SYNTHESIS OF 4-ALKYLPYRAZOLO[1,5-a]BENZIMIDAZOLES

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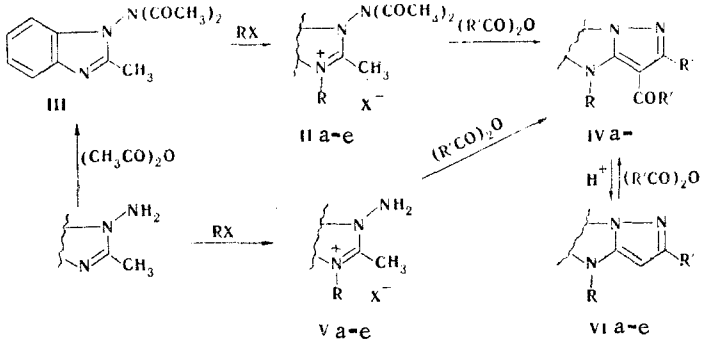
2,4-Disubstituted pyrazole[1,5-a]benzimidazoles were obtained by the action of carboxylic acid anhydrides on 1-amino-2-methyl-3-alkylbenzimidazolium salts in the presence of potassium carbonate.

N-Amino derivatives of azoles constitute a little-investigated but extremely promising class of starting compounds for the synthesis of condensed heterosystems, with a common nitrogen atom, particularly pyrazolo[1,5-a]benzimidazoles.

Up until now these compounds were synthesized by building on to the benzimidazole ring starting from 1-[o-amino(chloro)phenyl]-5-amino(hydroxy)pyrazoles [1, 2]. As a result of this condensation, NH-unsubstituted pyrazolo[1,5-a]benzimidazoles are formed. Alkylation of the latter leads to a mixture of 2,4-dialkylpyrazolobenzimidazole and its quaternary salt [3]. An unsuccessful attempt to synthesize 4-alkyl derivatives of pyrazolobenzimidazole by 1,3-cycloaddition of substituted acetylenes to the 1-alkyl-3-iminobenzimidazolium ion is described in [4].

We were able to accomplish the synthesis of 4-alkylpyrazolo[1,5-a]benzimidazoles (I) via the scheme that is well known for certain azines [5] starting from 1-amino-2-methyl-3-alkylbenzimidazolium salts and carboxylic acid anhydrides. Taking into account the fact that the quaternization of 1-aminobenzimidazole with alkyl halides proceeds ambiguously [6], 1-amino-2-methylbenzimidazole was initially acylated to obtain salt II, and the resulting diacetyl derivative III was heated in an ampul (at 100°C) with excess methyl iodide. The formation of a pyrazole ring takes place readily when salt II is refluxed with acetic anhydride in the presence of potassium carbonate, during which the 3 position is simulteneously acetylated.

The PMR spectrum of 3-acetyl derivative IVa contains three singlets with identical intensities at δ 2.4 (C—CH_3), 2.55 ($COCH_3$), and 3.45 ppm (N—CH_3); a signal of four aromatic protons appears in the form of a multiplet at δ 7.3 ppm. As in the case of its structural analogs [7, 8], the band of stretching vibrations of the carbonyl group in the IR spectrum of IVa is shifted to the low-frequency region (1630-1645 cm^{-1}).



II, IV, V, VI a,b,e R = CH_3; c R = C_2H_5; d R = C_3H_7; IV, VI a,c,d R' = CH_3; b R' = C_2H_5; e R' = C_6H_5

It was subsequently found that prior protection of the amino group is not necessary, since the corresponding 3-carbonyl derivatives IV are formed in high yields from V.

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3-Benzoyl-2-phenylpyrazolo[1,5-a]benzimidazole (IVe) is formed when salt Ve and benzoic anhydride are heated at 170°C with potassium carbonate or when Ve is refluxed with benzoyl chloride in pyridine for many hours. However, in the latter case the reaction is accompanied by pronounced resinification, and the yield of IVe does not exceed 30%.

Like its π-electron analogs imidazo- and pyrrolo[1,2-a]benzimidazoles [7, 8], 3-acetyl derivatives IVa-d undergo smooth hydrolysis to 2,4-dialkylpyrazolobenzimidazoles VI in an acidic medium. The protons of the methyl groups in the PMR spectrum of 2,4-dimethylpyrazolo-[1,5-a]benzimidazole (VIa) appear at 2.13 and 3.7 ppm, and a multiplet of four aromatic protons at δ 7.2 and a singlet signal of the 3-H proton at 5.3 ppm are observed.

3-Benzoyl-substituted IVe is considerably more resistant to acid hydrolysis. Up to 60% of the starting compound is regenerated even after prolonged refluxing (40 h) in concentrated HCl. Attempts to saponify Ve in alkali or by means of sodium amide by the Haller—Bauer method [9] were unsuccessful.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Tesla BS-467 spectometer with hexamethyldisiloxane as the internal standard.

1-Amino-2-methylbenzimidazole. A solution of 45 g (0.4 mole) of hydroxylamine-O-sulfonic acid in 50 ml of water previously neutralized with sodium bicarbonate was added at 65-70°C to a solution of 20 g (0.15 mole) of 2-methylbenzimidazole and 35 g (0.62 mole) of KOH in 500 ml of water. After the mixture had cooled spontaneously to 50°C, the precipitate was removed by filtration and washed with cold water to give 15.6 g (70%) of colorless needles with mp 158-159°C (from water) (mp 158-160°C [10]).

1-Diacetamido-2-methylbenzimidazole (III). A solution of 4.5 g (0.03 mole) of 1-amino-2-methylbenzimidazole in 10 ml of acetic anhydride was heated at 100°C for 30 min, after which it was treated with 50 ml of water and neutralized with sodium bicarbonate. The resulting precipitate was removed by filtration and washed with water to give 6.2 g (89%) of colorless needles with mp 122°C (from ethyl acetate). IR spectrum: 1737 and 1748 cm^{-1} [$N(COCH_3)_2$]. Found %: C 62.1; H 5.8; N 18.3. $C_{12}H_{13}N_3O_2$. Calculated %: C 62.3; H 5.7; N 18.2.

1,2-Dimethyl-3-diacetamidobenzimidazolium Iodide (IIa). A mixture of 10.2 g (0.04 mole) of III and 5 ml of methyl iodide in 20 ml of alcohol was heated in an ampul at 100°C for 3 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with acetone to give 15 g of colorless prisms with mp 216-217°C (dec., from alcohol). Found %: C 42.0; H 4.5; I 33.9; N 11.1. $C_{13}H_{16}IN_3O_2$. Calculated %: C 41.8; H 4.3; I 34.0; N 11.3.

1,2-Dimethyl-3-aminobenzimidazolium Iodide (Va). A solution of 1.47 g (0.01 mole) of 1-amino-2-methylbenzimidazole and 0.5 ml of methyl iodide in 15 ml of alcohol was refluxed for 5 h, after which it was cooled, and the precipitate was removed by filtration and washed with alcohol and ether to give 2.6 g (90%) of colorless prisms with mp 204-205°C (dec., from alcohol). IR spectrum: 3200 and 3270 cm^{-1} (N—NH_2). Found %: C 37.2; H 4.3; I 44.0; N 14.3. $C_9H_{12}IN_3$. Calculated %: C 37.4; H 4.2; I 43.9; N 14.5.

1-Ethyl-2-methyl-3-aminobenzimidazolium Iodide (Vc). This compound, with mp 158-159°C (dec., from alcohol with ethyl acetate), was obtained as colorless needles in 90% yield by the method indicated above. IR specrtum: 3110, 3150, and 3245 cm^{-1} (N—NH_2). Found %: C 39.5; H 4.7; I 42.0; N 14.0. $C_{10}H_{14}IN_3$. Calculated %: C 39.6; H 4.6; I 41.9; N 13.9.

1-Propyl-2-methyl-3-aminobenzimidazolium Iodide (Vd). This compound was similarly obtained. Workup gave colorless plates, with mp 186-187°C (dec., from ethyl acetate with alcohol), in 76% yield. IR spectrum: 3115, 3175, and 3220 cm^{-1} (N—NH_2). Found %: C 41.5; H 4.9; I 40.2; N 13.5. $C_{11}H_{16}IN_3$. Calculated %: C 41.4; H 5.0; I 40.1; N 13.6.

2,4-Dimethyl-3-acetylpyrazolo[1,5-a]benzimidazole (IVa). A) A mixture of 2 g (5 mmole) of salt IIa and 1.4 g (10 mmole) of anhydrous K_2CO_3 in 10 ml of acetic anhydride was refluxed for 2 h, after which it was cooled and poured over 50 g of ice. The aqueous mixture was neutralized with $NaHCO_3$, and the black precipitate was removed by filtration, washed with water, and purified by chromatography with a column filled with Al_2O_3 (elution with chloroform) to give 1.05 g (92%) of cream-colored needles with mp 220°C (from alcohol). PMR spectrum (in CF_3COOH): 2.4 (3H, s, C_2—CH_3), 2.55 (3H, s, $COCH_3$), 3.45 (3H, s, N—CH_3), and 7.3

ppm (4H, m). IR spectrum: 1645 cm^{-1} (C=O). Found %: C 69.0; H 5.6; N 18.7. $C_{13}H_{13}N_3O$. Calculated %: C 68.7; H 5.7; N 18.5.

B) A mixture of 1.6 g (5.5 mmole) of iodide Va and 1.4 g (10 mmole) of anhydrous K_2CO_3 in 10 ml of acetic anhydride was refluxed for 3 h, after which it was cooled and diluted with water. The aqueous mixture was neutralized with ammonia, and the gray precipitate was removed by filtration and purified by chromatography on Al_2O_3 (elution with chloroform) to give 1 g(80%) of cream-colored needles with mp 219-220°C (from alcohol). No melting-point depression was observed for a mixture of this product with a sample of the product obtained in experiment A.

2-Methyl-4-ethyl-3-acetylpyrazolo[1,5-a]benzimidazole (IVc). A mixture of 4 g (13 mmole) of salt Vc and 1.6 g (12 mmole) of potassium carbonate in 20 ml of acetic anhydride was refluxed for 3 h, after which IVc was isolated and purified as in experiment A. The yield of light-yellow prisms with mp 150-151°C (from heptane with benzene) was 2.5 g (78%). IR spectrum: 1640 cm^{-1} (C=O). Found %: C 70.0; H 6.0; N 17.5. $C_{14}H_{15}N_3O$. Calculated %: C 69.7; H 6.2; N 17.4.

2-Methyl-4-propyl-3-acetylpyrazolo[1,5-a]benzimidazole (IVd). This compound was obtained in 75% yield by the method indicated above. The light-yellow needles had mp 89-90°C (from heptane). IR spectrum: 1640 cm^{-1} (C=O). Found %: C 70.4; H 6.7; N 16.3. $C_{15}H_{17}N_3O$. Calculated %: C 70.6; H 6.7; N 16.5.

2-Ethyl-4-methyl-3-propionylpyrazolo[1,5-a]benzimidazole (IVb). This compound was obtained in 73% yield from salt Va and propionic anhydride under conditions similar to those in the preparation of IVa. The colorless needles had mp 156-157°C (from alcohol). IR spectrum: 1645 cm^{-1} (C=O). Found %: C 70.5; H 6.6; N 16.5. $C_{15}H_{17}N_3O$. Calculated %: C 70.6; H 6.7; N 16.5.

2-Phenyl-4-methyl-3-benzoylpyrazolo[1,5-a]benzimidazole (IVe). A) A mixture of 0.75 g (2.6 mmole) of iodide Va, 0.36 g (2.6 mmole) of potassium carbonate, and 2 g (8.8 mmole) of benzoic anhydride was heated at 170°C for 3 h, after which it was cooled and treated with 50 ml of a saturated solution of sodium carbonate. The resulting mixture was warmed to decompose the excess anhydride, and the precipitate was removed by filtration and washed with water to give 0.75 g (86%) of light-yellow needles with mp 172°C (from alcohol). IR spectrum: 1630 cm^{-1} (C=O). Found %: C 78.6; H 5.0; N 12.1. $C_{23}H_{17}N_3O$. Calculated %: C 78.7; H 4.8; N 12.0.

B) A mixture of 0.75 g (2.6 mmole) of iodide Va and 0.8 ml (7 mmole) of benzoyl chloride in 4 ml of pyridine was refluxed for 6 h, after which it was cooled and poured into 50 ml of water. The aqueous mixture was extracted with 30 ml of benzene, and the benzene extract was washed several times with water to remove the pyridine and chromatographed with a column filled with Al_2O_3 (elution with benzene) to give 0.25 g (28%). The product was identical to a previously described sample with respect ot its physicochemical properties.

2,4-Dimethylpyrazolo[1,5-a]benzimidazole (VIa). A solution of 2.27 g (10 mmole) of IVa in 30 ml of concentrated HCl was refluxed for 3 h, after which it was cooled and neutralized with 22% NH_4OH, and the resulting oil was extracted with chloroform. Workup of the extract gave 1.66 g (90%) of colorless needles with mp 92°C (from hexane) (mp 80°C [13]). PMR spectrum (in C_6F_6): 2.13 (3H, s, C–CH_3), 3.7 (3H, s, N–CH_3), 5.3 (1H, s, C_3–H), and 7.2 ppm (4H, m). Found %: C 71.5; H 6.0; N 22.5. $C_{11}H_{11}N_3$. Calculated %: C 71.3; H 5.9; N 22.7. 3-Acetyl derivative IVa was formed in 80% yield by refluxing VIa with acetic anhydride in the presence of potassium carbonate for 3 h.

2-Methyl-4-ethylpyrazolo[1,5-a]benzimidazole (VIc) Hydrochloride. This compound was obtained in 90% yield by the method indicated above. The colorless crystals had mp 234-235°C (from alcohol with ethyl acetate). Found %: C 60.8; H 5.4; Cl 15.0; N 18.0. $C_{12}H_{13}N_3 \cdot HCl$. Calculated %: C 61.0; H 5.6; Cl 15.2; N 17.8.

2-Ethyl-4-methylpyrazolo[1,5-a]benzimidazole (VIb) Hydrochloride. This compound was obtained in 75% yield from IVb under conditions similar to those in the preparation of VIa. The light-pink prisms had mp 232-233°C (dec., from alcohol with ethyl acetate). Found %: C 60.9; H 5.5; Cl 15.1; N 17.7. $C_{12}H_{13}N_3 \cdot HCl$. Calculated %: C 61.0; H 5.6; Cl 15.2; N 17.8.

2-Methyl-5-propylpyrazolo[1,5-a]benzimidazole (VId) Hydrochloride. This compound was obtained in 98% yield under conditions similar to those in the preparation of VIa. The

colorless prisms had mp 189-190°C (from alcohol with ethyl acetate). Found %: C 62.5; H 6.3; Cl 14.1; N 17.0. $C_{13}H_{15}N_3 \cdot HCl$. Calculated %: C 62.4; H 6.4; Cl 14.2; N 16.8.

2-Phenyl-4-methylpyrazolo[1,5-a]benzimidazole (VIe). A mixture of 0.5 g (1.4 mmole) of IVe in 30 ml of concentrated HCl and 10 ml of alcohol was refluxed for 40 h, after which it was cooled, and 0.3 g (60%) of starting compound was removed by filtration. Workup of the filtrate after neutralization with 22% NH_4OH gave 0.15 g (40%) of colorless needles of VIe with mp 98-100°C (from alcohol). Found %: C 77.5; H 5.1; N 16.8. $C_{16}H_{13}N_3$. Calculated %: C 77.7; H 5.3; N 17.0.

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SYNTHESIS, STRUCTURE, AND TAUTOMERISM OF FORMAZANS THAT CONTAIN 1-ARYL-2-BENZIMIDAZOLYL RESIDUES

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1,5-Bis(1-aryl-2-benzimidazolyl)-3-methyl- and 1-(p-tolyl)-3-methyl-5-(1-aryl-2-benzimidazolyl)formazans were synthesized. It was shown by IR spectroscopy (from the change in the spectral characteristics of the NH groups) that the formazans exist in the imino form in solutions in CCl_4, whereas a tautomeric equilibrium between the amino and imino forms of the investigated compounds is observed in solutions in $CHCl_3$.

It has been shown [1] that formazans that contain 1-alkyl- or 1-benzyl-2-benzimidazolyl groups in the 1(5) position exist in the open imino form, regardless of the substituent (methyl or phenyl) in the 3 position. The localization of the proton attached to the heterocyclic nitrogen atom in benzimidazolylformazans was explained by the considerable basicity of the benzimidazole ring. In [2] it was demonstrated experimentally that, depending on the character of the ring and the medium, hydrazones with various benzazolyl substituents can exist in a state of tautomeric amino—imino equilibrium.

It is known [3, 4] that the introduction of a phenyl group in the 1 position decreases the basicity of imidazole and benzimidazole. Proceeding from this, one might have expected that the amino form could also be observed for N-phenyl-substituted formazans in the equilibrium of tautomeric forms. The introduction of an ortho substituent will give rise to still greater noncoplanarity of the phenyl group [5] and will increase the shift of the equilibrium to favor the amino form.

In this connection, we synthesized a group of unsymmetrical (Ia-c) and symmetrical (IIa-c) formazans:

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