1-AMINO-2-ALKYLAMINOBENZIMIDAZOLES AND THEIR REACTIONS WITH CARBONYL-CONTAINING COMPOUNDS

T. A. Kuz'menko, V. V. Kuz'menko,
A. F. Pozharskii, and A. M. Simonov

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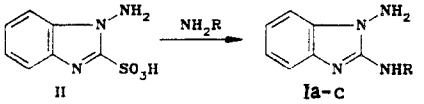
1-Amino-2-alkylaminobenzimidazoles were synthesized by a reaction involving exchange of the sulfo group in 1-aminobenzimidazole-2-sulfonic acid. 3-Alkyl-3H-1,2,4-triazolo[1,5-a]benzimidazoles and 4-alkyl-4H-1,2,4-triazinol[2,3-a]benzimidazol-3-ones were obtained on the basis of them.

In contrast to the relatively well-investigated 1,2-diaminobenzimidazole [1-3], 1-amino-2-alkylaminobenzimidazoles I have been unknown up until now. In the present paper we describe a method for the synthesis of these compounds and their conversion to 1,2,4-triazolo- and 1,2,4-triazinobenzimidazoles under the influence of carbonyl-containing compounds.

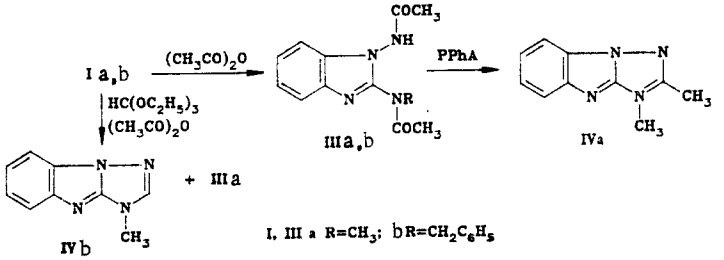
Our attempt to obtain 1-amino-2-methylaminobenzimidazole (Ia) by amination of 2-methylaminobenzimidazole by means of hydroxylamine-O-sulfonic acid (HASA) was unsuccessful — probably because of the insufficient solubility of the starting compound in aqueous alkali and the difficulty involved in the formation of the N anion. To obtain amines I we therefore selected another pathway, which consists in the N-amination of benzimidazole-2-sulfonic acid with subsequent exchange of the sulfo group for an amine residue. 1-Aminobenzimidazole-2-sulfonic acid (II) is formed in 73% yield by the action of HASA on benzimidazole-2-sulfonic acid in an alkaline medium. Replacement of the sulfo group by amines proceeds in high yields at 140-160°C in 30-40 min. Compounds Ia-c were obtained in this way.



II Ia-c

I aR=CH$_3$; bR=CH$_2$C$_6$H$_5$; cR=CH$_2$CH$_2$OH

It is known that 1,2-diaminobenzimidazole undergoes smooth cyclization to the corresponding 1,2,4-triazolo[1,5-a]benzimidazoles on refluxing with carboxylic acid anhydrides [1]. We have established that under similar conditions amines Ia, b are not converted to triazolo[1,5-a]benzimidazoles but form, with acetic anhydride, for example, only diacylation products IIIa, b. Cyclization also did not occur in a sealed ampul at 180-200°C or when perchloric acid, magnesium perchlorate, or boron trifluoride etherate was used as the catalyst. We were able to obtain 2,3-dimethyl-1,2,4-triazolo[1,5-a]benzimidazole (IVa) in 62% yield by heating diacetyl derivative IIIa in polyphosphoric acid (PPA, PPhA) at 200°C. In the case of benzyl-substituted IIIb the corresponding cyclic product was not isolated because of resinification of the reaction mixture.



IVb IIIa,b IVa

I, III a R=CH$_3$; bR=CH$_2$C$_6$H$_5$

The IR spectrum of triazolobenzimidazole IVa does not contain the characteristic absorption bands of C=O and NH groups that are observed in the spectrum of diacetyl derivative IIIa at 1715 and 3140 cm^{-1}, respectively, whereas it does contain bands at 1600 and 1645 cm^{-1},

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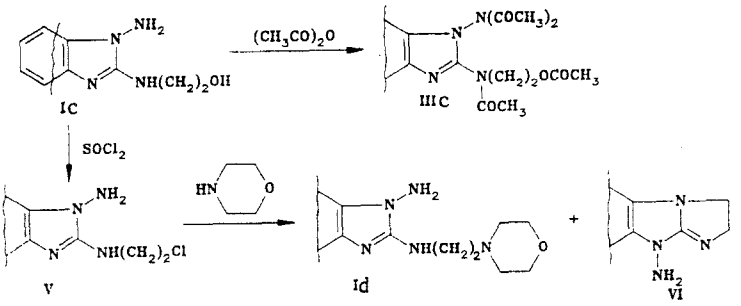
which correspond to the vibrations of a tricyclic system. 3-Methyl-3H-1,2,4-triazolo[1,5-a]-benzimidazole (IVb) is formed in 19% yield upon prolonged refluxing of amine Ia in ethyl orthoformate–acetic anhydride (1:1). The principal product in this case also is diacetyl derivative IIIa.

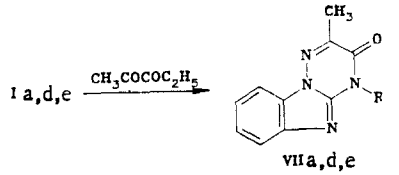
The pharmacological properties of 1,2,4-triazolo[1,5-a]benzimidazoles have not been previously studied. In order to obtain the most promising (in this respect) 3-(β-dialkylamino)alkyl derivatives we attempted to accomplish the cyclization of 1-amino-2-(2-hydroxyethylamino)benzimidazole (Ic) under the conditions used to obtain IVa. Refluxing of amino alcohol Ic in acetic anhydride leads to a compound, which, according to the PMR spectral data, is tetraacetyl derivative IIIc. However, its cyclization in PPA proceeds in a complex manner, and separation of the reaction mixture proved to be extremely difficult. Since the ambiguous character of the occurrence of this reaction may be due to the presence of a free alcohol group in the molecule, we decided to use genuine samples of 2-(2-dialkylaminoethylamino)benzimidazoles Id, e as the starting compounds.



1-Amino-2-(2-chloroethylamino)benzimidazole (V) is formed smoothly in the chlorination of amino alcohol Ic with thionyl chloride, but the subsequent nucleophilic exchange of the halogen in this compound upon refluxing with amines in benzene is accompanied by an undesirable side process – intramolecular cyclization to 9-amino-2,3-dihydroimidazo[1,2-a]benzimidazole (VI); the yields of the desired amines Id, e do not exceed 50-60%. It is therefore more convenient to synthesize 1-amino-2-(2-dialkylaminoethylamino)benzimidazoles Id, e from sulfonic acid II and the corresponding ethylenediamines (in 86-88% yields), although the latter are also considerably less accessible than 2-aminoethanol. 9-Aminobenzimidazole VI was obtained in close-to-quantitative yield from V by thermal cyclization without a solvent, which is a method previously proposed for the synthesis of 9-alkyl-2,3-dihydroimidazo[1,2-a]-benzimidazoles [4]. The structure of VI is in agreement with the IR and PMR spectral data and is also confirmed by the formation of the corresponding azomethine in the reaction with p-nitrobenzaldehyde.

The acylation of amine Id and subsequent cyclization of the resulting diacetyl derivative IIId in PPA lead to 2-methyl-3-(2-morpholinoethyl)-1,2,4-triazolo[1,5-a]benzimidazole (IVd) in 30% yield. Triazolobenzimidazole IVd is also formed directly from amine Id by heating in PPA in the presence of acetic acid.

In the case of pyruvic ester it was shown that, like 1,2-diaminobenzimidazole [1, 2], 1-amino-2-alkylaminobenzimidazoles I readily undergo condensation in acetic acid or ethanol (in the presence of $HClO_4$) with α-dicarbonyl compounds to give 4-alkyl-4H-1,2,4-triazino-[2,3-a]benzimidazolones VII.



I, VII a R=CH_3; d R=$CH_2CH_2N(CH_2CH_2)_2O$; e R=$CH_2CH_2N(C_2H_5)_2$

Thus, with respect to reactivities, 1-amino-2-alkylaminobenzimidazoles I differ little from 1,2-diaminobenzimidazole with respect to α-dicarbonyl compounds but undergo cyclization to 1,2,4-triazolo[1,5-a]benzimidazoles with considerably greater difficulty.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a Tesla BS-487 spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The course of the reactions and the purity of the compounds were monitored by TLC on plates with activity II aluminum oxide using chloroform as the eluent and development with iodine vapors.

1-Aminobenzimidazole-2-sulfonic Acid (II). A solution of 25 g (0.2 mole) of the sodium salt of HASA in 50 ml of water was added in portions in the course of 3-5 min at 35-40°C to a solution of 22 g (0.11 mole) of benzimidazole-2-sulfonic acid and 23.1 g (0.33 mole) of potassium hydroxide in 120 ml of water. After 5 min, a colorless precipitate began to form; the precipitate gradually turned pink and increased in volume. After spontaneous cooling to 20°C, the reaction mixture was acidifed with concentrated HCl to pH 1, and the precipitate was removed by filtration and washed with water to give 17.2 g (73%) of pale-pink needles with mp 252-253°C (from water). IR spectrum: 1075, 1232 (SO_3^-); 3220, 3365 cm^{-1} (NH_2). Found: C 39.6; H 3.2; N 20.0; S 14.9%. $C_7H_7N_3O_2S$. Calculated: C 39.4; H 3.3; N 19.7; S 15.0%.

1-Amino-2-methylaminobenzimidazole (Ia). A suspension of 6.4 g (30 mmole) of sulfonic acid II in 20 ml of a 25% solution of methylamine was heated for 1 h in a sealed ampul at 140°C, after which it was cooled, and the precipitate was removed by filtration and washed with cold water to give 4.2 g (87%) of colorless prisms with mp 173-174°C (from water). IR spectrum: 1610, 1655; 3145, 3280, 3418 cm^{-1} (NH, NH_2). Found: C 59.2; H 6.1; N 34.7%. $C_8H_{10}N_4$. Calculated: C 59.3; H 6.2; N 34.6%.

1-Amino-2-benzylaminobenzimidazole (Ib). A stirred mixture of 0.53 g (2.5 mmole) of sulfonic acid II and 1.5 ml (14 mmole) of benzylamine was heated for 45 min at 160°C. It was then cooled and treated with 30 ml of ether, and the precipitate was removed by filtration and washed with ether and hot water to give 0.45 g (76%) of colorless shiny crystals with mp 180-181°C (from ethyl acetate). IR spectrum: 1610, 1635; 3260, 3410 cm^{-1} (NH, NH_2). Found: C 70.3; H 6.1; N 23.3%. $C_{14}H_{14}N_4$. Calculated: C 70.6; H 5.9; N 23.5%.

1-Amino-2-(2-hydroxyethylamino)benzimidazole (Ic). A mixture of 6.4 g (0.03 mole) of sulfonic acid II and 7.2 ml (0.12 mole) of 2-aminoethanol was heated with stirring for 45 min at 160°C, after which it was cooled and treated with 15 ml of water, and the mixture was allowed to stand in a refrigerator for 2 h. The resulting precipitate was removed by filtration and washed with a small amount of ice water to give 4 g (69%) of colorless prisms with mp 184-185°C (from alcohol). IR spectrum: 1612, 1635, 2500-3300, 3325, 3360 cm^{-1}. Found: C 56.3; H 6.2; N 29.3%. $C_9H_{12}N_4O$. Calculated: 56.3; H 6.3; N 29,2%.

1-Acetamido-2-[(N-acetyl)methylamino]benzimidazole (IIIa). A solution of 0.32 g (2 mmole) of amine Ia in 3 ml of acetic anhydride was refluxed for 3 h, after which the excess acetic anhydride was removed by distillation to dryness under reduced pressure. The residue was triturated with ether, and the precipitate was removed by filtration to give 0.3 g (68%) of colorless crystals with mp 184-185°C (from ethyl acetate); the product was soluble in water. IR spectrum: 1715 (CO), 3140 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 1.85 (3H, s, $COCH_3$), 1.90 (3H, s, $COCH_3$), 3.0 (3H, s, N–CH_3), 7.13 (3H, m, 4-H–6-H), 7.5 (1H, m, 7-H), 10.15 ppm (1H, m, NH, vanishes after deuteration). Found: C 58.5; H 5.7; N 23.1%. $C_{12}H_{14}N_4O_2$. Calculated: C 58.5; H 5.7; N 22.8%.

1-Acetamido-2-[(N-acetyl)benzylamino]benzimidazole (IIIb). This compound was obtained in 87% yield by a method similar to that used to prepare IIIa. The colorless prisms had mp 177-179°C (from aqueous alcohol). Found: C 67.1; H 5.9; N 17.2%. $C_{18}H_{18}N_4O_2$. Calculated: C 67.1; H 5.6; N 17.4%.

2,3-Dimethyl-1,2,4-triazolo[1,5-a]benzimidazole (IVa). A stirred mixture of 0.74 g (3 mmole) of diacetyl derivative IIIa and 7 g of PPA was heated for 45 min at 200°C, after which it was cooled and treated with 20 ml of water, and the aqueous mixture was made alkaline to pH 10 with 20% KOH solution. The liberated dark oil was extracted with chloroform (three 20-ml portions) and purified by chromatography with a column packed with Al_2O_3 (2.5 by 20 cm) by elution with chloroform. The fraction with Rf 0.5 was selected and worked up to give 0.35 g (62%) of colorless prisms with mp 201-202°C (from benzene). IR spectrum: 1570, 1600, 1645 cm^{-1}. PMR spectrum ($CDCl_3$): 2.28 (3H, s, 2-CH_3), 3.48 (3H, s, N–CH_3), 7.13 (2H, m, aromatic), 7.6 ppm (2H, m, aromatic). Found C 64.4; H 5.6; N 29.9%. $C_{10}H_{10}N_4$. Calculated: C 64.5; H 5.4; N 30.1%.

Reaction of 1-Amino-2-methylaminobenzimidazole with Ethyl Orthoformate–Acetic Anhydride. A solution of 0.97 g (6 mmole) of amine Ia in 20 ml of ethyl orthoformate–acetic anhydride (1:1) was refluxed for 24 h, after which the excess reagent was removed by distillation to dryness at reduced pressure. The residue was dissolved in 10 ml of chloroform and chromatograhed with a column (2 by 30 cm) packed with Al_2O_3 by elution with chloroform. Workup of the first fraction (Rf 0.35) gave 0.2 g (19%) of 3-methyl-3H-1,2,4-triazolo[1,5-a]benzimidazole (IVb) in the form of colorless crystals with mp 149-150°C (from heptane–benzene). IR spectrum: 1605, 1658 cm^{-1}. PMR spectrum ($CDCl_3$): 3.60 (3H, s, N–CH_3), 7.18 (2H, m, aromatic), 7.64 (2H, m, aromatic), 7.65 ppm (1H, s, 2-H). Found: C 62.8; H 4.8; N 32.4%. $C_9H_8N_4$. Calculated: C 62.8; H 4.7; N 32.6%.

Elution with ethyl acetate gave a fraction with Rf 0.1, which was identified as 1-acetamido-2-[(N-acetyl)methylamino]benzimidazole (IIIa). The yield was 0.7 g (44%). With respect to its physicochemical characteristics the compound was identical to the sample described above.

1-Diacetylamino-2-[(N-acetyl)-2-acetoxyethylamino]benzimidazole (IIIc). A solution of 1.53 g (8 mmole) of amino alcohol Ic in 10 ml of acetic anhydride was refluxed for 3 h, after which it was cooled and poured into 30 ml of water, and the resulting precipitate was removed by filtration and washed with water to give 1.8 g (64%) of colorless crystals with mp 132-133°C (from alcohol). IR spectrum: 1700, 1720, 1750 cm^{-1} (CO). PMR spectrum ($CDCl_3$): 1.88 (3H, s, $COCH_3$), 2.15 (3H, s, $COCH_3$), 2.38 (6H, s, $COCH_3$, $OCOCH_3$), 3.88 (2H, t, –CH_2), 4.28 (2H, t, –CH_2), 7.2 (3H, m, 4-H–6-H), 7.68 ppm (1H, m, 7-H). Found: C 56.5; H 5.6. N 15.3%. $C_{17}H_{20}N_4O_5$. Calculated: C 56.7; H 5.6; N 15.6%.

1-Amino-2-(2-chloroethylamino)benzimidazole (V). A suspension of 3.84 g (20 mmole) of amino alcohol Ic and 1.4 ml (20 mmole) of thionyl chloride in 60 ml of dry chloroform was refluxed for 2 h. During this time the caramel-like mass on the surface of the reaction mixture crystallized completely. The mixture was cooled, and the precipitated hydrochloride of V was removed by filtration, washed with chloroform, and dried. It was then suspended in 20 ml of water, and the suspension was treated with sodium bicarbonate solution. The precipitate was removed by filtration and washed with ice water to give 3.5 g (83%) of colorless shiny plates with mp 125-127°C (from benzene). IR spectrum: 1605, 1625; 3360, 3430 cm^{-1} (NH, NH_2). Found: C 51.5; H 5.5; N 26.3%. $C_9H_{11}ClN_4$. Calculated: C 51.3; H 5.2; N 26.6%.

1-Amino-2-(2-morpholinoethylamino)benzimidazole (Id). A) A solution of 0.84 g (4 mmole) of amine V and 0.7 ml (8 mmole) of morpholine in 15 ml of dry benzene was refluxed for 5 h, after which it was cooled, and the precipitated morpholine hydrochloride was removed by filtration. The solution was evaporated to a small volume, and the concentration was chromatographed with a column (2 by 20 cm) packed with Al_2O_3 by elution with chloroform. Workup of the fraction with Rf 0.3 gave 0.62 g (61%) of colorless crystals that were soluble in water and had mp 154-155°C (from ethyl acetate). Found: C 59.6; H 7.4; N 26.9%. $C_{13}H_{19}N_5O$. Calculated: C 59.8; H 7.3; N 26.8%.

B) A mixture of 2.13 g (10 mmole) of sulfonic acid II and 2.6 g (20 mmole) of N-(2-aminoethyl)morpholine was fused at 140°C for 30 min, after which it was cooled and dissolved in chloroform, and the solution was passed through a layer (3.5 by 20 cm) of Al_2O_3 by elution with chloroform. The yield was 2.3 g (88%). The compound was identical to the compound described in experiment A.

1-Amino-2-(2-diethylaminoethylamino)benzimidazole (Ie). This compound was obtained in 87% yield by a procedure similar to that used to obtain amine Id by method B. The colorless plates had mp 116-117°C (from isooctane). Found: C 63.5; H 8.2; N 28.5%. $C_{13}H_{21}N_5$. Calculated: C 63.2; H 8.5; N 28.3%.

9-Amino-2,3-dihydroimidazo[1,2-a]benzimidazole (VI) Hydrochloride. A 0.42-g (2 mmole) sample of chloro derivative V was maintained for 5 min at 130-135°C, during which it crystallized completely. After cooling, the substance was triturated with ether, and the precipitated material was removed by filtration to give 0.42 g (91%) of colorless crystals that were soluble in water and had mp 245-247°C (from alcohol). IR spectrum: 3150, 3225 (NH_2), 3375, 3470 cm^{-1} (H_2O). PMR spectrum (D_2O): 4.23 (4H, s, CH_2–CH_2), 7.28 ppm (4H, m, aromatic). Found: C 47.2; H 5.7; Cl 15.3%. $C_9H_{10}N_4 \cdot HCl \cdot H_2O$. Calculated: C 47.3; H 5.7; Cl 15.5%.

9-(p-Nitrobenzylideneamino)-2,3-dihydroimidazo[1,2-a]benzimidazole. A solution of 0.23 g (1 mmole) of the hydrochloride of 9-amino derivative VI, 0.15 g (1 mmole) of p-nitrobenzal-

dehyde, and 0.15 ml (1.5 mmole) of piperidine in 10 ml of alcohol was refluxed for 45 min, after which it was cooled, and the bright-red precipitate was removed by filtration and washed with water and alcohol to give 0.24 g (80%) of a product with mp 199-200°C (from alcohol). IR spectrum: 1670 cm^{-1} (C=N). Found: C 62.2; H 4.3; N 22.7%. $C_{16}H_{13}N_5O_2$. Calculated: C 62.5; H 4.2; N 22.8%.

1-Acetamido-2-[(N-acetyl)-2-morpholinoethylamino]benzimidazole (IIId). This compound was obtained in 64% yield by a procedure similar to that used to prepare acetyl derivative IIIa; the product had mp 156-157°C (from benzene–heptane). PMR spectrum ($CDCl_3$): 1.85 (3H, s, $COCH_3$), 2.1 (3H, s, $COCH_3$), 2.3 (4H, m, $-N(CH_2)_2$), 2.55 (2H, m, $CH_2-N<$), 3.55 (4H, m, $(O(CH_2)_2$), 3.9 (2H, m, CH_2NAc), 7.25 (3H, m, aromatic), 7.65 (1H, m, aromatic), 11.78 ppm (1H, m, NH, vanishes after deuteration). Found: C 58.9; H 6.6; N 20.1%. $C_{17}H_{23}N_5O_3$. Calculated: C 59.1; H 6.8; N 20.4%.

2-Methyl-3-(2-morpholinoethyl)-1,2,4-triazolo[1,5-a]benzimidazole (IVd) Dihydrochloride. This compound was obtained in 30% yield from acetyl derivative IIId by a procedure similar to that used to prepare triazolobenzimidazole IVa. Base IVd was a viscous oil and was identified in the form of the hydrochloride, which was obtained by treatment of an acetone solution of the base with concentrated HCl to pH 1. The colorless needles had mp 268-270°C (from alcohol). IR spectrum: 1675 (C=N), 2200-2700 ($\equiv\overset{+}{N}H$), 3140, 3235 cm^{-1} (H_2O). Found: C 47.6; H 6.0; Cl 19.1; N 18.4%. $C_{15}H_{19}N_5O \cdot 2HCl \cdot H_2O$. Calculated: C 47.9; H 6.1; Cl 18.9; N 18.6%.

2,4-Dimethyl-4H-1,2,4-triazino[2,3-a]benzimidazol-3-one (VIIa). A solution of 0.48 g (3 mmole) of amine Ia and 0.34 ml (3 mmole) of ethyl pyruvate in 3 ml of acetic acid was refluxed for 3 h, after which it was cooled, and the precipitate was removed by filtration and washed with ether to give 0.62 g (97%) of colorless needles with mp 232-233°C (from alcohol). IR spectrum: 1595, 1630; 1680 cm^{-1} (CO). PMR spectrum (CF_3COOH): 2.23 (3H, s, $C-CH_3$), 3.50 (3H, s, $N-CH_3$), 7.35 (3H, m, aromatic), 7.65 ppm (1H, m, aromatic). Found: C 61.7; H 4.9; N 26.0%. $C_{11}H_{10}N_4O$. Calculated: C 61.6; H 4.6; N 26.2%.

2-Methyl-4-(2-morpholinoethyl)-4H-1,2,4-triazino[2,3-a]benzimidazol-3-one (VIId). A solution of 1.04 g (4 mmole) of amine Id and 0.46 ml (4 mmole) of ethyl pyruvate in 10 ml of ethanol was refluxed for 2 h in the presence of two to three drops of 70% perchloric acid, and the precipitated perchlorate of VIId was removed by filtration and washed with alcohol. Treatment of the perchlorate with concentrated NH_4OH gave 0.8 g (86%) of VIId with mp 158-159°C (from ethyl acetate). IR spectrum: 1610, 1643; 1700 cm^{-1} (CO). Found: C 61.5; H 6.3; N 22.1%. $C_{16}H_{19}N_5O_2$. Calculated: C 61.3; H 6.1; N 22.4%.

4-(2-Diethylaminoethyl)-2-methyl-4H-1,2,4-triazino[2,3-a]benzimidazol-3-one (VIIe). This compound was obtained in 85% yield by a procedure similar to that used to prepare VIId. The colorless needles had mp 87-88°C (from heptane). Found: C 64.1; H 7.3; N 23.2%. $C_{16}H_{21}N_5O$. Calculated: C 64.2; H 7.0; N 23.4%.

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