55	6,97		0,92	1,33	1,55	2,51
	CCl_4	0,001	2,41							6,33	7,60	7,00					
	DMSO d_6	0,1	2,13							8,48	7,57	7,08		0,96	1,15	1,60	2,55

EXPERIMENTAL

The IR spectra of $5 \cdot 10^{-3}$ M solutions of the compounds in $CHCl_3$ and CCl_4 in quartz cuvettes with d = 1 cm and of $(5-7) \cdot 10^{-4}$ M solutions in CCl_4 in quartz cuvettes with d = 5 cm were recorded with a UR-20 spectrometer. The UV spectra of $5 \cdot 10^{-4}$ M solutions in ethanol were recorded with a Hitachi EPS-3T spectrophotometer in quartz cuvettes with d = 1 cm. The PMR spectra of $1 \cdot 10^{-3}$-1.0 M solutions of the compounds in $CHCl_3$, CCl_4, and d_6-DMSO were recorded with a Varian XL-100-12 spectrometer (100 MHz) with tetramethylsilane as the internal standard.

The 4-arylamino-2-(1H-pyrazol-1-yl)pyrimidines (VIII-X) were obtained from the corresponding 4-chloro-2-(1H-pyrazol-1-yl)pyrimidines [2, 3] by a method similar to that in [3]. The yields and the results of analysis are presented in Table 1.

2-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-methyl-4-(N-piperidyl)pyrimidine (XIII) was obtained by the method in [2].

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