SYNTHESIS AND STUDY OF 1-(2-PYRIMIDINYL)-1H-PYRAZOLO[3,4-b]PYRIDINE DERIVATIVES

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New 1-(2-pyrimidinyl)-1H-pyrazolo[3,4-b]pyridine derivatives were obtained. The reactivity in reactions involving nucleophilic substitution of the chlorine atom by amino, arylamino, and hydrazino groups was investigated. Data from the IR, UV, and PMR spectra are presented.

In the course of the synthesis of bidentate heteroaromatic ligands that contain groups that are potentially capable of forming intramolecular hydrogen bonds with anions that are included in a ring that contains a metal atom we obtained new 1-(2-pyrimidinyl)-1H-pyrazolo-[3,4-b]pyridine derivatives (Table 1) via the following scheme:

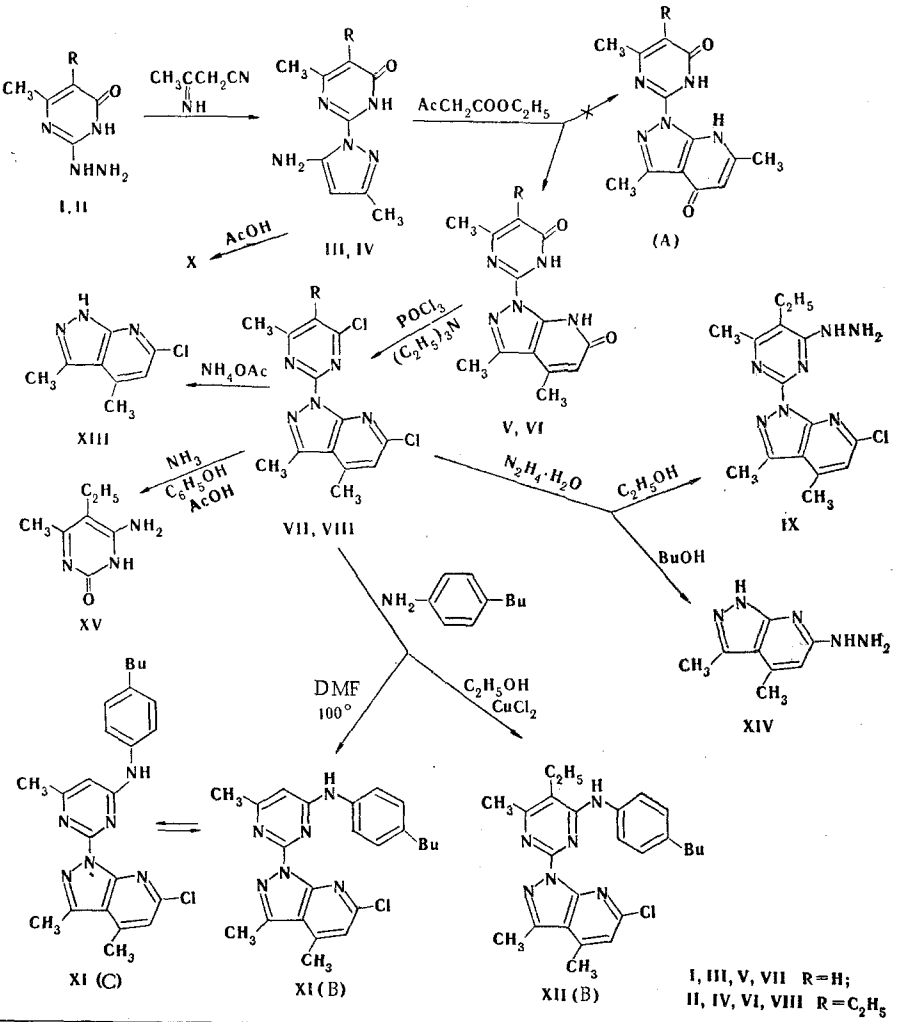

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TABLE 1. Characteristics of III-XV

Compound	mp,* °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	Cl	N		C	H	Cl	N	
III	215—217	52,4	5,6		33,9	$C_9H_{11}N_5O$	52,7	5,4		34,1	61
IV	182—184	56,4	6,3		29,8	$C_{11}H_{15}N_5O$	56,6	6,5		30,0	72
V	300	57,3	5,0		25,5	$C_{13}H_{13}N_5O_2$	57,6	4,8		25,8	37
VI	250	59,9	5,9		23,1	$C_{15}H_{17}N_5O_2$	60,2	5,7		23,4	63
VII	200—202	50,4	3,8	23,2	22,5	$C_{13}H_{11}Cl_2N_5$	50,6	3,6	23,0	22,7	61
VIII	175—177	53,3	4,7	21,3	20,5	$C_{15}H_{15}Cl_2N_5$	55,6	4,5	21,1	20,8	73
IX	193—195	54,2	5,6	10,9	29,8	$C_{15}H_{18}ClN_7$	54,3	5,5	10,7	29,6	45
X	201—203	56,6	6,0		11,3	$C_{13}H_{17}N_5O_2$	56,7	6,2		11,6	35
XI	120—122	69,6	5,9	8,7	20,4	$C_{23}H_{24}ClN_6$	65,8	5,8	8,4	20,0	30
XII	193—194	66,7	6,7	8,0	18,4	$C_{25}H_{29}ClN_6$	66,9	6,5	7,9	18,7	34
XIII	197—199	52,6	4,7	19,9	22,9	$C_8H_8ClN_3$	52,9	4,4	19,5	23,1	22
XIV	238—240	54,0	6,4		39,3	$C_8H_{11}N_5$	54,2	6,2		39,7	20
XV	280	54,7	7,5		26,8	$C_7H_{11}N_3O$	54,9	7,2		27,4	38

*The compounds were recrystallized: III, IV, VI, IX, X, XIV, and XV from ethanol, V from dimethylformamide, XI from methanol, and VII, VIII, and XII from heptane.

TABLE 2. UV and IR Spectra of III-XV

Compound	λ_{max}, nm (log ε), in ethanol	ν, cm⁻¹ (ε) in $CHCl_3$ (in CCl_4 for XI-XIII)	
		NH	C=O
III	237 (4,21), 290 (4,01)	3338 (240), 3492 (130)	1679 (1020)
IV	238 (4,17), 292 (4,02)	3338 (220), 3489 (120)	1668 (1060)
V	234 (4,24), 250 (4,30), 281 (4,24), 302 (4,18)[b], 314 (3,93)[c]	3325, 3438[a]	1628, 1660
VI	236 (4,15), 254 (4,29), 282 (4,30), 300 (4,23)[b], 314 (4,09)[c]	3325 (60)	1629 (860), 1647 (680)
VII	261 (4,47), 298 (4,09), 307 (4,06)[b]		
VIII	261 (4,46), 301 (4,13), 305 (4,11)[b]		
IX	246 (4,42), 290 (4,03)[b]	3330 (60), 3462 (150)	
X	230,5 (4,10)[c], 235 (4,14), 238 (4,13)[c]	3342 (160)	1572 (990)
XI	238 (4,15)[c], 256 (4,42), 295 (4,38)	3415 (80), 3445 (75)	
XII	235 (4,19)[b], 256 (4,42), 298 (4,35)	3464 (130)	
XIII	217 (4,45), 270 (3,63)[c], 276 (3,65), 300 (3,79), 307 (3,76)[c]	3475 (340)	
XIV	228 (4,12)[c], 307 (4,05)		
XV	214 (2,78)[c], 294 (2,54)	3350 (25), 3421 (141), 3520 (60), 3533 (75)	

[a]A saturated solution. [b]Shoulder. [c]Inflection.

We were able to avoid the well-known dual character of the reaction of α-aminoheteroaromic compounds with acetoacetic ester [1, 2] by carrying out this reaction in refluxing acetic acid, as in [1], and this enabled us to obtain only V and VI, the structures of which are confirmed by data from IR and PMR spectroscopy (Tables 2 and 3). Bands of an amide group at 1660 and 1628 cm^{-1} and bands of stretching vibrations of NH bonds at 3438 and 3325 cm^{-1}, which confirm their oxo form, are observed in the IR spectra of solutions of V and VI in $CHCl_3$ in the stretching-vibration region. The PMR spectra of these compounds in trifluoroacetic acid contain singlets of three protons of a methyl group in the 4 position and of a proton in the 5 position of pyrazolo[3,4-b]pyridine with chemical shifts of 2.73 (4-CH_3) and 6.73 ppm (5-H), which coincide with the analogous signals in the PMR spectrum of the known 1,3,4-trimethyl-1H-pyrazolo[3,4-b]pyridin-6(7H)-one and differ from the signals of these protons in the spectrum of the isomeric (of the A type) 1,3,4-trimethyl-1H-pyrazolo-[3,4-b]pyridin-4(7H)-one [3].

Compounds VII and VIII do not react with ammonia and p-butylaniline in refluxing ethanol; VIII reacts with hydrazine hydrate under these conditions to give hydrazino derivative IX. By carrying out the reaction with p-butylaniline in the presence of $CuCl_2$ or in dimethylformamide (DMF) at 100°C we were able to obtain XI and XII. According to the data from the IR spectrum, XII, as in [4], in solutions in $CHCl_3$ and CCl_4 is stabilized in the form of the B conformer (ν_{NH} 3464 cm^{-1}), while XI exists in the form of the B and C conformers (ν_{NH}^1 3445 and ν_{NH}^2 3417 cm^{-1}).

TABLE 3. PMR Spectra of V-IX and XI-XV[a]

Compound	Concn. (mole/liter); solvent; temp., °C	Pyrimidine ring					Pyrazolo[3,4-b]pyridine ring			
		5-R			6-CH_3	4-NH, br s	3-CH_3, s	4-CH_3	5-H	1-NH, br s
		H, q	1-CH_3, t	2-CH_2, q						
V	0,2; d_6-DMSO ; 160	6,20			2,31 d		2,42	2,38 s	5,99 s	
	CF_3COOH	6,85			2,80 d		2,70	2,73 s	6,73 s	
VI	0,2; d_6-DMSO ; 140		1,09	2,54	2,37 s		2,48	2,43 d	6,05 q	
	CF_3COOH		1,31	2,86	2,82 s		2,70	2,73 s	6,73 s	
VII	0,2; $CDCl_3$; 30	7,11			2,67 s		2,77	2,70 d	7,00 q	
		J=0,5 Hz					J=0,9 Hz			
VIII	0,2; $CDCl_3$; 30		1,22	2,83	2,69 s		2,76	2,68 d	7,00 q	
		J=0,9 Hz					J=0,9 Hz			
IX	0,2; d_6-DMSO		1,04	2,50	2,32 s		2,63	2,65 d	7,05 q	
XI	0,2; $CDCl_3$; 30	6,38			2,43 d	7,73	2,73	2,67 d	6,97 q	
XII	0,2; $CDCl_3$; 30		1,81	2,60	2,52 s	6,62	2,70	2,63 d	6,93 q	
XIII	0,2; $CDCl_3$; 30						2,67	2,65 d	6,82 q	11,45
XIV	0,2; d_6-DMSO						J=0,9 Hz		6,14 q	12,15
XV	0,2; d_6-DMSO		0,94 J=7 Hz	2,27	2,05 s	6,48 11,00 (3NH)	2,41	2,41 d		

[a]For the $NHNH_2$ group: IX, 8.44 br s (NH) and 4.50 br s (NH_2); XIV, 7.64 br s (NH) and 3.60 br s (NH_2).

Attempts to replace the chlorine atom in VIII under more severe conditions by a hydrazino group (by refluxing in butanol) and an amino group (by heating with ammonium acetate at 120°C or by treatment with gaseous ammonia at 140-160°C, as in [5]) lead to cleavage of the C–N bond between the heterorings with the liberation in a number of cases of substitution products XIV and XV. The data presented above make it possible to conclude that a chlorine atom in the 4 position of the pyrimidine ring is more reactive in nucleophilic substitution reactions than a chlorine atom in the 6 position of 1H-pyrazolo[3,4-b]-pyridine.

EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol ($5 \cdot 10^{-4}$ mole/liter) were recorded with a Shimadzu MPS-50L spectrophotometer. The IR spectra of solutions of the compounds in $CHCl_3$ (0.02-0.05 mole/liter) and in CCl_4 (10^{-3}-10^{-4} mole/liter) were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Varian X-100-12 spectrometer (100 MHz) with tetramethylsilane as the internal standard.

Compounds I and II were obtained by the method in [6].

2-(5-Amino-3-methyl-1-pyrazolyl)-6-methyl-4(3H)-pyrimidinone (III). A mixture of 28.0 g (0.20 mole) of I and 16.4 g (0.20 mole) of diacetonitrile [7] in 600 ml of ethanol was refluxed for 6 h, after which the mixture was cooled, and the precipitate was removed by filtration, dried, and crystallized from 50% aqueous ethanol to give 25.0 g of III as white needles that were soluble in ethanol, $CHCl_3$, benzene, mineral acids, alkalis, and hot water. The yield and the results of analysis are presented in Table 1. PMR spectrum (0.2 mole/liter in $CDCl_3$, 30°C): 10.2 (1H, broad s, 3-H), 5.95 (1H, q, 5-H), 2.26 (3H, d, J = 0.2-0.3 Hz, 4-CH_3), 2.13 (3H, s, pyrazole 3-CH_3), 5.22 (1H, s, 4-H), and 5.87 ppm (2H, broad s, 5-NH_2).

2-(5-Amino-3-methyl-1-pyrazolyl)-5-ethyl-6-methyl-4(3H)-pyrimidinone (IV). This compound was similarly synthesized from II and was obtained as white needles that were soluble in ethanol, $CHCl_3$, benzene, mineral acids, alkalis, and hot water. PMR spectrum (0.2 mole/liter in $CDCl_3$, 30°C): pyrimidine ring: 10.2 (1H, broad s, 3-H), 1.10 (3H, 5-CH_3), 2.51 (2H, q, 5-CH_2), and 2.28 ppm (3H, 4-CH_3); pyrazole ring: 2.14 (3H, s, 3-CH_3), 5.22 (1H, s, 4-CH), and 5.87 ppm (2H, broad s, 5-NH_2).

3,4-Dimethyl-1-[6-methyl-4(3H)-pyrimidinon-2-yl]-1H-pyrazolo[3,4-b]pyridin-6(7H)-one (V). A mixture of 20.5 g (0.10 mole) of III and 20 ml (0.15 mole) of acetoacetic ester in 60 ml of glacial acetic acid was refluxed for 4 h, after which it was cooled and diluted with 30 ml of water, and the resulting precipitate was removed by filtration, dried, and crystallized from DMF to give 9.9 g of white crystalline V, which was soluble in mineral acids and alkalis and in hot ethanol and DMF but insoluble in water.

1-[5-Ethyl-6-methyl-4(3H)-pyrimidinon-2-yl]-3,4-dimethyl-1H-pyrazolo[3,4-b]pyridin-6(7H)-one (VI). This compound was synthesized as in the preceding experiment from IV and was obtained as a white powder that was insoluble in water but soluble in mineral acids and alkalis and hot $CHCl_3$ and DMF.

6-Chloro-1-(4-chloro-6-methyl-2-pyrimidinyl)-3,4-dimethyl-1H-pyrazolo[3,4-b]pyridine (VII). A 4.0-g (14 mmole) sample of V was refluxed in 30 ml of phosphorus oxychloride with 1.0 ml of triethylamine for 3 h, after which the mixture was cooled and poured over ice. The aqueous mixture was made alkaline with ammonium hydroxide to pH 8-9, and the resulting precipitate was removed by filtration, dried, and crystallized from heptane to give 3.0 g of VII as a white finely crystalline substance that was soluble in $CHCl_3$, benzene, ethanol, DMF, and hot CCl_4 and heptane.

6-Chloro-1-(4-chloro-5-ethyl-6-methyl-2-pyrimidinyl)-3,4-dimethyl-1H-pyrazolo[3,4-b]-pyridine (VIII). This compound was similarly synthesized from VI and was obtained as a white finely crystalline substance that was soluble in CCl_4, $CHCl_3$, benzene, ethanol, and heptane.

6-Chloro-1-(4-hydrazino-5-ethyl-6-methyl-2-pyrimidinyl)-3,4-dimethyl-1H-pyrazolo[3,4-b]-pyridine (IX). A 3.0-g (1.0 mmole) sample of VIII and 1.0 ml (20 mmole) of 99% hydrazine hydrate were refluxed in 20 ml of ethanol for 6 h, after which the mixture was cooled, and the precipitate was removed by filtration, washed with water, dried, and crystallized from ethanol to give a white crystalline substance that was soluble in $CHCl_3$ and ethanol.

2-(5-Acylamino-3-methyl-1-pyrazolyl)-5-ethyl-6-methyl-4(3H)-pyrimidinone (X). A 2.5-g (11 mmole) sample of IV was refluxed in 15 ml of glacial acetic acid, after which the mixture was cooled and neutralized with ammonium hydroxide. The precipitate was removed by filtration, dried, and crystallized from ethanol to give a white crystalline substance that was soluble in $CHCl_3$ and ethanol. PMR spectrum (0.2 mole/liter in $CDCl_3$, 30°C): pyrimidine ring: 10.25 (1H, broad s, 3-H), 1.11 (3H, t, J = 7 Hz, 5-CH_3), 2.52 (2H, q, 5-CH_2), and 2.21 ppm (3H, s, 4-CH_3); pyrazole ring: 2.31 (3H, s, 3-CH_3), 6.62 (1H, q, 4-H), 11.54 (1H, broad s, 5-NH), and 2.21 ppm (3H, d, 5-CH_3).

6-Chloro-1-[4-(N-n-butylanilino)-6-methyl-2-pyrimidinyl]-3,4-dimethyl-1H-pyrazolo[3,4-b]-pyridine (XI). A mixture of 1.5 g (5 mmole) of VII, 3.0 g (20 mmole) of p-butylaniline, 0.4 g (20 mmole) of K_2CO_3, and 10 ml of DMF was stirred at 100°C for 6 h, after which it was cooled and poured into 10 ml of water. The precipitate was removed by filtration, dried, and crystallized from methanol to give a white crystalline substance that was soluble in CCl_4, $CHCl_3$, benzene, and ethanol.

6-Chloro-1-[4-(N-n-butylanilino)-5-ethyl-6-methyl-2-pyrimidinyl]-3,4-dimethyl-1H-pyrazolo[3,4-b]pyridine (XII). A mixture of 0.5 g (1.5 mmole) of VIII, 0.4 g (3.0 mmole) of p-butylaniline, and 0.05 g (0.5 mmole) of $CuCl_2$ in 20 ml of ethanol was refluxed for 6 h, after which it was cooled and poured into 20 ml of water. The precipitate was removed by filtration, dried, and crystallized from heptane to give white fine crystals that were soluble in CCl_4, $CHCl_3$, benzene, and ethanol.

6-Chloro-3,4-dimethyl-1H-pyrazolo[3,4-b]pyridine (XIII). A 0.7-g (22 mmole) sample of VII or 1.0 g (29 mmole) of VIII was stirred at 120°C with 15 g of ammonium acetate, after which the mixture was cooled and poured into 50 ml of water, and the precipitate was removed by filtration, dried, and crystallized from heptane to give white needles that were soluble in CCl_4, $CHCl_3$, benzene, and ethanol.

6-Hydrazino-3,4-dimethyl-1H-pyrazolo[3,4-b]pyridine (XIV). A mixture of 1.0 g (3 mmole) of VIII, 2.5 ml (50 mmole) of 99% hydrazine hydrate, and 20 ml of butanol was refluxed for 6 h, after which it was cooled, and the precipitate was removed by filtration, washed with water, and crystallized from ethanol to give a white crystalline substance that was soluble in hot $CHCl_3$ and ethanol.

4-Amino-5-ethyl-6-methyl-2(3H)-pyrimidinone (XV). This compound was isolated from the reaction mixture obtained by treatment of a mixture of 3.0 g (8 mmole) of VIII, 15 g of phenol, and 4.7 g of acetamide at 140-160°C with gaseous ammonia for 8 h. The phenol was removed by vacuum distillation, and the residue was dissolved in acetic acid. The solution was neutralized with 4 N NaOH, and the resulting precipitate was removed by filtration, dried, and crystallized from ethanol to give white needles that were soluble in DMSO and hot $CHCl_3$.

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VIBRATIONAL SPECTRA AND STRUCTURE OF 4-AMINO-1H-QUINAZOLIN-2-ONE 3-OXIDE

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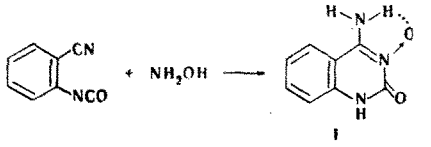
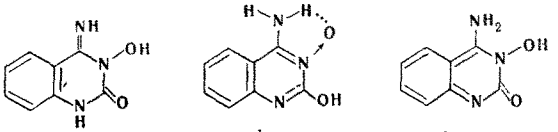
On the basis of a study of the vibrational spectra in the solid state of the product of the reaction of 2-cyanophenyl isocyanate with hydroxylamine and its isotopic analogs ($^{15}N \rightarrow O$ and $^{15}NH_2$) it was demonstrated that the compound obtained has the 4-amino-1H-quinazolin-2-one 3-oxide structure.

It has been demonstrated [1] that the reaction of 2-cyanophenyl isocyanate with hydroxylamine leads to I, for which the 4-amino-1H-quinazolin-2-one 3-oxide structure was proposed:



I

However, one might have assumed that I exists in the various tautomeric forms Ia-c:



Ia Ib Ic

To confirm the structure of I we obtained its ^{15}N isotopic analogs, viz., I with the ^{15}N isotope in the 3 position of the quinazoline system (I ^{15}NO) and I with a ^{15}N-labeled amino group (I $^{15}NH_2$), and investigated their vibrational spectra. The IR and Raman spectra of I (^{15}NO) and I ($^{15}NH_2$) are presented in Table 1.

Compound I is very slightly soluble in ordinary solvents, and this makes it impossible to use NMR spectroscopy to establish the structure and limits the possibilities of IR spectroscopy.

The presence of an intense absorption band in the IR spectrum of I and its isotopic ^{15}N analogs at 1730 cm^{-1}, which is absent or very weak in the Raman spectrum, constitutes evidence for the presence of a carbonyl group in the compound and is not in agreement with the Ib form. The band at 1630 cm^{-1}, the intensity of which is comparable to that of the $\nu(CO)$ band, which is absent in the Raman spectrum and is shifted to 1620 cm^{-1} in the spectrum of isotopic analog I ($^{15}NH_2$), corresponds to the deformation vibrations of the NH

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