SYNTHESIS AND STUDY OF 2,4-DIAMINO- AND 2-AMINO-4-(1H-PYRAZOL-1-YL)PYRIMIDINE DERIVATIVES

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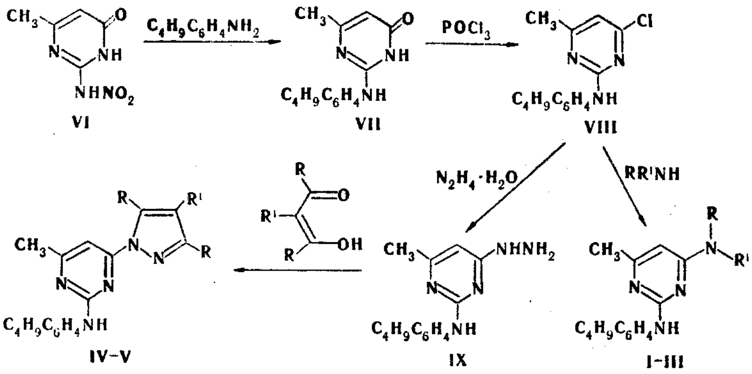
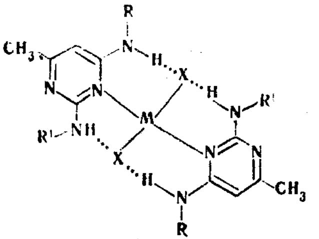
New 2,4-diamino- and 2-amino-4-(1H-pyrazol-1-yl)pyrimidine derivatives, which are of interest as mono- and bidentate ligands, were synthesized. From an examination of the UV, IR, and PMR spectra of the synthesized compounds it was concluded that they exist in the "amino" form.

Continuing our research on the synthesis of heteroaromatic ligands that contain a pyrimidine ring [1] and the study of their complexes [2] we synthesized new ligands in the series of derivatives of 2,4-diamino- (I-III) and 2-amino-4-(1H-pyrazol-1-yl)pyrimidine (IV, V). Derivatives I-III and IV, Vwere obtained by known transformations [1, 3] for pyrimidine derivatives via the scheme

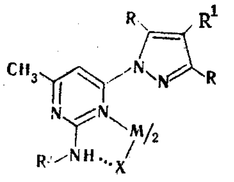


I R—R¹=(CH₂)₅; II R=*n*-C₄H₉, R¹=H; III R=*p*-*n*-C₄H₉C₆H₄, R¹=H; IV R=*n*-C₃H₇, R¹=C₂H₅; V R=CH₃, R¹=H

Compounds II-V are of special interest as ligands, since their "amino" form is potentially capable of reacting with salts of transition metals to give complexes that are stabilized by additional chelate rings that include intramolecular hydrogen bonds (X, XI) [4].



X



XI

X, XI M — metal X — anion R, R¹, R² — alkyl, aryl, or alkylaryl

However, it is known [5] that heteroaromatic compounds that contain an amidine grouping with a labile hydrogen atom are capable of prototropic tautomerism. In this connection, to ascertain the structures of the synthesized compounds we studied their IR, UV, and PMR spectra. The IR spectra of dilute solutions of pyrimidine derivatives I-IX in CCl_4 (Table 2) contain an intense absorption band of the stretching vibrations of an unassociated NH bond at 3434-3442 cm^{-1}, which is characteristic for 2-(N-arylamino)pyrimidines [6].

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C[a]	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
I	83,7—85,7	74,2	8,8	17,3	$C_{20}H_{28}N_4$	74,0	8,7	17,3	46
II[b]	143,5—144,5	55,1	6,8	13,7	$C_{19}H_{19}N_4ClO_4$[c]	55,3	7,1	13,6	48
III	225,0—226,0	77,4	8,2	14,3	$C_{25}H_{32}N_4$	77,3	8,3	14,4	50
IV	60,5—61,5	74,1	8,7	16,7	$C_{26}H_{37}N_5$	74,4	8,9	16,7	44
IV[b]	124,5—125,5	59,8	7,2	13,3	$C_{26}H_{38}N_5ClO_4$[d]	60,1	7,4	13,5	80
V	85,5—87,0	72,0	7,3	21,0	$C_{20}H_{25}N_5$	71,6	7,5	20,9	79
VII	195,5—196,0	70,2	7,3	16,4	$C_{15}H_{19}N_3O$	70,0	7,4	16,5	64
VIII	51,8—52,3	65,3	6,2	15,1	$C_{15}H_{18}N_3Cl$[e]	65,3	6,6	15,2	61
IX	155,5—156,5	66,2	7,7	25,7	$C_{15}H_{21}N_5$	66,4	7,8	25,8	99

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[a] The compounds were recrystallized: I from petroleum ether; II, VII, and IX from ethanol; III from toluene; IV from hexane; and IV (perchlorate), V, and VIII from heptane. [b] Perchlorate. [c] Found: Cl 8.3%. Calculated: Cl 8.6%. [d] Found: Cl 6.4%. Calculated: Cl 6.8%. [e] Found: Cl 13.0%. Calculated: Cl 12.9%.

TABLE 2. UV and IR Spectra of I-IX

Compound	UV spectra of solutions, λ_{max} (log ε), nm		IR spectra (in CCl_4), ν_{NH}, cm^{-1} (ε)
	in ethanol	in aqueous-ethanolic 1 M HCl	
I	272 (4,45), 290[a] (4,21)	260 (4,45)	3440 (170)
II	272 (4,61), 290[a] (4,43)	260 (4,47)	3440 (250)
III	275 (4,53), 305[a] (4,25)	270 (4,28) 305 (4,27)	3442 (209)
IV	278 (3,84)	297 (3,92)	3440 (175)
V	270 (4,79)	290 (4,49)	3400—3010
VII[b]	260 (4,46), 286[a] (4,39)	260 (4,54)	3434 (238)
VIII	278 (4,51)	260 (4,30)	3442 (300)
IX	271 (4,54)	254 (4,48)	3390 (53)

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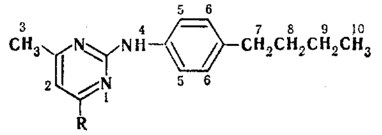
[a] Shoulder. [b] Spectrum in a 0.2 N solution of KOH in ethanol, λ_{max}(log ε): 295 (4.34) and 303 nm (4.38).

TABLE 3. PMR Spectra of the Synthesized I-IX



Compound	Concn. and solvent	1	2	3	4	5	6	7	8	9	10
I	0,1 M CCl_4		5,73s	2,17s	6,98s	7,37d	6,93d	2,52t	1,70—	1,15m	0,91t
II	0,2 M $CDCl_3$		5,62s	2,21s	7,13s	7,47d	7,02d	2,55t	1,70—	1,15m	0,92t
	0,1 M CCl_4		5,53s	2,16s	7,05s	7,40d	6,93d	2,53t	1,67—	1,18m	0,95t
	0,2 M $CDCl_3$[a]	10,25s	6,03s	2,22s	8,36s	7,42d	7,09d	2,57t	1,53m	1,33m	0,90t
		10,64s	5,87s	2,35s							
III	0,2 M $CDCl_3$		6,47s	2,19s	9,74s	7,37d	7,00d	2,57t	1,51m	1,35m	0,92t
IV	0,1 M CCl_4		6,99s	2,36s	6,95s	7,33d	7,08d	2,56t	1,80—	1,17m	0,93t
	0,1 M CCl_4[a]	11,23 br	7,34s	2,51s	9,23s	7,25d	7,05d	2,51t	1,80—	1,17m	0,94t
V	0,1 M CCl_4		7,14s	2,36s	7,14s	7,34d	6,98d	2,54t	1,54m	1,34m	0,92t
VII	0,1 M CCl_4	11,04 br	5,50s	2,09s	9,29s	7,45d	7,00d	2,56t	1,54m	1,38m	0,92t
VIII	0,1 M CCl_4		6,49s	2,33s	7,05s	7,40d	7,00d	2,55t	1,52m	1,35m	0,93t
IX	0,2 M DMSO-d_6		5,97s	2,14s	8,73s	7,66d	6,97d	2,47t	1,44m	1,28m	0,88t

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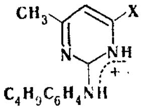
[a] This is the spectrum of the perchlorate.

Only one intense band at 3440 cm^{-1}, which has increased intensity (ε 250) as compared with the intensity of the analogous bands (ε 170-210) in the spectra of I, IV, and V, is observed in the IR spectrum of II in the region of the stretching vibrations of the NH bond. This provides a basis for the assumption that the band at 3440 cm^{-1} in the spectrum of II is the sum of the bands of the stretching vibrations of the NH bonds of secondary amino groups [the high-intensity ν_{N-H} band of the p-n-butylanilino group and the low-intensity ν_{N-H} band of the n-butylamino group or the 4(3H)-butylimino group], while the closeness of its UV spectrum (Table 2) to the spectrum of I, which is a "fixed" tautomer, convincingly confirms the 2,4-diamino structure of II. The IR and UV spectra of IX and its "fixed" tautomers IV and V, which attest to a "2-amino-4-hydrazino" structure for IX, can be similarly interpreted.

The IR spectrum of a dilute solution of VII in CCl_4 contains a broad absorption band at 3010-3440 cm^{-1}, which has a fine structure; this fine structure is due to the stretching vibrations of associated N–H bonds. A number of maxima (3440, 3313, 3305, 3260, 3210, 3190, 3160, etc.) can be isolated on this band. The first two bands evidently correspond to the stretching vibrations of the N–H bonds of, respectively, the p-n-butylamino and amido groups.

The UV spectrum of an alcohol solution of VII contains a band at 260 nm and a shoulder at 290 nm. A bathochromic shift of these bands, associated with a change in the conjugation chain during formation of the anion, is observed in the spectrum of an alkaline solution (Table 2), while the shoulder at 290 nm vanishes in the spectrum of a solution of VII in 1 M aqueous alcoholic HCl; however, the band at 260 nm remains unchanged. Considering the fact that the UV spectrum of a solution of 2-[N-(p-n-butylanilino)]-4-chloro-6-methylpyrimidine in 1 M aqueous alcoholic HCl also contains one absorption band at 260 nm, it may be assumed that the protonation of VII takes place at the carbonyl group with the formation of a cation that has the same chain of conjugation of the electrons as the cation of VIII, for which one may assume structure XII. The protonated forms of I, II, and IX evidently have a similar structure, since their UV spectra also have one absorption band that is shifted hypsochromically as compared with the spectra of their neutral molecules (Table 2).



XII

X = Cl, OH, NHC_4H_9, $N(CH_2)_5$, $NHNH_2$

The PMR spectra of the synthesized compounds contain signals of the 5-H proton of the pyrimidine ring at 5.50-7.34, of the protons of the $6-CH_3$ group at 2.09-2.51, of the proton of the 2-NH group at 6.95-9.74, of the 2,6- and 3,5-protons of the 1,4-phenylene ring at, respectively, 7.25-7.66 and 6.93-7.00, of the protons of the butyl group at 0.88-0.95 ($1-CH_3$), 1.15-1.38 ($2-CH_2$), 1.44-1.70 ($3-CH_2$), and 2.47-2.57 ppm ($4-CH_2$), as well as signals of the protons of the substituents in the 4 position of the pyrimidine ring. The PMR spectra are in good agreement with the data from IR and UV spectroscopy and confirm the structures of the synthesized compounds.

EXPERIMENTAL

The IR spectra of $1\cdot10^{-3}$-$1\cdot10^{-4}$ M solutions of the compounds in CCl_4 at 2800-3600 cm^{-1} were recorded with a UR-20 spectrometer (quartz cuvettes with d 50 mm). The UV spectra of $(1.63\text{-}5.38)\cdot10^{-5}$ M solutions of the compounds in ethanol and 1 M aqueous ethanolic HCl were recorded with a Hitachi EPS-3T spectrophotometer. The PMR spectra were recorded with a Varian XL-100-12 spectrometer (100 MHz) with tetramethylsilane as the internal standard.

2-[N-(p-n-Butylanilino)]-6-methyl-4-(N-piperidino)pyrimidine (I). A 1.4-g (5 mmole) sample of VIII and 1.08 g (12 mmole) of piperidine were refluxed in 50 ml of ethanol for 6 h, after which the reaction mixture was poured into 50 ml of water, and the precipitate was removed by filtration, dried, and recrystallized from petroleum ether. The yield and the results of analysis are presented in Table 1.

4-(n-Butylamino)-2-[N-(p-n-butylanilino)]-6-methylpyrimidine (II). This compound was similarly synthesized from VIII and n-butylamine. The reaction mixture was poured into water, and the aqueous mixture was extracted with benzene. The extract was dried with sodium sulfate, and the benzene was removed by vacuum distillation to give II as a colorless viscous oil.

2,4-Bis[N-(p-n-butylanilino)]-6-methylpyrimidine (III). This compound was synthesized from VIII and p-n-butylaniline as described above. The reaction mixture was poured into water, the excess p-n-butylaniline was removed by steam distillation, and the residue was cooled. The precipitate was removed by filtration and recrystallized from toluene.

2-[N-(p-Butylanilino)]-4-(4-ethyl-3,5-di-n-propylpyrazol-1-yl)-6-methylpyrimidine (IV). A 4.1-g (15 mmole) sample of IX and 2.76 g (15 mmole) of 5-ethylnonane-4,6-dione were refluxed in 20 ml of ethanol for 5 h, after which the mixture was poured into water. The aqueous mixture was extracted with benzene, and the extract was dried with sodium sulfate. The benzene was removed by vacuum distillation to give IV as a colorless viscous oil.

2-[N-(p-n-Butylanilino)]-4-(3,5-dimethylpyrazol-1-yl)-6-methylpyrimidine (V). A 4.1-g (15 mmole) sample of IX and 1.5 g (15 mmole) of acetylacetone are refluxed in 20 ml of ethanol for 5 h, after which the mixture was cooled, and the precipitate was removed by filtration and dried to give V.

2-[N-(p-n-Butylanilino)]-6-methyl-4(3H)-pyrimidinone (VII). A 47.3-g (0.278 mole) sample of VI and 50 g (0.336 mole) of p-n-butylaniline were refluxed in 500 ml of butyl alcohol for 3 h, after which the mixture was cooled, and the precipitate was removed by filtration, washed on the filter with ethanol, and dried to give VII.

2-[N-(p-n-Butylanilino)]-4-chloro-6-methylpyrimidine (VIII). A mixture of 65 g (0.253 mole) of VII and 250 ml of phosphorus oxychloride was refluxed for 2 h, after which 150 ml of phosphorus oxychloride was removed by vacuum distillation, and the residue was poured over ice. The aqueous mixture was neutralized to pH 8-9 with concentrated ammonium hydroxide, and the precipitate was removed by filtration, dried, and crystallized from heptane.

2-[N-(p-n-Butylanilino)]-4-hydrazino-6-methylpyrimidine (IX). A mixture of 15.0 g (0.0545 mole) of VIII, 15 ml of 80% hydrazine hydrate, and 50 ml of ethanol was refluxed for 4 h, after which it was cooled, and the precipitate was removed by filtration, and washed successively on the filter with water and ethanol to give IX.

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