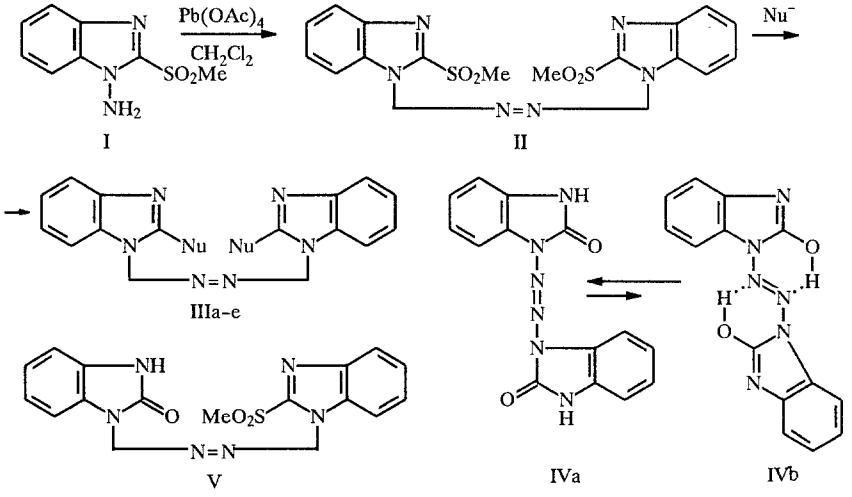
2,2'-DIALKOXY, 2,2'-DIHYDROXY, and 2,2'-DIAMINO DERIVATIVES OF 1,1'-AZOBENZIMIDAZOLE. THE FIRST SYNTHESIS OF HETEROCYCLIC TETRAZENES BY MEANS OF A NUCLEOPHILIC SUBSTITUTION REACTION

V. V. Kuz'menko, I. M. Nanavyan, and A. F. Pozharskii

2,2'-Dimethanesulfonyl-1,1'-azobenzimidazole is prepared by the oxidation of 1-amino-2-methanesulfonylbenzimidazole with lead tetraacetate. The reaction of this tetrazene with alkali in DMSO, with sodium alkoxides in the corresponding alcohol or ammonia, or with primary or secondary amines leads to the formation of 2,2'-dihydroxy, 2,2'-dialkoxy, or 2,2'-diamino derivatives of 1,1'-azobenzimidazole.

Earlier we showed that 1-aminobenzimidazole and its 2-methyl, 2-phenyl, and 2-chloro derivatives are converted to the corresponding 1,1'-azobenzimidazoles by oxidation with lead tetraacetate and a number of other oxidants [1]. At the same time, the sole products of the oxidation of 1,2-diaminobenzimidazole and 1-aminobenzimidazole are the corresponding 3-aminobenzo-1,2,4-triazene and benzo-1,2,4-triazen-3-one, which are formed by expanding the imidazole ring [1, 2]. In the present work we set the goal of developing an alternate method of synthesizing the unknown tetrazenes of the benzimidazole series containing hydroxy, alkoxy, or amino groups in the 2-position.

It seemed possible to us to first synthesize a 1,1'-azobenzimidazole containing a functional group in the 2- and 2'-positions that readily undergoes nucleophilic substitution and then to replace it by OH, OAlk, NH_2, etc., groups. As such a compound, we selected 2,2'-dimethanesulfonyl-1,1'-azobenzene (II). Such an approach to the synthesis of tetrazenes has not been used before, possibly because of the well-grounded opinion that heterocyclic and, in particular, nonheterocyclic tetrazenes must be unstable toward nucleophilic or electrophilic reagents.



IIIa Nu=OMe, b Nu=OEt, c Nu=NH_2, d Nu=NHMe, e Nu=NMe_2, f Nu= piperidine

1-Amino-2-methanesulfonylbenzimidazole (I) was obtained in a 35% yield by the amination of 2-methanesulfonylbenzimidazole with hydroxylamine-O-sulfonic acid in aqueous alkali. Its oxidation with lead tetraacetate in methylene chloride gives tetrazene II in a 26% yield. The use of N-bromosuccinimide as the oxidant increases the yield of compound II to 50%.

The action of excess sodium methylate or ethylate in the corresponding alcohol on tetrazene II replaces the methanesulfonyl groups even at 20-50°C. As a result, 2,2'-dialkoxy derivatives of 1,1'-azobenzimidazole IIIa and IIIb are obtained in yields of 41 and 54%, respectively. We also attempted to synthesize tetrazenes IIIa and IIIb by the traditional method of oxidizing 1-amino-2-alkoxybenzimidazoles. However, the synthesis of the latter by the action of the sodium alkoxides on compound I did not succeed; only the deamination of I was observed. On treatment of tetrazene II with an excess of sodium hydroxide in

Rostov State University, Scientific-Research Institute of Physical and Organic Chemistry, Rostov-on-Don 344006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 190-193, February, 1992. Original article submitted December 7, 1990.

 0009-3122/92/2802-0154$12.50

DMSO at room temperature, compound IV was obtained. Judging from the IR spectrum (the presence of an intense $\nu_{C=O}$ band at 1745 cm^{-1}) it exists in the oxo form, IVa, not in the hydroxy form, IVb, which would seem able to be stabilized by an intramolecular hydrogen bond. With the use of 1 equiv. of alkali, we obtained unsymmetrical tetrazene V.

Replacement of the methanesulfonyl groups in tetrazene II by amino, methylamino, and dimethylamino groups was accomplished by heating II in a sealed ampul with an aqueous solution of ammonia, methylamine, or dimethylamine at 95-100°C. Yields of compounds IIIc-e were 63, 87, and 69%, respectively. On attempting to carry out the analogous replacement of the methanesulfonyl groups by piperidino or morpholino groups, we observed only the destruction of the azo group and obtained in high yield the 2-piperidino- and 2-morpholinobenzimidazoles. Compound IIIf was successfully synthesized by the action of potassium piperidide on tetrazene II in dimethoxyethane at 85°C. Note that the replacement of the methanesulfonyl groups is not brought about by the action of potassium amide on tetrazene II in liquid ammonia at —70 to —30°C.

The structure of the compounds obtained was established with the aid of the UV, PMR, and mass spectra. The UV spectra were especially informative since all 1,1′-azobenzimidazoles have an absorption band at 340 nm which is missing in initial benzimidazoles. In addition, a characteristic qualitative reaction for the tetrazene structure is the energetic, explosive decomposition of tetrazenes when they are introduced into a flame on the tip of a spatula.

EXPERIMENTAL

The PMR spectra were recorded on Tesla BS-487 (compound I), Tesla BS-567 (compounds II, IIIa, b, e, IV, and V), and Bruker WH-90 (compounds IIId and IIIf) spectrometers with working frequencies of 80, 100, and 90 MHz, respectively, and a TMS internal standard. The IR spectra were measured on a Specord IR-75 instrument in mineral oil, and the electronic spectra on a Specord M-40 spectrometer in methanol (IIId, e, f) and DMSO (II, IIIa, b, and IV). The mass spectra were obtained on a Finnigan 4021 spectrometer by direct introduction into the ion source; accelerating potential 1 kV, ionizing electron energy 70 eV. The course of the reactions and the purity of compounds obtained were checked by TLC on standard activity Brokman Al_2O_3. Melting points were taken in sealed capillaries on a PTP instrument. The elementary analyses for C, H, and N for compounds I, II, IIIa-d, and IV-VII corresponded to the calculated values.

1-Amino-2-methanesulfonylbenzimidazole (I, $C_8H_9N_3O_2$). A solution of 33.9 g (340 mmole) of sodium hydroxylamine-O-sulfonate in 25 ml of water is added to a solution of 19.6 g (0.1 mole) of 2-methanesulfonylbenzimidazole [3] and 14.8 g (370 mmole) of NaOH in 100 ml of water at 40-45°C with stirring. After 5-10 min a precipitate forms in the orange solution. The mixture is stirred for 1 h at 40-45°C, then cooled. The crystals that separate are filtered off, washed with 30 ml of cold water, and dried at 100°C. The dry residue is extracted with chloroform in a Soxhlet extractor, and the solvent distilled off to obtain 7.4 g (35%) of amine I. Colorless prisms with T_{mp} 192-193°C (decomp., from chloroform). IR spectrum: 1620, 3220, 3287, 3330 cm^{-1}. PMR spectrum ($CDCl_3$): 3.53 (3H, s, CH_3); 6.45 (2H, bd s, disappears on deuteration, NH_2); 7.30-7.85 ppm (4H, m, 4-7-H).

2,2′-Dimethanesulfonyl-1,1′-azobenzimidazole (II, $C_{16}H_{14}N_6O_4S_2$). A. Over a 30-min period 12.4 g (28 mmole) of lead tetraacetate is gradually poured into a solution of 5.35 g (25 mmole) of amine I in 120 ml of absolute dichloromethane at 0-4°C. The solution gradually becomes yellow, then brown. The mixture is stirred for 1 h at 0-8°C, 3 ml of ethylene glycol are then added and, over another 15 min, 60 ml of water. The precipitate that forms is filtered off and washed with 50 ml of water. Colorless crystals with T_{mp} 245-247°C (decomp., from aqueous DMF). IR spectrum: 1593, 1673 cm^{-1}; UV spectrum, λ_{max} (log ε): 270 (3.63), 295 (3.30), 360 nm (3.30). PMR spectrum (DMSO-d_6): 3.75 (3H, s, CH_3); 7.64 (2H, m, 5,6-H); 8.0 (1H, m, 4-H); 8.61 ppm (1H, m, 7-H). Yield 1.4 g (26%).

B. In portions, 1.78 g (10 mmole) of N-bromosuccinimide is added to a suspension of 1.05 g (5 mmole) of amine I in 50 ml of absolute methylene chloride at 5-10°C, upon which the solid dissolves. A finely crystalline precipitate then separates from the red solution, is filtered off after 40 min, and washed with water. Colorless crystals with T_{mp} 245-247°C (decomp., from aqueous DMF), identical in physical chemical properties with the sample from experiment A. Yield 0.52 g (50%).

2,2′-Dimethoxy-1,1′-azobenzimidazole (IIIa, $C_{16}H_{14}N_6O_2$). To a solution of sodium methylate, prepared from 0.12 g (5 mmole) of metallic sodium in 10 ml of methanol, is added 0.22 g (0.5 mmole) of compound II. The suspension is stirred for 45 min at 20°C. After being filtered off and washed with 5 ml of methanol, the solid weighs 0.18 g. It is purified chromatographically on a column with Al_2O_3 (chloroform eluent), the first fraction, with R_f 0.55, being taken. Colorless crystals with T_{mp} 213-214°C (decomp., from a mixture of alcohol with chloroform). IR spectrum: 1567, 1620 cm^{-1}. UV spectrum, λ_{max} (log ε): 270 (3.60), 340 nm (3.60). Mass spectrum, m/z (I_{rel}, %): 322 (39) M^+, 294 (6.7) $[M - N_2]^+$; 279 (2.4) $[M - N_2 - CH_3]^+$; 147 (100) $[(M - N_2)/2]^+$; 132 (20); 119 (44.6); 104 (15.5); 92 (23.4); 90 (26.9). PMR spectrum (DMSO-d_6): 3.75 (3H, s, OCH_3); 7.26-7.62 (2H, m, 5,6-H); 8.0 (1H, m, 4-H); 8.60 ppm (1H, m, 7-H). Yield 0.07 g (41%).

2,2′-Diethoxy-1,1′-azobenzimidazole (IIIb, $C_{18}H_{18}N_6O_2$). To a solution of sodium ethylate, prepared from 0.06 g (2.5 mmole) of metallic sodium and 8 ml of ethanol, is added 0.11 g (0.25 mole) of tetrazene II. The suspension is stirred at 50°C for 2 h while the solid completely dissolves. After being cooled, the solution is diluted twofold with water, and the precipitate that forms is separated and washed with 20 ml of water. Colorless needles with T_{mp} 203-204°C (decomp., from alcohol). IR spectrum: 1567, 1620 cm^{-1}. UV spectrum, λ_{max} (log ε): 270 (3.7), 340 nm (3.6). Mass spectrum, m/z (I_{rel}, %): 350 (56) M^+; 322 (2.2) $[M - N_2]^+$; 161 (31) $[(M - N_2)/2]^+$; 133 (100); 118 (5.6). Yield 0.05 g (54%).

2,2′-Diamino-1,1′-azobenzimidazole (IIIc, $C_{14}H_{12}N_8$). A mixture of 0.25 g (0.6 mmole) of tetrazene II in 6 ml of 22% ammonia solution is heated in a sealed ampul for 20 h at 95-100°C. After having cooled, the yellow precipitate is filtered off and washed with water and alcohol. Pale cream crystals with T_{mp} 234-236°C (decomp., from butanol). IR spectrum: 1560, 1600, 1655, 3315, 3480 cm^{-1}. Because of the very low solubility in organic solvents, the PMR spectrum could not be taken. Yield 0.11 g (63%).

2,2′-Di(methylamino)-1,1′-azobenzimidazole (IIId, $C_{16}H_{16}N_8$). A mixture of 0.21 g (0.5 mmole) of tetrazene II in 5 ml of a 25% solution of methyl amine is heated in an ampul for 4 h at 95-100°C. On cooling, the yellow crystals are filtered off and washed with water and cold alcohol. Bright yellow crystals with T_{mp} 183-184°C (decomp., from alcohol). IR spectrum: 1580, 1640, 3250, 3425 cm^{-1}. UV spectrum, λ_{max} (log ε): 275 (4.6), 340 nm (4.3). PMR spectrum ($CDCl_3$): 3.3 (3H, d, J = 5.1 Hz, $NHCH_3$); 5.16 (1H, bd s, disappears on deuteration, NH); 7.22 (2H, m, 5,6-H); 7.49 (1H, m, 4-H); 7.73 ppm (1H, m, 7-H). Yield 0.14 g (87%).

2,2-Bis(dimethylamino)-1,1′-azobenzimidazole (IIIe). A mixture of 0.21 g (0.5 mmole) of tetrazene II in 5 ml of 33% aqueous dimethylamine solution is heated in an ampul for 4 h at 95-100°C. After cooling, the solution is evaporated to dryness under reduced pressure, and the residue purified on an Al_2O_3 column (chloroform eluent), selecting the fraction with R_f 0.73. Colorless crystals with T_{mp} 120-121°C (decomp., from alcohol), which agrees with the data in [1]. Yield 0.12 g (69%).

2,2′-Bis(piperidino)-1,1′-azobenzimidazole (IIIf). A. A solution of potassium amide is prepared by dissolving 0.16 g (4 mmole) of metallic potassium in 40 ml of liquid ammonia, and 2 ml (20 mmole) of piperidine is added to it dropwise. The ammonia is evaporated off and 20 ml of absolute dimethoxyethane added to the residue. Then, 0.42 g (1 mmole) of tetrazene II is introduced into the reaction mixture, the temperature raised to 85°C, and the mixture stirred at this temperature for 2 h. The solvent is distilled off under reduced pressure, and the residue dried over P_2O_5 in a vacuum desiccator. The dry residue is purified chromatographically on anAl_2O_3 column (chloroform eluent), taking the first fraction, with R_f 0.85. Pale yellow crystals with T_{mp} 168-169°C (decomp., from alcohol). IR spectrum: uninformative. UV spectrum, λ_{max} (log ε): 217 (4.57), 275 (4.52), 341 nm (4.13). PMR spectrum ($CDCl_3$): 1.67-1.99 (6H, m, β,γ-H) 3.64 (4H, m, α-H); 7.1-7.4 (2H, m, 5,6-H); 7.5-7.63 (1H, m, 4-H); 7.99-8.14 ppm (1H, m, 7-H). Yield 0.15 g (35%).

B. To a solution of 0.535 g (2.5 mmole) of 1-amino-2-piperidinobenzimidazole in 25 ml of dry dichloromethane is gradually added with stirring at 0-5°C over a 3-5 min period 1.22 g (2.75 mmole) of lead tetraacetate. The mixture is stirred for 30 min at 0°C, 1 ml of ethylene glycol added, and, after another 10 min, 25 ml of water. The aqueous layer is separated from the organic layer and extracted with 30 ml of methylene chloride. The organic layers are combined, the solvent distilled off, and the residue purified chromatographically on an Al_2O_3 column (chloroform eluent), taking the first fraction, with R_f 0.85. Pale yellow crystals identical in physical chemical properties to the sample from experiment A. Yield 0.026 g (5%).

1,1′-Azobenzimidazolen-2,2′-dione (IV, $C_{14}H_{10}N_6O_2$). To a suspension of 0.06 g (1.5 mmole) of powdered sodium hydroxide in 7 ml of absolute, freshly distilled DMSO is added 0.22 g (0.5 mmole) of tetrazene II. The dark brown solution is stirred for 4 h at 20°C. Ten ml of water is added and the solution brought to a pH of 6 with acetic acid. The yellow precipitate that forms is filtered off and washed with chloroform. Yellow crystals with T_{mp} 212-215°C (decomp., from a large volume of alcohol). IR spectrum: 1527, 1744, 3244 cm^{-1}. UV spectrum, λ_{max} (log ε): 270 (3.2), 340 nm (2.97). Yield 0.03 g (20%).

1-(2-Methanesulfonylbenzimidazolyl-1-azo)benzimidazolen-2-one (V, $C_{15}H_{12}N_6O_3 \cdot H_2O$). A suspension of 0.154 g (2.2 mmole) of powdered 80% potassium hydroxide and 0.3 g (0.27 ml, 2 mmole) of triethylene glycol in 30 ml of DMSO is added at 50-55°C to a solution of 0.84 g (2 mmole) of tetrazene II in 140 ml of freshly distilled DMSO. The solution, which turns orange in 10 min, is stirred for 3 h at 50°C, the DMSO then distilled off under vacuum, and the residue recrystallized from butanol. Yellow crystals with T_{mp} 223-225°C (decomp., from butanol). IR spectrum: 1735, 3100-3200 cm^{-1}. PMR spectrum (DMSO-d_6): 3.68 (3H, s, CH_3); 7.16 (3H, m, 4′-6′-H); 7.62 (2H, m, 5,6-H); 7.96 (1H, m, 4-H); 8.32 (2H, m, 7,7′-H); 11.67 ppm (1H, m, NH). Yield 0.2 g (26%). The material contains impurities.

2-Piperidinobenzimidazol (VI, $C_{12}H_{15}N_3$). A. A mixture of 0.25 g (0.6 mmole) of tetrazene II in 3 ml (30 mmole) of piperidine is heated in an ampul at 95-100°C for 40 min. The resultant orange solution is evaporated to dryness and chromatographed on an Al_2O_3 column (chloroform eluent), taking the fraction with R_f 0.35. The solvent is distilled off and the material dried in a vacuum desiccator to obtain 0.1 g (83%) of 2-piperidinobenzimidazol with T_{mp} 276-278°C (decomp.,

from alcohol) according to[4]. T_{mp} 263-265°C. IR spectrum: 1570, 1629, 3045 cm^{-1}.

B. A solution of 1.98 (10 mmole) of benzimidazol-2-sulfonic acid in 10 ml (100 mmole) of piperidine is boiled for 3 h. The solution is evaporated, the residue is pulverized in 50 ml of ether, filtered off, and washed with cold water. The crude product is dried and chromatographed on an Al_2O_3 column (chloroform eluent), selecting the first fraction with R_f 0.35. Colorless crystals with T_{mp} 276-278°C (decomp., from alcohol). A mixed melting point taken with a sample from experiment A was not depressed.

2-Morpholinobenzimidazole (VII, $C_{11}H_{13}N_3O$). A. Obtained in an 80% yield under conditions analogous to those for compound VI (method A). Colorless crystals with T_{mp} 288-290°C (decomp., from alcohol) and R_f 0.2. IR spectrum: 1580, 1620, 2670 cm^{-1}.

B. Benzimidazol-2-sulfonic acid is boiled for 3 h in a tenfold excess of morpholine and then purified on an Al_2O_3 column (chloroform eluent) to obtain compound VII in a 40% yield. The product is identical to a sample from the previous experiment.

LITERATURE CITED

1. A. F. Pozharskii, I. M. Nanavyan, V. V. Kuz'menko, A. I. Chernyshev, Yu. V. Orlov, and N. A. Klyuev, *Khim. Geterotsikl. Soedin.*, No. 11, 1486 (1989).
2. A. V. Zeiger and M. M. Joulie, *J. Org. Chem.*, **42**, 542 (1977).
3. E. Hoggarth, *Chem. Soc.*, 3311 (1949).
4. P. P. Zarin, É. S. Lavrinovich, A. K. Aren, and S. K. Germane, USSR Inventor's Certificate 417,421; *Byull. Izobret.*, No. 8 (1974).