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INVESTIGATION OF THE REACTION OF 3,5-DIAMIDINO-4-NITROPYRAZOLE WITH AMINES

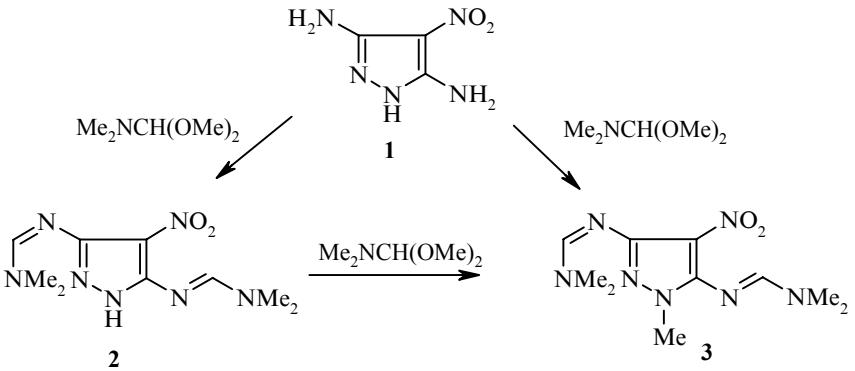
V. A. Makarov[1], O. B. Ryabova[1], L. M. Alekseeva[1], V. V. Chernyshev[2], and V. G. Granik[1]

The interaction of 3,5-bis(N,N-dimethylaminomethylene)amino-1-methyl-4-nitropyrazole with amines proceeds regioselectively with the formation of 3-amino-5-(N,N-dimethylaminomethylene)amino-1-methyl-4-nitropyrazole. Amines are converted in this way into N,N-dimethylformamidine derivatives. The structures of the compounds obtained were proved by ^{1}H and ^{13}C NMR spectroscopy and by X-ray crystallographic analysis.

Keywords: DMF acetal, 4-nitropyrazole, formamidine, X-ray crystallographic analysis.

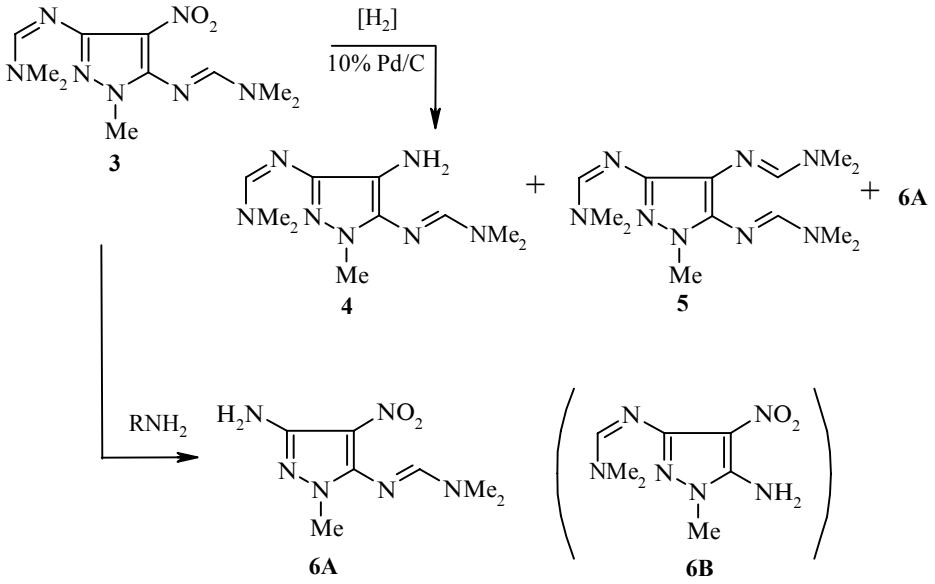
From one of the most available push-pull enamines, α-nitro-β-amino-β-dimethylaminoacrylonitrile, the synthesis of 3,5-diamino-4-nitropyrazole (**1**) has been realized and certain chemical and physicochemical properties of this compound have been studied [1-5]. In particular, its reaction with β-dicarbonyl compounds leading to pyrazolo[1,5-*a*]pyrimidines [5] has been investigated, and also the condensation with DMF diethylacetal with the formation of the bisamidine 3,5-bis(dimethylaminomethylene)amino-1-ethyl-4-nitropyrazole [3]. The present work is devoted to the investigation of the interaction of bisamidines of this type with amino derivatives.

The interaction of pyrazole **1** with DMF dimethylacetal proceeds in two stages. Initially bisamidine **2** is formed, which on further heating with the acetal is transformed into the N-methyl derivative **3**. The alkylation by amide acetals of various acidic compounds (the acidity of pyrazole **1** is pK_a 8.48 [3], which is higher than the acidity of phenol) is well known. The same 3,5-bis(dimethylaminomethylene)amino-1-methyl-4-nitropyrazole (**3**) is obtained in one step in high yield on refluxing diaminonitropyrazole **1** directly with an excess of DMF acetal.

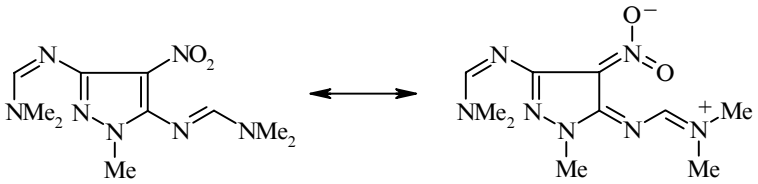


[1] NIOPIK State Scientific Center of the Russian Federation, Moscow 103787, Russia; e-mail: makar-cl@ropnet.ru. [2] Moscow M. V. Lomonosov State University, Moscow 119899, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii., No. 8, pp. 1087-1094, August, 2002. Original article submitted November 17, 1999.

It seemed of interest to study the possibility of reduction of the nitro group in the diamidines obtained, which may provide an approach to 3,4,5-triaminopyrazoles, presently unknown. These compounds may be interesting synthons for further heterocyclic synthesis. However on attempting catalytic reduction of pyrazole **3** a complex mixture was obtained containing (judging by high resolution mass spectra after separating the mixture by HPLC) as main products 16% desired 4-amino-3,5-diamidine **4**, 14% 3,4,5-triamidinopyrazole **5**, and 28% 5-amidino-3-amino-4-nitropyrazole **6** (mass spectra: **4** *m/z* 237.17010, $C_{10}H_{19}N_7$; **5** *m/z* 292.21380, $C_{13}H_{24}N_8$; **6** *m/z* 212.20899, $C_7H_{12}N_6O_2$). The structures for **4** and **5** do not raise doubts but two variants are possible for amidine **6**, i.e. the amidine fragment may be found at position 5 (**6A**) or 3 (**6B**). With the aim of isolating individual **6A** or **6B**, and also for studying the nontrivial and unobvious process of obtaining the trisamidine **5** we investigated the interaction of nitrobisamidine **3** with various amines (*p*-anisidine, benzylamine, and ammonia, pK_a 5.29, 9.37, and 9.25 respectively). *p*-Anisidine is four orders of magnitude less basic than the remainder, but the presence of a bulky substituent in benzylamine (compared with ammonia) may create steric hindrance in the process of nucleophilic attack. Heating pyrazole **3** with each of the investigated amines led to removal of one of the amidine groupings with the formation of **6A** or **6B**. The reaction rates



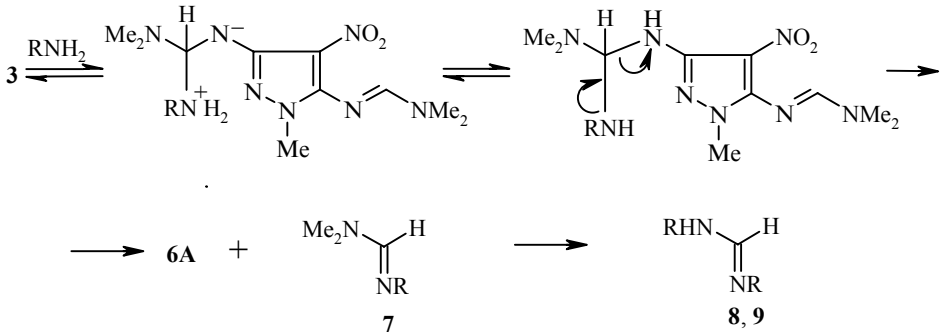
differed extremely significantly. For completion of the process (TLC) ammonia required 3 h refluxing in methanol, for benzylamine 24 h, and for the least basic *p*-anisidine 72 h. For the reactions with *p*-anisidine and benzylamine, in addition to the pyrazole monoamidine (**6A** or **6B**), N-dimethylaminomethylene-*p*-anisidine (**7**), N,N'-bis-*p*-methoxyphenylformamidine (**8**), and N,N'-bisbenzylformamidine (**9**) were successfully isolated as the hydrochlorides. The structure of the initial bisamidine may be represented in the following way.



Starting from this, it seemed that the interaction with amines should primarily be effected at the amidine *meso* carbon atom of the grouping at position 5. It is clear that such a consideration is formal to a significant extent, considering the aromatic nature of the pyrazole ring. However it is evident that there are no preferences

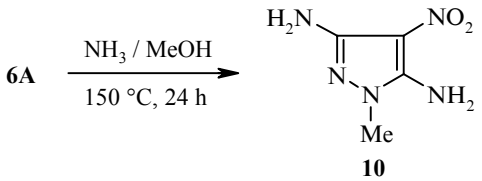
in the effect of the electron-withdrawing nitro group for the amidine fragment of one series or the other. At the same time there is no doubt that that the deamidination process (i.e. transformation of the amidine into an amino group) proceeds regioselectively. The data of ^{13}C NMR spectra taken in modes without suppression of the coupling with protons and selective resonance support structure **6A**. The spectrum contains the following signals: $C_{(4)}$ (110 ppm, $^3J_{C4,NH_2}$ = 3.8 Hz), a doublet of quartets for $C_{(5)}$ (147.4 ppm, $^3J_{C5,H5a}$ = 6.9, $^3J_{C5,1\text{-}CH_3}$ = 2.3 Hz), a singlet for $C_{(3)}$ (150.3 ppm), and a doublet, each component of which has the form of a multiplet due to coupling with the protons of $N(CH_3)_2$, for $C_{(5a)}$ (159.1 ppm, $^1J_{C5a,5a\text{-}H}$ = 182 Hz). On suppressing the interaction with the protons of the 1-CH_3 and NH_2 groups and the vinylic proton the following changes were observed in the spectra. The signal of the $C_{(5)}$ atom was converted into a doublet ($^3J_{C5,5a\text{-}H}$ = 6.9 Hz), the triplet of the $C_{(4)}$ atom into a singlet, and the signals of $C_{(5a)}$ and $C_{(5)}$ into a singlet and a quartet ($^3J_{C5,1\text{-}CH_3}$ = 2.3 Hz). We note that for structure **6B** the presence might have been expected of a doublet signal for the $C_{(3)}$ atom (due to the interaction with 3a-H), and also a different multiplicity (probably quartet) for the signal of $C_{(5)}$. As a result a different character of changes is expected in the spectrum on selective decoupling (suppression of the interaction with the 1-CH_3 protons and the vinylic proton). In this way the spectral data obtained indicate unequivocally that amine **6A** is formed by the reduction of the nitro group of compound **3**. Compound **6A** is also the only product of the reaction of **3** with various amines (apart from amidines **7-9** formed in parallel by cleavage of the amidine fragment).

The interaction of bisamidine **3** with amines may be described by the following scheme which explains the dependence of the reaction rate on the basicity of the amine and its sensitivity to the bulk of the substituent on the amino group.

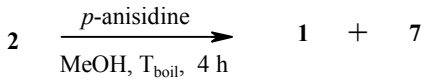


7, **8** R = *p*-$MeOC_6H_4$; **9** R = CH_2Ph

We have presumed that the regioselectivity of the interaction of pyrazole **3** with amines, i.e. the selective attack of the amine only at the amidine grouping at position 3, is caused by steric factors. The presence of methyl and dimethylformamidine groups side-by-side at positions 1 and 5 leads to escape of the latter from the plane of the pyrazole ring, a weakening of the electronegative effect of both the nitro group and the pyrazole ring on it, and correspondingly a reduction in the partial positive charge on the *meso* carbon atom and consequently in the rate of nucleophilic attack. This effect is so significant that the reaction of amidine **6A** with *p*-anisidine and benzylamine does not take place even under extremely rigid conditions (bomb, methanol, 150°C, 30 h), and only carrying out the analogous reaction under the same conditions with ammonia (which is characterized by a small volume and high basicity) leads to 3,5-diamino-1-methyl-4-nitropyrazole (**10**).

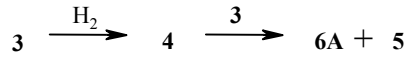


An argument in favor of the hypothesis of the importance of the steric effect connected with the overlap of the 5-amidine and 1-methyl groups in compound **3** is the fact that the N-unsubstituted amidine **2** reacts smoothly and fairly readily with *p*-anisidine with the formation of the initial diaminopyrazole **1** and amidine **7**.

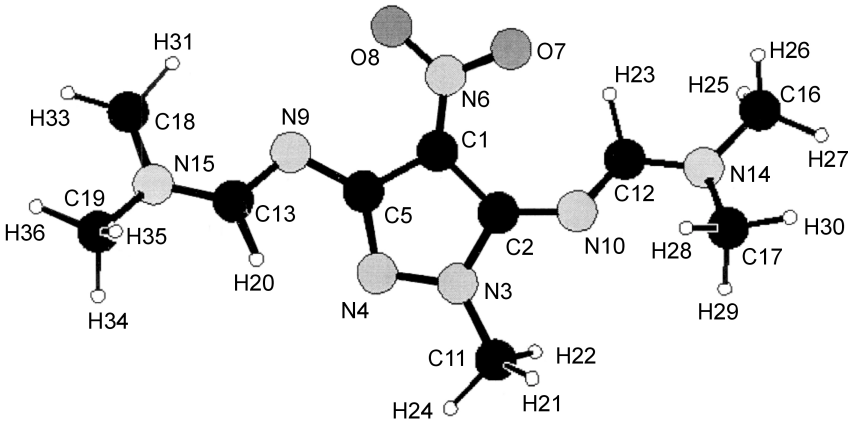


This hypothesis is completely confirmed by the data of X-ray crystallographic analysis (Fig. 1). In reality, as is seen from the figure, the amidine grouping, lying between the nitro and methyl groups, comes out of the plane of the molecule and nucleophilic attack by amines is hindered significantly. Bond lengths and valence angles are given in Tables 1 and 2.

The investigations carried out and discussed above also make it possible to explain the unexpected formation of trisamidine **5** in the reduction of compound **3**. This process probably proceeds in the following way.



In other words, the reduced compound **4** plays the role of an amine which attacks the *meso* carbon atom of the amidine grouping in position 3 of the molecule of the initial nitropyrazolediamidine **3**, being transformed into trisamidine **5** at the same time as monoamidine **6A** is formed from **3**.



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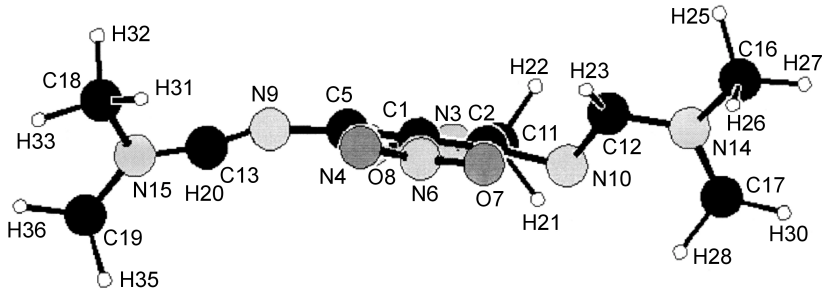

b

Fig. 1. Structure of compound **3** from X-ray structural analysis. View from a) above and b) the side.

TABLE 1. Bond Lengths in the Structure of Compound **3**

Bond	*l*, Å	Bond	*l*, Å
$C_{(1)}$–$C_{(2)}$	1.4471	$N_{(6)}$–$O_{(8)}$	1.2255
$C_{(1)}$–$C_{(5)}$	1.4581	$N_{(9)}$–$C_{(13)}$	1.3162
$C_{(1)}$–$N_{(6)}$	1.4237	$N_{(10)}$–$C_{(12)}$	1.3337
$C_{(2)}$–$N_{(3)}$	1.3980	$C_{(12)}$–$N_{(14)}$	1.3585
$C_{(2)}$–$N_{(10)}$	1.3724	$C_{(13)}$–$N_{(15)}$	1.3804
$N_{(3)}$–$N_{(4)}$	1.3535	$N_{(14)}$–$C_{(16)}$	1.4434
$N_{(3)}$–$C_{(11)}$	1.4461	$N_{(14)}$–$C_{(17)}$	1.4245
$N_{(4)}$–$C_{(5)}$	1.3626	$N_{(15)}$–$C_{(18)}$	1.4356
$C_{(5)}$–$N_{(9)}$	1.3804	$N_{(15)}$–$C_{(19)}$	1.4292
$N_{(6)}$–$O_{(7)}$	1.2141		

TABLE 2. Valence Angles in the Structure of Compound **3**

Angle	ω, deg.	Angle	ω, deg.
$C_{(5)}$–$C_{(1)}$–$N_{(6)}$	129.58	$C_{(1)}$–$N_{(6)}$–$O_{(8)}$	118.22
$C_{(2)}$–$C_{(1)}$–$N_{(6)}$	125.27	$C_{(1)}$–$N_{(6)}$–$O_{(7)}$	127.81
$C_{(2)}$–$C_{(1)}$–$C_{(5)}$	105.15	$O_{(7)}$–$N_{(6)}$–$O_{(8)}$	113.84
$C_{(1)}$–$C_{(2)}$–$N_{(10)}$	131.87	$C_{(5)}$–$N_{(9)}$–$C_{(13)}$	99.15
$C_{(1)}$–$C_{(2)}$–$N_{(3)}$	104.48	$C_{(2)}$–$N_{(10)}$–$C_{(12)}$	122.86
$N_{(3)}$–$C_{(2)}$–$N_{(10)}$	123.64	$N_{(10)}$–$C_{(12)}$–$N_{(14)}$	122.24
$C_{(2)}$–$N_{(3)}$–$C_{(11)}$	120.04	$N_{(9)}$–$C_{(13)}$–$N_{(15)}$	115.85
$C_{(2)}$–$N_{(3)}$–$N_{(4)}$	113.74	$C_{(12)}$–$N_{(14)}$–$C_{(17)}$	123.16
$N_{(4)}$–$N_{(3)}$–$C_{(11)}$	126.22	$C_{(12)}$–$N_{(14)}$–$C_{(16)}$	122.42
$N_{(3)}$–$N_{(4)}$–$C_{(5)}$	106.66	$C_{(16)}$–$N_{(14)}$–$C_{(17)}$	114.38
$C_{(1)}$–$C_{(5)}$–$N_{(4)}$	109.96	$C_{(13)}$–$N_{(15)}$–$C_{(19)}$	120.94
$N_{(4)}$–$C_{(5)}$–$N_{(9)}$	126.59	$C_{(13)}$–$N_{(15)}$–$C_{(18)}$	119.10
$C_{(1)}$–$C_{(5)}$–$N_{(9)}$	123.40	$C_{(18)}$–$N_{(15)}$–$C_{(19)}$	119.82

The reaction between diamidinonitropyrazole **3** and amines is probably interesting by itself both in practical and theoretical respects. However it is evident to the authors that for completeness of this investigation it is necessary to study similar reactions for compounds containing other electron-withdrawing groups at position 4 of the pyrazole, to which a separate communication will be devoted.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on an Oxford UNITI Plus 400 (400 MHz) spectrometer, internal standard was TMS. The mass spectra were obtained on a Finnigan SSQ 700 spectrometer with insertion of the sample directly into the ion source. A check on the purity of products and the progress of reactions was effected by TLC on Fluka TLC Cards of Silica gel 60778.

3,5-Bis(dimethylaminomethylene)amino-4-nitropyrazole (2). A suspension of 3,5-diamino-4-nitropyrazole (**1**) (3.0 g, 20.7 mmol) and DMF dimethylacetal (6.0 ml) in ethyl alcohol (20 ml) was refluxed for 3 h and intensely cooled. The precipitated orange solid was crystallized from isopropyl alcohol, and a coarsely crystalline substance (2.1 g, 40%) was obtained; mp 178-180°C. $M^{+\cdot}$ 253. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.07 (12H, s, two ($N(CH_3)_2$)); 8.06 (2H, s, two CH); 10.5 (1H, br. s, NH). Found, %: C 42.51; H 6.20; N 38.53. $C_9H_{15}N_7O_2$. Calculated, %: C 42.68; H 5.97; N 38.71.

3,5-Bis(dimethylaminomethylene)amino-1-methyl-4-nitropyrazole (3). A suspension of compound **1** (3.0 g, 20.7 mmol) and DMF dimethylacetal (6.6 ml) was maintained at 100°C for 4 h. The reaction mixture was evaporated in vacuum to an oily residue, which was treated with boiling hexane. The residual thick oil was frozen in the refrigerator, and after crystallization from isopropyl alcohol a bright yellow substance (2.2 g, 39%) was obtained; mp 185-186°C. $M^{+\cdot}$ 267. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.87, 2.91, 2.94 (12H, s, two ($N(CH_3)_2$); 3.37 (3H, s, 1-CH_3); 7.77, 7.91 (2H, s, two CH). Found, %: C 44.73; H 6.28; N 37.03. $C_{10}H_{17}N_7O_2$. Calculated, %: C 44.94; H 6.41; N 36.68.

Reduction of 3,5-Bis(dimethylaminomethylene)amino-1-methyl-4-nitropyrazole 3. Palladium on carbon (10%, 0.19 g) was added to a solution of compound **3** (2.0 g, 13.8 mmol) in methanol (60 ml) and the mixture was reduced with hydrogen at normal pressure. After 3 h the reaction mixture was filtered and evaporated in vacuum to a completely solid red residue, which was dried over P_2O_5, and analyzed.

Reactions of 3,5-Bis(dimethylaminomethylene)amino-1-methyl-4-nitropyrazole 3 with Amines. A solution of compound **3** (0.35 g, 1.3 mmol) in methanol (30 ml) was heated with the appropriate amine (4.0 mmol) until disappearance of the starting material according to TLC (72 h for *p*-anisidine, 24 h for benzylamine, and 3 h for a methanolic solution of ammonia). The reaction mixture was cooled intensely and the precipitated bright red solid 3-amino-5-(dimethylaminomethylene)amino-1-methyl-4-nitropyrazole **6A** was separated, and crystallized from ethanol; mp 191-193°C. $M^{+\cdot}$ 212. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.99, 3.08 (6H, s, $N(CH_3)_2$); 3.36 (3H, s, 1-CH_3); 6.00 (2H, br. s, NH_2); 8.12 (1H, s, CH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 33.8 ($N(CH_3)_2$); 40.2 ($CH_{3(1)}$), 110.0 ($C_{(4)}$); 147.4($C_{(5)}$); 150.3 ($C_{(3)}$); 159.1 ($C_{(5a)}$). Found, %: C 40.00; H 5.92; N 39.38. $C_7H_{12}N_6O_2$. Calculated, %: C 39.62; H 5.70; N 39.60.

The filtrate was evaporated to dryness and the oily residue treated with 6% methanolic hydrochloric acid solution until a weakly acid reaction was obtained. The obtained hydrochlorides of substituted formamidines of *p*-anisidine **7**, **8**, and benzylamine **9** were filtered off and crystallized from absolute alcohol.

N,N-Dimethylamino-N'-(4-methoxyphenyl)iminoformamide (7). Mp 126-128°C. $M^{+\cdot}$ 178. Found, %: C 55.86; H 6.97; N 13.31. $C_{10}H_{14}N_2$.HCl. Calculated, %: C 55.94; H 7.04; N 13.05.

N,N'-Bis(4-methoxyphenyl)iminoformamide (8). Mp 134-138°C. $M^{+\cdot}$ 256. Found, %: C 61.55; H 6.01; N 9.39. $C_{15}H_{16}N_2O_2$.HCl. Calculated, %: C 61.54; H 5.85; N 9.57.

N,N''-Dibenzyliminoformamide (9). Mp 126-128°C. $M^{+\cdot}$ 224. Found, %: C 66.55; H 6.79; N 9.93. $C_{15}H_{16}N_2$.HCl.½H_2O. Calculated, %: C 66.78; H 6.72; N 10.38.

3,5-Diamino-1-methyl-4-nitropyrazole (10). A solution of pyrazole **6** (1.0 g, 4.7 mmol) in 20% methanolic ammonia solution (4 ml) and methanol (40 ml) was heated in a bomb at 140°C for 24 h. The reaction mixture was evaporated in vacuum and the residue recrystallized from isopropyl alcohol with a yield of 0.7 g (97%) of a bright red crystalline substance; mp 181-183°C. $M^{+\cdot}$ 157. Found, %: C 30.42; H 4.54; N 44.38. $C_4H_7N_5O_2$. Calculated, %: C 30.58; H 4.49; N 44.57.

Reaction of 3,5-Bis(dimethylaminomethylene)amino-4-nitropyrazole (2) with *p*-Anisidine. A solution of compound **2** (0.6 g, 2.4 mmol) and *p*-anisidine (0.6 g, 4.9 mmol) in methanol (40 ml) was refluxed for 4 h. The reaction mixture was cooled, and compound **1** (0.3 g, 90%) was filtered off (bright red solid). The filtrate was evaporated to dryness, and treated with 6% methanolic hydrochloric acid solution until a weakly acid reaction was obtained. The solid compound **7** formed was separated, and crystallized from absolute alcohol.

X-ray Structural Investigation. A finely crystalline powder was synthesized for the determination of the crystal structure. The powder diffraction spectrum was measured at room temperature in a Gine camera (Cu*K/I* radiation, the spectrum was plotted with a photofilm photodensitometer with a step of 0.01°, the sample was prepared by a special procedure for smoothing out textural effects). The parameters of the triclinic unit cell were determined with the ITO indexing program [6]. The crystal structure was solved by the systematic search method of [7] and refined by the Ritveld method with the MRIA program [8] (all details of the experiment, indexing, solution, and refinement of the structure, and also the coordinates and thermal parameters of atoms are given in a separate publication [9]).

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