# REACTIONS OF 4,5-DIAMINO-3-METHYL-1-PHENYLPYRAZOLE WITH AROMATIC HALOKETONES

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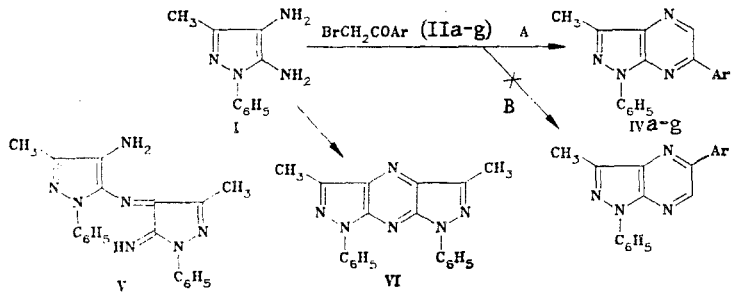
Reaction of 4,5-diamino-3-methyl-1-phenylpyrazole with ω-bromoacetophenones yields pyrazolo[4,5-b]pyrazines. A side product is 1-phenyl-3-methyl-5-imino-4-[(1-phenyl-3-methyl-4-aminopyrazol-5-yl)imino]-2-pyrazoline obtained by dimerization of the starting diaminopyrazole with loss of ammonia and a molecule of hydrogen.

One of the methods for synthesizing pyrazines with an annelated aromatic or heterocyclic nucleus is the reaction of 1,2-diamines with ω-bromoacetophenones [1]. As a rule the intermediate formed dihydropyrazines are unstable and readily aromatized [2].

In this work we have synthesized pyrazolo[4,5-b]pyrazines from 4,5-diamino-3-methyl-1-phenylpyrazole (I) and para-substituted ω-bromo-acetophenones (IIa-g). Interest in these compounds is due to the high pharmacological activity, peculiar to certain members of the series [3, 4]. We have also studied the possible reaction of diamine I with 1,3-diaryl-2,3-dibromo-1-propanones (III).

Refluxing ketones II with diamine I in methanol in the presence of sodium acetate (for reagent II) or triethylamine (for III) gives the pyrazolo[4,5-b]pyrazines (IVa-g) and the side product V in appreciable yield (up to 20%). Experiments with the dibromides III and diamine I gave V as the basic reaction product.




II, IV a Ar=$C_6H_5$; b Ar=$C_6H_4CH_3$-*p*; c Ar=$C_6H_4OCH_3$-*p*; d Ar=3,5-$Br_2$-4-$NH_2$-$C_6H_2$; e Ar=$C_6H_4C_6H_5$-*p*; f Ar=$C_6H_4Cl$-*p*, g Ar=$C_6H_4NO_2$-*p*

Formation of the 3-methyl-1-phenyl-6-aryl-1H-pyrazolo[4,5-b]-pyrazines (IV) was confirmed by elemental analytical data and spectral characteristics (Table 1). Thus the IR spectra showed intense bands at 1590-1600 $cm^{-1}$ ($\nu_{C=N}$) and the absence of $\nu_{C=O}$ and $\nu_{N-H}$ bands characterizing the starting and intermediate compounds. Compounds IVa-g have similar electronic spectra in which the long wave absorption consists of two bands. As was to be expected based on the rigid pyrazolopyrazine structure compounds IVa-g show clearly marked fluorescence properties. The PMR spectra of these compounds show a singlet methyl signal at ~2.6 ppm and a pyrazine ring CH at ~9.15 ppm as well as aromatic proton multiplets.

The question arises of the nonequivalence of the amino groups in the diamine I and the course of the reaction with ketones II. The reaction of aromatic o-diamines with ω-bromoacetophenones occurs in two stages with nucleophilic substitution of the bromine atom followed by

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condensation at the carbonyl group [5]. Because the nucleophilicity of the amino group at position 4 of the diamine I is significantly greater than the amino group at 5 [6] it is logical to propose that it is this amino group which takes part in the nucleophilic substitution stage. An additional factor which routes the reaction course through path A is probably a steric effect of the phenyl radical in the pyrazole ring. This proposal is supported by formation of two isomers in the reaction of 4,5-diamino-3-hydroxy-1H-pyrazole with α-diketones [7].

The occurrence of the reaction by route A was confirmed by independent synthesis of 5-amino-4-nitroso-3-methyl-1-phenylpyrazole with acetophenone and of phenylglyoxal with diamine I. Compound IVa was obtained via these reactions and was controlled by TLC, melting point, and spectral characteristics.

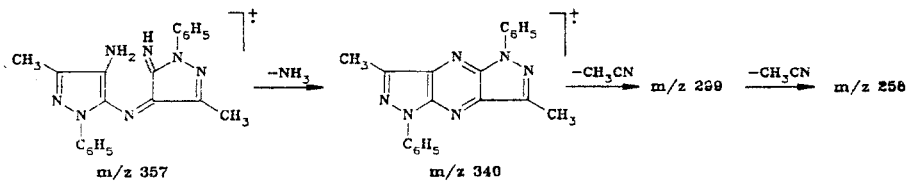
The proposed reaction course is in agreement with data from [8] according to which the reaction of 5-amino-4-phenylazo-3-methylpyrazole with acetophenone gives 1,6-diphenyl-3-methylpyrazolo[4,5-b]pyrazine (IVa).

The 1,2-dihydropyrazolo[4,5-b]pyrazines are undoubtedly the intermediates in the reactions of diamine I with bromoketones II as implicated in the study of analogous reactions of o-phenylenediamine with ω-bromoacetophenones [2]. In attempting to isolate the dihydro derivatives we have varied the reaction temperature and the catalyst (triethylamine, alkali) carrying out the reaction in an inert (methane) atmosphere. Isolation of the dihydro derivatives proved unsuccessful, the strong tendency towards dehydrogenation probably being explained by annelation of the dihydropyrazine ring with the pyrazole.

In the experiments described above the formation of IV was always accompanied by V. Its appearance was also observed in the absence of the bromoketone II. Moreover, refluxing an alcohol solution of diamine I which contained 3% (by volume) of acetic acid increased the rate of formation and the yield of V. Thus it followed that compound V was also the main product of the reaction of diamine I with dibromide III. Carrying out this reaction instead in refluxing toluene led to formation of chalcones, ammonium bromide, and luminescent compound VI. The chalcones were identified from the UV spectra of the corresponding chromatographic fractions and by separation and investigation of their 2,4-dinitrophenylhydrazones. Their formation signifies that the process of debromination of III is of a general nature for the described reaction conditions.

Compounds V and VI were identified by elemental analysis and by spectral methods (Table 1). Thus characterizing the electronic spectrum of V is the appearance of two visible bands ($\lambda_{max}$ 431 and 390 nm) pointing to the presence of an extended chromophoric system. The IR spectrum showed three bands in the N–H bond region (3397, 3310, and 3281 $cm^{-1}$) and intense $\nu_{C=N}$ band at 1601 $cm^{-1}$.

The PMR spectra of V were measured in $CDCl_3$, $C_5D_5N$, and $CF_3COOH$ and showed methyl group singlets at 2.58 and 2.64 ppm (2.56 and 2.23 ppm in $CF_3COOH$) and an aromatic multiplet at 7.4-8.1 ppm. Unambiguous identification of the $NH_2$ or NH PMR signals could not be made. The main structural support for V came from its mass spectrum. The mass spectral molecular weight for V was equal to twice that of the starting diamine I minus 19 atomic mass units ($M^+$ 357, $NH_3$ and $H_2$). The peak of maximum intensity $[M - 17]^+$ (m/z 340) can be explained by formation of a stable bispyrazolopyrazine structure via elimination of ammonia from $M^+$. The second most intense peak (82%) is that of the phenyl cation. The overall fragmentation scheme can be represented by the scheme




In contrast to V compound VI showed electronic absorption at shorter wavelength (Table 1), the absence of an NH band in the IR spectrum, and the presence of fluorescence at $\lambda_{max}$ 492 nm. The PMR spectrum showed only one methyl singlet (δ2.62 ppm) and an aromatic multiplet in the intensity ratio 3:5. This data and that from elemental analysis indicates that VI is formed by dimerization of I with loss of two molecules of ammonia and one of hydrogen. It has been

TABLE 1. Parameters for IVa-g, V, and VI

| Compound | mp, °C | $R_f$ | $\lambda_{max}$, nm ($\varepsilon \cdot 10^{-3}$) (in ethanol) | Found N, % | Empirical formula | Calculated N, % | Yield, % |
|---|---|---|---|---|---|---|---|
| IV a | 185 | 0,25 | 241 (20,2), 272 (22,7), 318 (14,0), 334 sh | 19,5 | $C_{18}H_{14}N_4$ | 19,5 | 56 |
| IV b | 194 | 0,19 | 252 (25,5), 273 (23,4), 338 (17,4) | 18,6 | $C_{19}H_{16}N_4$ | 18,6 | 55 |
| IV c | 180 | 0,11 | 256 (37,9), 275 sh., 355 (21,3) | 17,6 | $C_{19}H_{16}N_4O$ | 17,7 | 40 |
| IV d | 256 | 0,20 | 263 (23,1), 325 sh, 375 (19,8) | 15,1 | $C_{18}H_{14}Br_2N_5$ | 15,3 | 38 |
| IV e | 238 | 0,29 | 259 (20,1), 281 sh., 348 (13,6) | 15,4 | $C_{24}H_{18}N_4$ | 15,5 | 52 |
| IV f | 200 | 0,18 | 244 (25,2), 273 (24,6), 327 (15,1) | 17,4 | $C_{18}H_{13}ClN_4$ | 17,4 | 51 |
| IV g | 205—206 | 0,20 | 259 (20,1), 323 (23,7), 325 (20,9) | 21,0 | $C_{18}H_{13}N_5O_2$ | 21,1 | 50 |
| V* | 274 | 0,05 | 274 (25,9), 403 (22,3), 433 (24,8) | 27,5 | $C_{20}H_{19}N_7$ | 27,5 | 42 |
| VI | 204 | 0,45 | 250 (32,6), 279 (37,3), 360 (9,1), 407 sh | 24,7 | $C_{20}H_{16}N_6$ | 24,7 | 69 |

*IR spectrum (KBr): 3281 ($\nu_{NH}$), 3310, and 3397 $cm^{-1}$ ($\nu_{NH_2}$).

reported before [9] as the product of the reaction of 5-amino-3-methyl-1-phenylpyrazole with its 4-nitroso derivative in glacial acetic acid. Because of the insignificant differences in melting points and $\lambda_{max}$ for our preparation of VI and the literature report we have reproduced the previously reported experiment. The products of both reactions were identical in all respects.

It can be assumed that V is an intermediate in the process of forming VI but attempts to cyclize V to VI have proved unsuccessful (refluxing alcohol, toluene, or DMF solutions in the presence of HCl, HOAc or triethylamine). V was recovered unchanged. This also served as a basis for preferring the first of the possible dimer structures, viz., 4,5', 4,4' and 5,5'. It should also be noted that the 5-aminopyrazoles tended to amine-enamine tautomerism [10]. This process is probably the first step to dimerization, the participation of one or the other amino groups of the second molecule of I determining the formation of V or VI.

Formation of the bispyrazolopyrazine is only possible via its dihydro derivative. It is suggested that the dibromide takes part in an oxidative-reductive interaction with it since chalcones can be extracted from the reaction mixture along with VI. There is, however, no direct demonstration of the occurrence of this reaction.

## EXPERIMENTAL

Electronic absorption spectra were measured on a Specord UV-vis for ethanol solutions at concentrations of $(2-3) \cdot 10^{-5}$ μ. PMR spectra were recorded on a Tesla-80 in $CDCl_3$ with TMS as internal standard and IR spectra on a Specord IR-75 for KBr tablets. Mass spectra were recorded by direct probe insertion on a Varian MAT-311A with accelerating intensity 3 kV, inlet temperature 160°C, cathode emission current 30 μA, and ionization intensity 70 V. Sample purity was controlled by TLC on Silufol UV-252 plates with chloroform eluant.

3-Methyl-1,6-diphenylpyrazolo[4,5-b]pyrazine (IVa). A solution containing 3-methyl-1-phenyl-4,5-diaminopyrazole (1.88 g, 0.01 mole), ω-bromoacetophenone (1.99 g, 0.01 mole), and sodium acetate (0.83 g, 0.01 mole) was refluxed for 1.5 h. The precipitate was filtered off, recrystallized from methanol, and purified by chromatography on an $Al_2O_3$ column (chloroform eluant) to give the pyrazolopyrazine (IVa, 1.6 g, 56%) with mp 185°C (lit. mp 186°C [8]).

Compounds IVb-g were obtained similarly.

1-Phenyl-3-methyl-5-imino-4-[(1-phenyl-3-methyl-4-aminopyrazol-5-yl)imino]-2-pyrazoline (V). HOAc (1 ml) was added to a solution of 3-methyl-1-phenyl-4,5-diaminopyrazole (1.88 g, 0.01 mole) in methanol (20 ml) and refluxed for 1 h. The bright yellow, fibrous crystals precipitated from the hot solution were filtered off and crystallized from methanol to give V (0.7 g, 40%) with mp 274°C; $M^+$ 357.

3,5-Dimethyl-1,7-diphenylbispyrazolo[3,4-b; 4',3'-e]pyrazine (VI). A solution of 3-methyl-1-phenyl-4,5-diaminopyrazole (1.88 g, 0.01 mole) in toluene (30 ml) was refluxed for

2 h. After cooling the precipitated crystals were filtered off and crystallized from alcohol to give VI (1.18 g, 69%).

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# HOMOLYTIC ALKYLATION OF BENZIMIDAZOLE BY 1,4-DIOXANE


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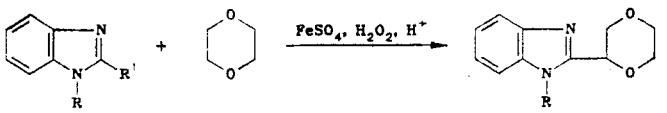
The homolytic alkylation of benzimidazoles by 1,4-dioxane has been studied. Introduction of an ethyl group at position 1 and a sulfonic group at position 2 of the heterocycle lowers the yield of products of substitution of hydrogen or the sulfonic group at position 2 by a dioxanyl radical.


The synthesis of 2-hydroxymethylbenzimidazoles by alkylation of benzimidazoles with methanol in the presence of $AgNO_3$ + $(NH_4)_2S_2O_8$ initiator has been reported [1]. Various 2-substituted benzimidazoles have also been synthesized [2] by homolytic alkyldesulfonation of benzimidazole-2-sulfonic acids using the above system with organic acids as the alkyl radical source.

We have investigated the homolytic substitution of hydrogen and the sulfonic group in benzimidazole (I), the 2-sulfonic acid (III), and their 1-ethylsubstituted analogs (II, IV) by the radical derived from the cyclic ether 1,4-dioxane.

It has been shown that, with initiation using the $FeSO_4$ + $H_2O_2$ oxidation-reduction system, benzimidazole (I) protonated by sulfuric acid forms 2-(1,4-dioxan-2-yl)benzimidazole (V) in 75% yield (~70% conversion based on I). The alkylation is carried out with a 20:1 molar reagent ratio of dioxane:I in an atmosphere of argon at 20°C. In the absence of the initiator system formation of V was not observed.




I–IV V, VI

I, III, V R=H; II, IV, VI R=$C_2H_5$; I, II R'=H; III, IV R'=$SO_3H$

Similar conditions gave 1-ethyl-2-(1,4-dioxan-2-yl)benzimidazole (VI) from 1-ethylbenzimidazole (II) but the yield of VI was somewhat lower (51%) and the conversion of starting II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