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SYNTHESIS OF 2-AZIDO-1-METHYL-AMINOBENZIMIDAZOLE

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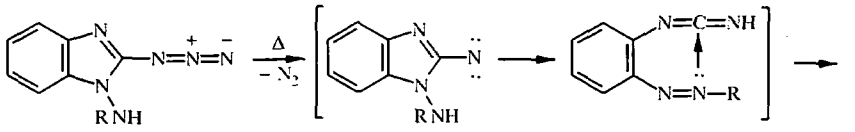
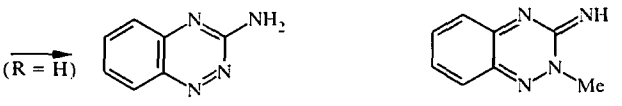
1-Methylamino-2-hydrazinobenzimidazole was synthesized by the sequential action of hydrogen peroxide and hydrazine hydrate on 1-(acetylmethylamino)benzimidazoline-2-thione. Nitrosation of the former with nitrous acid led to 2-azido-1-(nitrosomethylamino)benzimidazole, which exists as a mixture of s-cis and s-trans conformers with hindered rotation about the N–NO bond. 2-Azido-1-methylaminobenzimidazole was obtained by treatment of the nitrosation product with conc. hydrochloric acid.

It was shown recently in our laboratory that thermolysis of 1-amino-2-azidobenzimidazole (Ia) leads to the formation of 3-aminobenzo-1,2,4-triazine (II) in high yield [1]. Presumably the process occurs through the C-nitrene III, which then recyclizes into compound II through the diazene intermediate IV. It seemed of interest to introduce 2-azido-1-methylaminobenzimidazole Ib into a similar conversion. The probable thermolysis product in this case might prove to be 2-methylbenzo-1,2,4-triazine-3-imine (V).



Ia,b III IV



II V

I a R = H; b R = Me

We carried out the synthesis of the previously unknown compound Ib starting from 1-(acetylmethylamino)benzimidazoline-2-thione (VI). The action of 30% hydrogen peroxide on compound VI gave the sulfonic acid VII which was treated without isolation with 80% hydrazine hydrate. As a result 2-hydrazino-1-methylaminobenzimidazole (VIII) was obtained in 73% yield. The latter was also synthesized from 1-methylamino-2-thiobenzimidazole (IX). However the yield of compound VIII in this case was 46% and the aminothione X (23%) was formed as a by-product.

Nitrosation of compound VIII with nitrous acid at 0-5°C even using a strictly equimolar quantity of $NaNO_2$ occurs not only at the hydrazino but also at the methylamino group and leads to 2-azido-1-(nitrosomethylamino)benzimidazole XI. According to the data of ^1H NMR spectra compound XI exists in solution as a mixture (s-*cis* and s-*trans* conformers, caused by the hindered rotation about the N–NO bond) as indicated by the doubling

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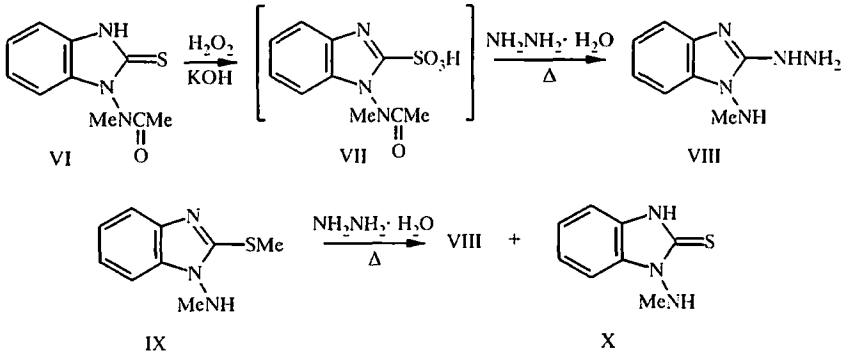
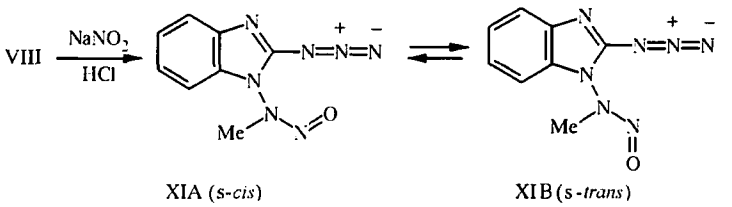
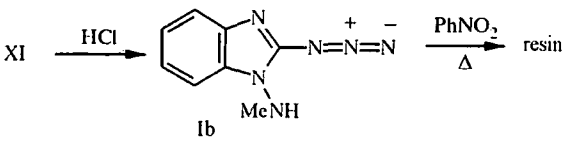
of all the proton signals. The ratio of the rotational isomers s-*cis*/s-*trans* (XIA/XIB) in $CDCl_3$ solution at 20°C was 46:54, but in DMSO-d_6 it was 37:63. Similar conformers have also been observed in the case of other 1-(nitrosoalkylamino)benzimidazoles [2].



The azide XI is subject to denitrosation on treatment with hydrochloric acid (20°C, 14 days) forming 2-azido-1-methylaminobenzimidazole (Ib) in 82% yield. It was not possible to obtain compound Ib from 1-methylamino-2-methylthiobenzimidazole (IX) and sodium azide by nucleophilic substitution of the methylthio group (heating in EtOH or DMSO solution). Only the thione X was isolated from the reaction mixture.



The azide Ib was an extremely unstable bright yellow oil decomposing completely at room temperature in several days. It completely resinified on short heating (90-100°C) in nitrobenzene solution. This is possibly the result of the formation of imine V which proved to be unstable due to its quinonoid structure and is rapidly destroyed.



EXPERIMENTAL

The IR spectra were measured on a UR 20 instrument in vaseline oil. The ^1H NMR spectra were recorded on a Unity 300 (300 MHz) instrument in $CDCl_3$ or DMSO-d_6 solutions. A check on the progress of reactions and the purity of compounds obtained was carried out by TLC on plates with Al_2O_3 of Brockmann activity grade IV, eluent was chloroform, and visualization was with iodine vapor. Melting points were measured on a PTP instrument in sealed glass capillaries and are not corrected.

2-Hydrazino-1-methylaminobenzimidazole (VIII). A. Hydrogen peroxide (30%, 20 ml) was added dropwise with stirring to a solution of thione VI [3] (4.4 g, 0.02 mol) and KOH (2.2 g, 0.04 mol) in water (30 ml) maintaining the temperature below 40°C. The reaction mixture was kept at room temperature for 20 h, then

neutralized to pH 7 with conc. ammonia solution. The water was evaporated, the dry residue dissolved in 80% hydrazine hydrate (10 ml), and the solution boiled for 1 h. After cooling, the reaction mixture was diluted with water (20 ml), and the colorless precipitate of compound VIII filtered off. Yield of fine colorless crystals gradually darkening in the air was 2.6 g (73%); mp 168-170°C (with decomposition, from ethanol). ^{1}H NMR spectrum (DMSO-d_6): 2.65 (3H, d, ^3J = 5.56 Hz, NHC$\underline{H}_3$); 4.27 (2H, br s, NH$\underline{NH}_2$); 6.13 (1H, q, ^3J = 5.57 Hz, $\underline{NH}$CH$_3$); 6.96 (2H, m, 5-H,6-H); 7.19 (2H, m, 4-H,7-H); 7.48 ppm (1H, s, $\underline{NH}$NH$_2$). Found, %: C 53.98; H 6.41; N 39.14. $C_8H_{11}N_5$. Calculated, %: C 54.22; H 6.26; N 39.52.

B. A solution of benzimidazole IX (0.5 g, 2.6 mmol) in 80% hydrazine hydrate (6 ml) was boiled for 24 h, then diluted with water (10 ml), and the precipitate of compound VIII filtered off. Yield 0.16 g (46%); mp 167-170°C (decomp., from ethanol). Mixed with a sample obtained by method A the product gave no depression of melting point. The mother liquor was extracted with chloroform and the extract chromatographed on a column (3 × 1 cm) of silica gel, eluting with chloroform, and collecting the fraction with Rf 0.1. After evaporation of the chloroform 1-methylaminobenz-imidazoline-2-thione (X) (0.11 g, 23%) was obtained as colorless crystals; mp 183-184°C (benzene). A mixed melting point of product X with an authentic sample gave no depression.

2-Azido-1-(nitrosomethylamino)benzimidazole (XI). A mixture of benzimidazole VIII (0.885 g, 5 mmol) and conc. hydrochloric acid (10 ml) was heated until the crystals had completely dissolved. The mixture was cooled to -5 to 0°C when compound VIII was partially precipitated once again. A solution of sodium nitrite (0.354 g: 5 mmole) in water (5 ml) was added to the mixture with stirring, keeping the temperature below 0°C. The reaction mixture was kept at this temperature for 30 min then neutralized with conc. ammonia solution, and extracted with chloroform (3 × 10 ml). The extract was chromatographed on a column (20 × 2 cm) of silica gel, eluting with chloroform, and collecting the fractions with R_f 0.4. After evaporating the chloroform, compound XI (0.375 g, 40%) was obtained as beige crystals; mp 60-62°C (decomp., from ethanol). IR spectrum: 1500, 1550, 1570, 1590, 2055, 2070 cm^{-1} (N_3). ^{1}H NMR spectrum ($CDCl_3$): 3.48 (3H, NCH_3, conformer B); 4.29 (3H, s, NCH_3, A); 6.90 (1H, d, ^3J = 7.62 Hz, 4-H, A); 7.14 (1H, d, ^3J = 7.62 Hz, 4-H, B); 7.28 (2H, m, 5-H,6-H, A,B); 7.63 (1H, d, ^3J = 8.21 Hz, 7-H, A); 7.70 ppm (1H, d, ^3J = 8.11 Hz, 7-H, B). ^{1}H NMR spectrum (DMSO-d_6): 3.58 (3H, s, NCH_3, B); 4.34 (3H, NCH_3, A); 7.36 (3H, m, 4-H,6-H, A,B); 7.63 (1H, d, ^3J = 7.62 Hz, 7-H, A); 7.70 ppm (1H, d d, ^3J = 6.88 Hz, ^4J = 1.26 Hz, 7-H, B). Found, %: C 44.49; H 3.52; N 45.01. $C_8H_7N_7O$. Calculated, %: C 44.24; H 3.25; N 45.1.

2-Azido-1-methylaminobenzimidazole (Ib). A solution of benzimidazole XI (0.177 g, 1 mmol) in conc. hydrochloric acid (20 ml) was kept at room temperature for 14 days. The hydrochloric acid was evaporated, the residue treated with conc. ammonia solution (5 ml), and the resulting emulsion extracted with chloroform (3 × 5 ml). The extract was chromatographed on a column (20 × 1 cm) of Al_2O_3, eluting with chloroform, and collecting fractions with R_f 0.3. Compound Ib (0.154 g, 82%) was obtained as a bright yellow oil, decomposing rapidly in the air and in chloroform solution. IR spectrum (thin film): 1500, 1585, 1600, 2070 (N_3), 3260 (NH). ^{1}H NMR spectrum ($CDCl_3$): 2.90 (3H, d, ^3J = 5.57 Hz, NHC$\underline{H}_3$); 4.92 (1H, q, ^3J = 5.86 Hz, $\underline{NH}$CH$_3$); 7.22 (2H, m, 5-H,6-H); 7.33 (1H, m, 4-H); 7.58 ppm (1H, m, 7-H). Found, %: C 51.35; H 4.10; N 44.77. $C_8H_8N_6$. Calculated, %: C 51.06; H 4.28; N 44.66.

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