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SOME PROPERTIES OF 1-(NITROPHENYL)-AMINOBENZIMIDAZOLES

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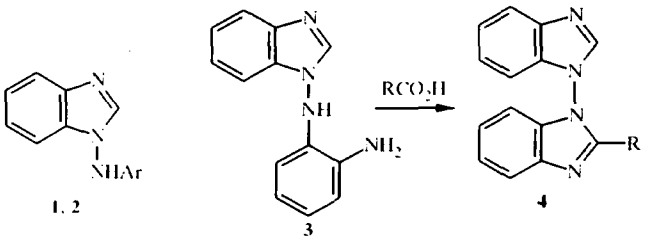
The chemical properties of previously synthesized 1-[2(4)-nitrophenyl]aminobenzimidazoles, in particular, alkylation at the NH group, thiolation, and reduction were studied.

Keywords: 1-(nitrophenylamino)benzimidazoles, alkylation, reduction, thiolation.

The previously established possibility of direct arylation of the N-amino group in 1-formylaminobenzimidazole [1] makes it possible to conclude that the CHO group is split off spontaneously during the arylation of its potassium salt, as a result of which the corresponding 1-arylaminobenzimidazoles are formed. The *o*- and *p*-nitroaryl halides enter readily into the reaction. In particular, 1-(2-nitrophenyl)- and 1-(4-nitrophenyl)aminobenzimidazoles (**1**) and (**2**) were synthesized in this way. Since there are hardly any data on the reactivity of N-arylaminoazoles, it seemed interesting to investigate the chemical characteristics of compounds **1** and **2**. It was particularly tempting to realize the reduction of the nitro group in *o*-nitro derivative **1**, since the appearance of diamine **3** opened up the way to the synthesis of almost unknown 1,1'-dibenzimidazolyls **4** by cyclizations.



1, **2** **3** **4**

1 Ar = 2-$O_2NC_6H_4$; **2** Ar = 4-$O_2NC_6H_4$

During the action of hydrogen on compound **1** in the presence of 2% Pd/C the reduction of the nitro group is accompanied by cleavage of the N–N bond, as a result of which benzimidazole and *o*-phenylenediamine are formed as practically the only reaction products. Similarly, benzimidazole and *p*-phenylenediamine are obtained during the reduction of compound **2**. Similar instability of the nitrogen–nitrogen bond in N-aminoazoles has been observed already under the conditions of reduction [2].

Unlike 1-alkylaminobenzimidazoles [3], compounds **1** and **2** do not undergo N-nitrosation by nitrous acid on account, probably, of the reduced electron density at the nitrogen atom of the amino group. It was also not possible to realize their N-formylation, e.g., during boiling in 100% formic acid in the presence of boron trifluoride etherate, although 1-aminobenzimidazole itself is easily formylated under these conditions [4]. At the same time arylamines **1**, **2** are easily methylated by methyl iodide in DMSO in the presence of potassium hydroxide, forming N-methyl derivatives **5**, **6** with yields up to 90%. Like their unmethylated analogs, compounds **5**, **6** undergo

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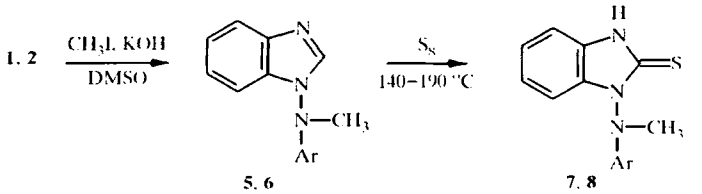
degradation in the course of catalytic hydrogenation with the formation of benzimidazoles and the corresponding N-methylphenylenediamine. We were able to realize the thiolation of N-methyl derivatives **5**, **6** by heating them with sulfur at 140-160°C, and as a result we obtained thiones **7** and **8** with yields of 40-45%. The reaction is accompanied by the removal of the N-arylamino group, as shown by the formation of a certain amount (~15%) of benzimidazole as side product. It was not possible to realize the thiolation of unmethylated compounds **1** and **2** under these conditions or at higher temperature on account of the complete resinification of the reaction mixture. The presence of even one free NH group in 1-aminobenzimidazoles significantly complicates their thiolation, although it can nevertheless be realized in the case of 1-alkylaminobenzimidazoles [5].



5, 6 7, 8

1, 5, 7 Ar = 2-$O_2NC_6H_4$; 2, 6, 8 Ar = 4-$O_2NC_6H_4$

EXPERIMENTAL

The IR spectra of the synthesized compounds were recorded in vaseline oil on a UR-20 spectrometer. The PMR spectra were obtained on a Bruker 250 instrument at 250 MHz. The UV spectra were recorded on a Specord M-40 instrument in methanol. The reactions and the purity of the obtained compounds were monitored by TLC on plates with aluminum oxide of III-IV Brockman activity with development in iodine vapor. The melting points were determined in sealed capillaries on a PTP bench and were not corrected.

1-Methyl(2-nitrophenyl)aminobenzimidazole (5). Suspension of powdered potassium hydroxide (1.32 g, 24 mmol) in DMSO (50 ml) was stirred at room temperature for 5 min, and 1-(2-nitrophenyl)aminobenzimidazole **1** (2 g, 7.8 mmol) was added. The mixture was stirred for further 15 min, methyl chloride (0.8 ml, 12 mmol) was added, and the stirring was continued for 2.5 h. The color of the reaction mass gradually changed from bright-red to yellow. The mixture was diluted with 50 ml of water and extracted with chloroform (3 × 20 ml). The extract was washed with water (3 × 20 ml), the solvent was evaporated, and 1.89 g (88%) of compound **5** were obtained. The product formed bright-orange crystals; mp 92-94°C (pentane). IR spectrum, cm^{-1}: 1370, 1460, 1530, 1600. UV spectrum, λ_{max} (log ε), nm: 236 (4.36), 275 (3.86), 282 (3.73), 346 (3.43). PMR spectrum ($CDCl_3$, δ, ppm): 3.42 (3H, s, NCH_3); 6.99 (1H, dd, 6'-H, ^3J = 8.36, ^4J = 1.10 Hz); 7.14 (1H, m, 4'-H); 7.29 (3H, m, 4-, 6-H); 7.44 (1H, m, 5'-H); 7.69 (1H, dd, 3'-H, ^3J = 8.06, ^4J = 1.56 Hz); 7.81 (1H, m, 7-H); 8.06 (1H, s, 2-H). Found, %: C 62.51; H 4.30; N 21.04. $C_{14}H_{12}N_4O_2$. Calculated, %: C 62.68; H 4.51; N 20.88.

1-Methyl(4-nitrophenyl)aminobenzimidazole (6). The compound **6** was obtained similarly to compound **5** from 1-(4-nitrophenyl)aminobenzimidazole **2** (2 g, 7.8 mmol) and methyl iodide (0.8 ml, 12 mmol). The product formed pale-yellow crystals. Yield 1.98 g (90%); mp 155-157°C (octane). IR spectrum, cm^{-1}: 1335, 1460, 1500, 1590. UV spectrum, λ_{max} (log ε), nm: 238 (4.10), 275 (3.82), 282 (3.84), 336 (4.21). PMR spectrum, $CDCl_3$ (δ, ppm): 3.63 (3H, s, NCH_3); 6.55 (2H, d, 2'-, 6'-H, ^3J = 9.36 Hz); 7.15 (1H, d, 4-H, ^3J = 7.44 Hz); 7.31 (2H, m, 5-, 6-H); 7.89 (1H, d, 7-H, ^3J = 7.55 Hz); 8.09 (1H, s, 2-H); 8.12 (2H, d, 3'-, 5'-H, ^3J = 9.36 Hz). Found, %: C 62.78; H 4.40; N 20.97. $C_{14}H_{12}N_4O_2$. Calculated, %: C 62.68; H 4.51; N 20.88.

Reduction of 1-(4-Nitrophenyl)aminobenzimidazole (1). To solution of compound **1** (0.1 g, 0.39 mmol) in methanol (50 ml) 2% Pd/C (0.1 g) was added. The reaction mixture was saturated with hydrogen during 3.5 h under shaking at 40°C. The catalyst was filtered off, two thirds of the volume of methanol were distilled off, and the residue was evaporated to dryness. To the dark-gray residue we added 2 ml of 10% solution of potassium hydroxide. Undissolved *o*-phenylenediamine was filtered off. The product formed yellowish crystals. Yield 0.025 g (58%); mp 100-102°C (water). A mixed melting test with an authentic sample of *o*-phenylenediamine did not give melting point depression. The alkaline solution was neutralized to pH 6-7 with concentrated hydrochloric acid.

The precipitate was filtered off, and 0.02 g (40%) of benzimidazole were obtained in the form of colorless crystals; mp 169-170°C (water). A mixed melting test with an authentic sample of benzimidazole did not give a melting point depression.

Reduction of 1-(4-Nitrophenyl)aminobenzimidazole (2). To solution of compound **2** (0.1 g, 0.39 mmol) in methanol (50 ml) 2% Pd/C (0.1 g) was added. The reaction mixture was saturated with hydrogen for 3 h by shaking at 40°C. The catalyst was filtered off, two thirds of the volume of methanol were distilled off, and the residue was evaporated to dryness. The dark-gray residue was dissolved in 10 ml of chloroform and passed through a column of aluminum oxide (l = 15 cm, d = 1.2 cm) with chloroform as eluent, and two fractions were collected. The first (R_f 0.25) was *p*-phenylenediamine. Yield 0.017 g (40%). The product formed reddish plates; mp 136-138°C (heptane). A mixed melting test with an authentic sample of *p*-phenylenediamine did not give melting point depression. The second fraction (R_f = 0.1) was benzimidazole. Yield 0.03 g (46%). The product formed colorless crystals; mp 169°C (water). A mixed melting test with an authentic sample of benzimidazole did not give melting point depression.

1-Methyl(2-nitrophenyl)aminobenzimidazoline-2-thione (7). Mixture of compound **5** (0.25 g, 0.93 mmol) and sulfur (0.03 g, 0.93 mmol) was heated at 140-150°C and kept at this temperature for 2 h. On cooling, chloroform (5 ml) was added to the reaction mass, and 0.013 g (12%) of the insoluble precipitate (benzimidazole) were filtered off. The product formed colorless crystals; mp 168-170°C (water). A mixed melting test with an authentic sample of benzimidazole did not give melting point depression. The chloroform solution was passed through a column of aluminum oxide (l = 20 cm, d = 2 cm), and two fractions were collected. The first product, forming bright-orange crystals, was N-methyl-*o*-nitroaniline. Yield 0.035 g (25%); mp 31-33°C, (petroleum ether). The second fraction (R_f 0.2) was compound **7**. The product formed yellow crystals. Yield 0.12 g (43%); mp 224-226°C (ethanol). PMR spectrum (δ, ppm): 3.43 (3H, s, NCH_3); 7.04 (1H, m, 4'-H); 7.14 (1H, d, 6'-H, ^3J = 8.38 Hz); 7.41 (2H, m, 5'-, 7-H); 7.66 (1H, dd, 3'-H, ^3J = 8.07, ^4J = 1.46 Hz); 10.32 (1H, br. s, NH). Found, %: C 56.25; H 4.31; N 18.42; S 10.49. $C_{14}H_{12}N_4O_2S$. Calculated, %: C 55.99; H 4.03; N 18.65; S 10.67.

1-Methyl(4-nitrophenyl)aminobenzimidazoline-2-thione (8). Mixture of compound **6** (0.28 g, 1.04 mmol) and sulfur (0.034 g, 1.04 mmol) was heated at 180-190°C and kept at this temperature for 2 h. On cooling, chloroform (5 ml) was added to the reaction mass, and 0.016 g (13%) of benzimidazole was filtered off. The product formed colorless crystals; mp 160-170°C (water). A mixed melting test with an authentic sample of benzimidazole did not give melting point depression. The chloroform solution was passed through a column of aluminum oxide (l = 25 cm, d = 2 cm) with chloroform as eluent. The fraction with R_f 0.65 was collected. After evaporation of chloroform 0.03 g (19%) of N-methyl-*p*-nitroaniline were obtained as yellow crystals; mp 145-147°C (ethanol). PMR spectrum, $CDCl_3$ (δ, ppm): 2.92 (3H, d, $N-CH_3$); 4.57 (1H, s, NH); 6.51 (2H, d, 2-, 6-H, ^3J = 9.22 Hz); 8.08 (2H, d, ^3J = 9.22 Hz, 3,5-H). The solvent for chromatography was replaced by 3:1 mixture of deuterochloroform and methanol, and the fraction with R_f 0.15 was collected. Compound **8** was obtained as yellow crystals. Yield 0.141 g (45%); mp 232-234°C (benzene–hexane, 1:1). PMR spectrum, DMSO-d_6 (δ, ppm): 3.55 (3H, s, NCH_3); 6.69 (d, 2'-, 6'-H, ^3J = 9.16 Hz); 7.25 (4H, m, 4-, 7-H); 8.13 (d, 3'-, 5'-H, ^3J = 9.43 Hz); 13.21 (1H, br. s, NH). Found, %: C 56.19; H 4.38; N 18.76; S 10.32. $C_{14}H_{12}N_4O_2S$. Calculated, %: C 55.99; H 4.03; N 18.65; S 10.67.

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