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REACTION OF 3,5-DIAMINO-4-NITROPYRAZOLE WITH ELECTROPHILIC REAGENTS

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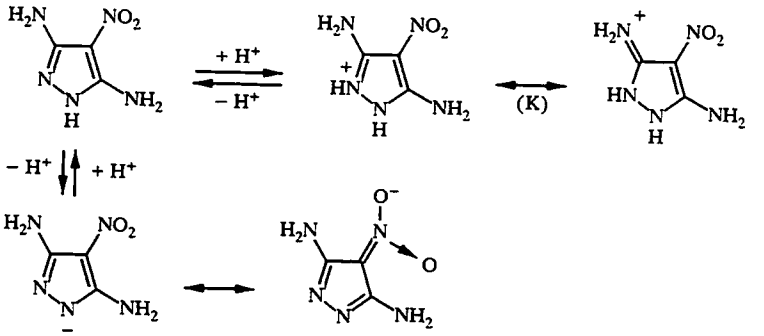
The interaction of 3,5-diamino-4-nitropyrazole with such electrophilic reagents as acetic anhydride, dimethylformamide acetal, orthoformic ester, and ketones has been studied. Derivatives of pyrazolo[1,5-a]pyrimidines were formed on reaction with 1,3-diketones and some of their properties have been studied.

We recently developed a new synthesis of 3,5-diamino-4-nitropyrazole (I) by reacting enediamines (II) or amidinoenamines (III) with hydrazine hydrate [1]. Previously, pyrazole (I) had been obtained by a complex five-stage synthesis [2] starting from 4-nitropyrazole-3,5-dicarboxylic acid with the aim of studying its diazotization and the properties of the bisdiazonium salts. Other properties of diaminopyrazole (I) were not investigated.

3,5-Diamino-4-nitropyrazole is a compound capable of displaying both acidic and basic properties, which mainly determine its chemical properties. Its ionization constants in water were determined by potentiometric titration. The pK_a for basicity (addition of proton) was 5.56 and for acidity (removal of proton) was 8.48, i.e., pyrazole (I) is a somewhat stronger base than pyridine (pK_a 5.17) [3] and has approximately the same acidity as p-nitrophenol (pK_a 8.5) [4]. The acid–base equilibria for pyrazole (I) may be expressed by the following scheme.



The relatively high basicity of pyrazole (I) indicates the possibility of salt-formation and of carrying out electrophilic substitution reactions at an amino group. In fact, a salt is formed rapidly on treatment with a methanolic solution of hydrochloric acid, and boiling aminopyrazole (I) in acetic anhydride leads to the monoacetate derivative (IV) in quantitative yield. The presence in pyrazole (I) of primary amino groups affords the possibility of reaction with DMF diethylacetal, though one must keep in mind that the relatively high acidity of the compound assists its N-alkylation by amide acetals (see, e.g., the O-alkylation of phenols, carboxylic acids or the N-alkylation of hydroxypyrimidines by acetals of amides and lactams [5]). Such processes have also been described in the 3-aminopyrazole series [6]. Thus the reaction of 3-amino-4-cyanopyrazole with dimethylformamide acetal leads in the first stage to the formation of an amidine derivative which is then converted by ethylation at the NH of the pyrazole ring. On reacting pyrazole (I) with dimethylformamide acetal, we successfully demonstrated the

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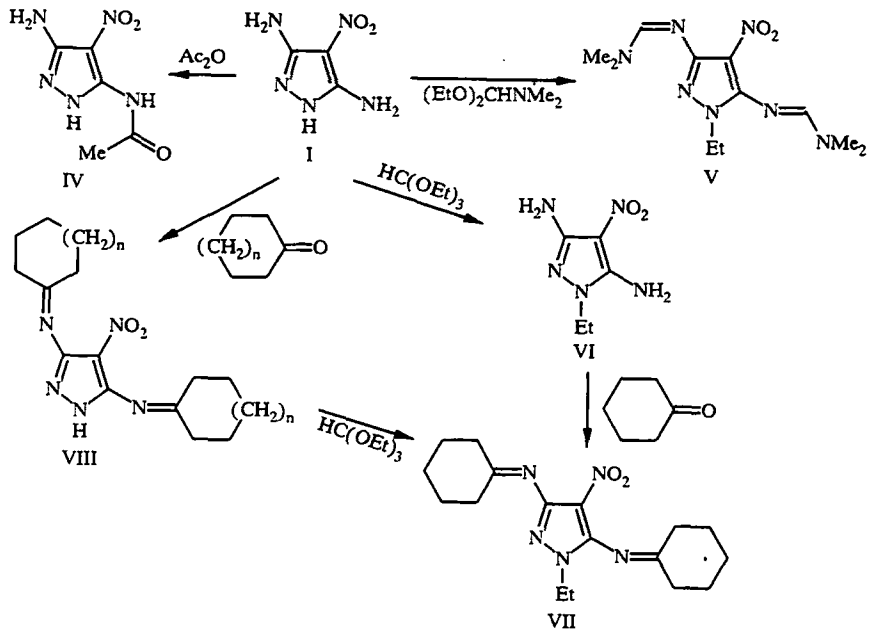
presence of only the ethylated diamidine derivative (V) in 71% yield. Changing the reaction conditions affected only the yield of (V) and did not change the structure of the final product.



VIII a n=1, b n=2

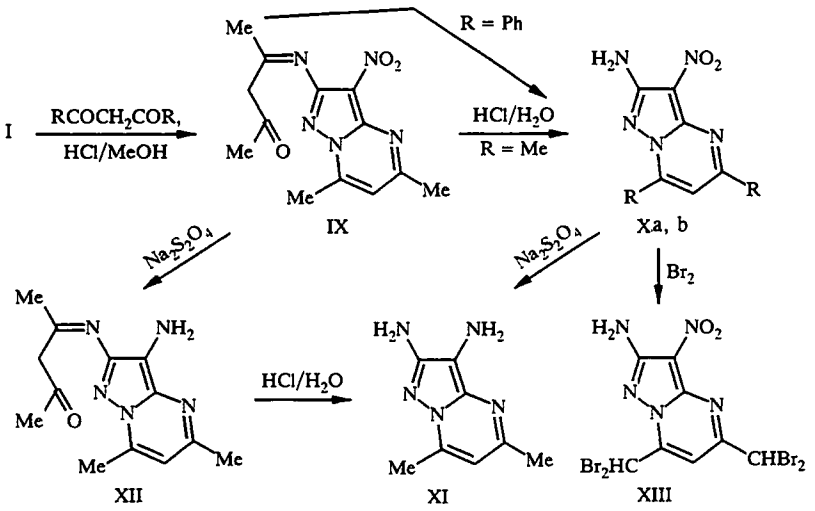
A different situation was observed on reacting the initial pyrazole with orthoformic ester. 3,5-Diamino-1-ethyl-4-nitropyrazole (VI) was isolated exclusively from the reaction mixture even on boiling for many hours. The difference in properties of the investigated pyrazole from 3-amino-4-cyanopyrazole [7] is displayed by this since the latter reacted under analogous conditions with the formation of a mixture of the ethoxymethylene derivative and the 1-ethylpyrazole in approximately equal ratio. The position of the ethyl group in compound (VI) was proved by an alternate synthesis. Reaction of diamine (VI) with cyclohexanone led to the 1-ethyl-4-nitropyrazole (VII) which was synthesized by the sequential reaction of pyrazole (I) with cyclohexanone to give the biscyclohexylideneamino-4-nitropyrazole (VIII) and then ethylation with orthoformic ester. It must be said that both this and the other route of synthesis of derivative (VII) gave good yields of final product (60-70%).

Ketones condense readily at an amino group in position 3 or 5 of the pyrazole ring, as is seen from the reaction of pyrazole (I) with cyclohexanone. It therefore seemed of interest to carry out the reaction of derivative (I) with 1,3-dicarbonyl compounds with the aim of producing pyrazolo[1,5-*a*]pyrimidines. Only symmetrical 1,3-dicarbonyl compounds were studied in the present work, since the formation of various isomeric derivatives difficult to identify might be expected if unsymmetrical compounds participated in the reaction indicated. Reaction of (I) with diketones occurs solely in the presence of a strong acid which is needed in an amount significantly less than equimolar. In the present case a 0.1 molar quantity of HCl was used, applied every time as a 9% solution in methanol. The condensation process did not take place in the absence of or with an excess of hydrochloric acid. It is clear that an excess of HCl leads to the formation of a cation (C) which is unable to attack the electrophilic reagent. A small quantity of H^+ is probably needed to activate the carbonyl in the methyleneamine intermediate for cyclization at the endocyclic pyrazole NH group with the formation of an aromatic pyrimidine ring, an irreversible reaction accompanied by an energy advantage. The fact that acid catalysis is needed probably excludes the possibility of initial attack at the endocyclic NH group.

Carrying out the reaction of pyrazole (I) with acetylacetone and dibenzoylmethane under the conditions indicated afforded a synthesis of derivatives (IX) and (Xa, b). It must be noted that brief boiling of derivative (IX) in aqueous hydrochloric acid leads to hydrolysis of the C=N bond, and the pyrazolopyrimidine (Xa) was isolated in quantitative yield. Only (Xb) was isolated from the reaction mixture when using dibenzoylmethane as dicarbonyl compound.

The possibility of reducing the nitro group and of brominating the synthesized pyrazolopyrimidines has been studied. Reduction of the aromatic nitro group in the pyrazolo[1,5,-*a*]pyrimidines (IX) and (Xa) with sodium hydrosulfite in alkaline medium gave a synthesis of the corresponding derivatives (XII) and (XI). Their final yields calculated on the recrystallized product did not exceed 50%, although acid hydrolysis of compound (XII) led to the 2,3-diamino derivative (XI) in quantitative

yield. In our opinion, the latter compound is a promising starting material for the synthesis of various tricyclic derivatives containing a pyrazolopyrimidine system.



X a R = Me, b R = Ph

Bromination of compound (X) using various ratios of starting materials led in every case to an inseparable mixture of isomers, since reaction occurred simultaneously at the methyl groups at positions 5 and 7 or at only one of these groups. Only under excess bromination conditions was a single product obtained in 76% yield, viz. the tetrabromide (XIII). On measuring the mass spectrum of this compound, the ratio of isotopic peaks of the molecular ion indicated unequivocally the presence of four bromine atoms in the molecule. The main decomposition of the molecular ion of (XIII) arises from the sequential elimination of three bromine atoms. Weakly intense peaks with m/z 171, 173, and 175 with an intensity ratio of 1:2:1 were observed in the spectrum, which may be assigned to the $CHBr_2^+$ ion. Peaks corresponding to the CBr_3^+ ion were not observed in the spectrum, which indicates symmetrical dibromination of each methyl of the pyrimidine ring.

When studying the push–pull properties of enamines, we also demonstrated the possibility of synthesizing pyrazoles (XV) substituted at the amino group from the corresponding cyclic enamines (XIV) by reaction with hydrazine hydrate. In this, reaction occurs by transamination of only one amino group of the enediamine with subsequent cyclization to a pyrazole ring and retention of an amino group in the substituent of the amino group at position 3 of the pyrazole (XV). The proposed scheme for carrying out these processes was described by us in [1]. Analogous ring closures in cyanoenamines with the formation of substituted pyrazoles was described in [8], however, we showed that reduction of the reaction time from 16 h to 30 min increased the yield of final product by 20%. It is probable that the authors of [8] were unsuccessful in synthesizing compound (XIVb) since such forcing conditions were used. Under our conditions the corresponding synthesis of pyrazole (XVb) was successfully carried out in 60% yield. The possibility of reacting pyrazole (XVa) with 1,3-diketones has been studied. Acetylacetone was selected as reactant. The corresponding pyrazolopyrimidine (XVI) was obtained in high yield by reaction under conditions analogous to those described above (acid catalysis).

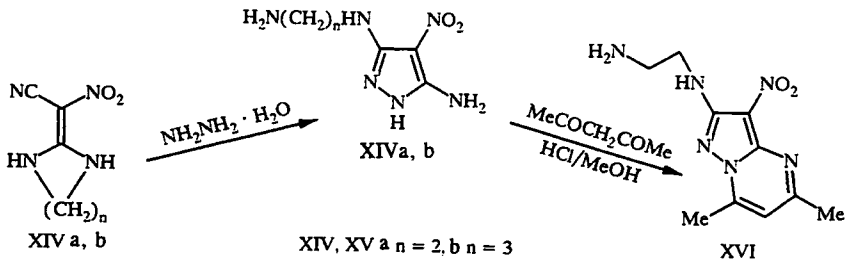


TABLE 1. Physicochemical Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, %			Calculated, %			mp, °C	Crystallization solvent	IR spectrum, cm^{-1}	M+	Yield, %
		C	H	N	C	H	N					
IV	$C_5H_7N_5O_3$	32,54	3,78	37,54	32,43	3,78	37,83	>260	DMF/water	3350...3120, 1710, 1610, 1356	185	93
V	$C_{11}H_{19}N_7O_2$	47,00	6,72	34,95	46,97	6,76	34,88	134...136	2-Propanol/ether	1665, 1610, 1455	281	71
VI	$C_5H_9N_5O_2$	35,24	5,01	40,83	35,08	5,26	40,93	194...195	2-Propanol/hexane	3250...3190, 1610, 1310	171	83
VII	$C_{17}H_{25}N_5O_2$	61,54	7,48	21,06	61,63	7,55	21,01	161...162	2-Propanol	1670, 1615, 1432, 1325, 908	331	
VIIIa	$C_{15}H_{21}N_5O_2$	59,51	6,53	23,34	59,40	6,93	23,10	132...135	2-Propanol	3210, 1654, 1612, 1354, 1102	303	62
VIIIb	$C_{17}H_{25}N_5O_2$	61,68	7,41	21,22	61,63	7,55	71,14	138...141	2-Propanol	3205, 1646, 1628, 1348	331	57
IX	$C_{13}H_{15}N_5O_3$	53,81	5,17	24,32	53,97	5,19	24,22	264...266	DMF	1728, 1650, 1612, 1521, 1423	289	96
Xa	$C_8H_9N_5O_2$	46,54	4,21	33,61	46,37	4,34	33,81	244...246	Water	3215...3180, 1664, 1543	207	95
Xb	$C_{18}H_{13}N_5O_2$	65,31	3,86	24,28	65,25	3,92	24,14	>270	DMF	3230...3180, 1654, 1512, 1456	331	87
XI	$C_8H_{11}N_5$	54,10	6,34	39,78	54,23	6,21	39,54	212...214	Ethanol	3400...3125, 1640	177	56
XII	$C_{13}H_{17}N_5O$	60,41	6,23	26,84	60,23	6,56	27,02	108...110	Water	3350...3120, 1705, 1651	259	61
XIII	$C_8H_5N_5O_2Br_4$	18,66	1,02	12,93	18,49	0,96	13,48	112...114	Ethanol.	3215...3150, 1653, 1517	519	73
XVI	$C_{10}H_{14}N_6O_2$	48,03	5,64	33,68	48,00	5,60	33,60	>260	DMF	3270...3170, 1652, 1520, 1410	250	91

In conclusion, it must be pointed out that investigation of the reactions of aminopyrazoles with electrophilic reagents is a basis for the synthesis of various polyheterocyclic compounds. This problem seems particularly important to us when it is considered that only one example of the synthesis of 2-aminopyrazolo[1,5-*a*]pyrimidine has been reported in the literature [9].

EXPERIMENTAL

The IR spectra were taken on a Perkin-Elmer spectrophotometer as Nujol mulls. The mass spectra were obtained on a Varian SSQ 700 spectrometer with direct insertion of substances into the ion source. A check on the purity of products and the progress of reactions was effected with TLC on Silufol UV 254 plates.

Syntheses of pyrazoles (I) and (XVa, b) have been given in [1].

The physicochemical characteristics of the synthesized compounds are given in Table 1.

3-Acetamido-5-amino-4-nitropyrazole (IV). A suspension of pyrazole (I) (1.0 g, 6.9 mmole) in acetic anhydride (5 ml) was boiled for 3 h. The reaction mixture was cooled and the bright yellow solid (IV) (1.2 g) was filtered off.

3,5-Bis(dimethylaminomethyleneamino)-1-ethyl-4-nitropyrazole (V). A solution of pyrazole (I) (1.0 g, 6.9 mmole) in dimethylformamide acetal (5 ml) was kept for 2 h at 100°C, then 2 days in the refrigerator. The precipitated coarsely crystalline solid was filtered off and washed with hexane. The yellow–green crystals obtained were dissolved in benzene (15 ml) and reprecipitated with hexane. Yellow crystalline substance (V) (1.4 g) was filtered off.

3,5-Diamino-1-ethyl-4-nitropyrazole (VI). A solution of pyrazole (I) (0.3 g, 2.1 mmole) in a mixture of ethanol (4 ml) and orthoformic ester (4 ml) was boiled for 3 h and the reaction mixture was evaporated in vacuum. The residue obtained was triturated with hexane, and bright yellow pyrazole (VI) (0.3 g) was filtered off.

3,5-Dicyclohexylideneamino-1-ethyl-4-nitropyrazole (VII). A. A suspension of pyrazole (VI) (0.3 g, 1.7 mmole) in cyclohexanone (5 ml) was boiled for 5 h and the reaction mixture evaporated. The residual oil was treated with a mixture (1:1) of ether and sulfuric acid, and bright yellow pyrazole (VII) (0.35 g, 60%) was filtered off.

B. A suspension of pyrazole (VIIIa) (0.4 g, 1.3 mmole) in orthoformic ester (5 ml) was boiled for 3 h. The reaction mixture was cooled and the yellow crystalline substance (0.35 g, 69%) filtered off. This was identical in physicochemical and spectral characteristics with pyrazole (VII) obtained by method A.

3,5-Dicyclohexylideneamino-4-nitropyrazole (VIIIa) and 3,5-Dicycloheptylideneamino-4-nitropyrazole (VIIIb). A solution of pyrazole (I) (0.4 g, 2.8 mmole) in cyclohexanone (5 ml) or cycloheptanone (5 ml) was boiled for 6 h. The reaction mixture was evaporated and the residual oil rubbed with diethyl ether until formation of solid yellow substance (VIII).

2-(4-Oxo-2-pentylideneamino)-5,7-dimethyl-3-nitropyrazolo[1,5-*a*]pyrimidine (IX), 2-Amino-3-nitro-5,7-diphenylpyrazolo[1,5-*a*]pyrimidine (Xb), and 2-(2-Aminoethylamino)-5,7-dimethyl-3-nitropyrazolo[1,5-*a*]pyrimidine (XVI). A suspension of the appropriate pyrazole (I) or (XVb) (35 mmole) in a mixture of acetylacetone (5 ml) (or 40 mmole dibenzoylmethane), methanol (5 ml), and 9% methanolic HCl solution (1.5 ml) was boiled for 1.5 h. The reaction mixture was cooled and the corresponding bright yellow solid pyrazolopyrimidine filtered off.

2-Amino-5,7-dimethyl-3-nitropyrazolo[1,5-*a*]pyrimidine (X). A solution of pyrazolopyrimidine (IX) (0.4 g, 1.4 mmole) in 5% aqueous HCl solution (5 ml) was cooled for 5 min in the refrigerator. The precipitated solid was filtered off, and 2-aminopyrazolopyrimidine (Xa)(0.26 g) was obtained.

2,3-Diamino-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (XI) and 3-Amino-5,7-dimethyl-2-(4-oxo-2-pentylideneamino)pyrazolo[1,5-*a*]pyrimidine (XII). Portions of dry sodium hydrosulfite and drops of 40% NaOH solution were added at the boiling point to a suspension of pyrazolopyrimidine (IX) or (Xa) (5 mmole) in a mixture of methanol (25 ml) and water (25 ml). A check on the course of the reaction was made chromatographically for the disappearance of starting material, the presence of unreacted sodium hydrosulfite was determined by the qualitative reaction for the decoloration of methylene blue, and the alkalinity with universal indicator. After the disappearance of the initial nitropyrazolopyrimidine (TLC in chloroform–methanol, 1:1) the reaction mixture was left for 1 h at room temperature, and then extracted with ethyl acetate (3 × 100 ml). The extract obtained was dried over Na_2SO_4, evaporated, and the dark yellow amino derivative obtained.

2-Amino-5,7-bis(dibromomethyl)-3-nitropyrazolo[1,5-*a*]pyrimidine (XIII). A suspension of pyrazolopyrimidine (Xa) (0.7 g, 3.4 mmole) and bromine (1.1 ml, 21 mmole) in acetic acid (25 ml) was boiled for 8 h, then left overnight. The reaction mixture was diluted with water (130 ml) and the voluminous yellow precipitate of (XIII) filtered off.

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