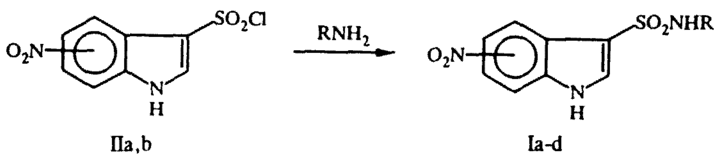
Chemistry of Heterocyclic Compounds, Vol. 32, No. 1, 1996

SYNTHESIS OF INDOLE SULFONAMIDES

V. N. Buyanov, V. E. Zhigachev, and N. N. Suvorov

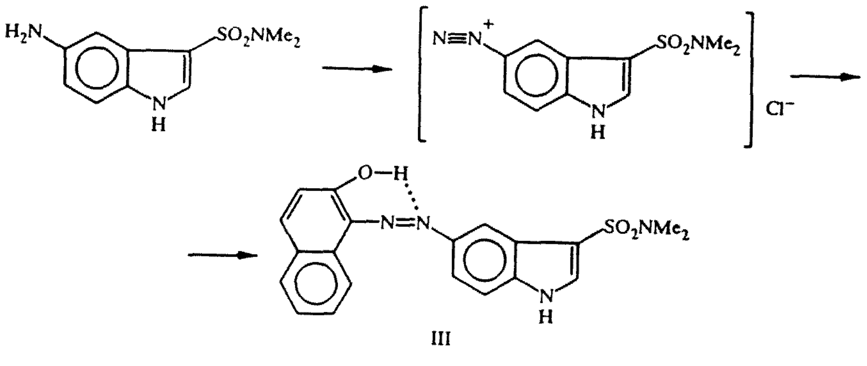
A preparative method is reported for the synthesis of indole sulfonamides from 3-indolesulfonyl chlorides and certain amines.

In our search for a synthesis of indole sulfonamides which are analogs of known sulfanilamide compounds [1] we have developed a convenient method for preparing 3-N-(2-diethylaminoethyl)sulfonamido-5- and -6-nitroindoles (Ia, b), 4-(5-nitroindole-3-sulfonyl)sulfanilamide (Ic), and 4-(6-nitroindole-3-sulfonyl)sulfanilamide (Id) from 5- and 6-nitro-3-indolesulfonyl chlorides (IIa, b, described before [2]) by reaction with 1-amino-2-(N,N-diethylamino)ethane and sulfanilamide respectively.



The IR spectra of sulfonamides Ia-d show typical stretching absorption bands for the NH group of the indole ring at 3390-3250 cm^{-1} and the nitro group at 1540-1520 and 1350-1320 cm^{-1}.

It is known that certain azo dyes based on indole sulfonic acids with the sulfo group in the benzene ring are light stable dyes used for dyeing both natural and synthetic fibers [3]. For this reason we synthesized 3-N,N-dimethylsulfonamido-5-(2-hydroxy-1-azonaphthyl)indole (III) by diazotization of 3-N,N-dimethylsulfonamide-5-aminoindole [2] and subsequent combination of the diazonium salt obtained with alkaline β-naphthol solution.



The IR spectrum of III shows absorption bands for the hydroxyl group at 3350 cm^{-1}, the indole NH at 3250 cm^{-1}, the azo group at 1580 cm^{-1}, and the sulfonamido group at 1380 and 1150 cm^{-1}.

The mass spectrum of III has a strong peak for the molecular ion at 394. Its subsequent fragmentation is in agreement with the proposed structure.

D. I. Mendeleev Chemicotechnological University, Moscow 125820. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 40-42, January, 1996. Original article submitted June 22, 1995.

0009-3122/96/3201-0035$15.00 ©1996 Plenum Publishing Corporation

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument for vaseline mulls, UV spectra on a Specord instrument using alcohol solvent, PMR spectra on a Bruker WP-200 SY spectrometer with DMSO-D_6 solvent and TMS internal reference, and mass spectra on a Varian MAT-311 with ionization intensity 70 eV, cathode emission current 1 mA, and accelerating voltage 3 kV. The evaporation temperature was varied in a linear programming mode from 30 to 300°C. Monitoring of the reaction course and purity of the compounds was performed using TLC on Silufol UV-254 plates.

C, H, and N elemental data for Ia-d and III agreed with that calculated as did the molecular weight determined from mass spectrometry.

3-N-(2′-Diethylaminoethyl)sulfonamido-5-nitroindole (Ia, $C_{14}H_{20}N_4O_4S$). 1-Amino-2-(N,N-diethylamino)ethane (0.6 ml, 5 mmole) was added at room temperature with constant stirring to a suspension of 5-nitro-3-indolesulfonyl chloride (IIa, 1.3 g, 5 mmole) in chloroform (30 ml) and the mixture was held at this temperature for 24 h. The product was evaporated to 1/3 initial volume and the precipitate filtered, washed with petroleum ether (bp 40-70°C, 50 ml), and dried to give product (1.5 g, 88%) with mp 215-217°C (from alcohol). IR spectrum: 3280, 3130 (NH), 1530 (NO_2), 1380, 1150 cm^{-1} ($-SO_2N=$). UV spectrum, λ_{max} (log ε): 210 (4.02), 258 (4.09), 344 nm (3.17). PMR spectrum: 11.77 (s, 1-H), 8.22 (2-H), 8.79 (s, 4-H), 8.15 (d, 6-H), 7.72 (d, 7-H), 2.91 (t, 1-CH_2), 2.56 (t, 2-CH_2), 2.51 (q, CH_2), 0.9 ppm (t, CH_3), $J_{6,7}$ = 9.14 Hz, $J_{4,6}$ = 2.14 Hz, $J_{2\text{-}CH2,3\text{-}CH2}$ = 7.3 Hz, $J_{CH2,CH3}$ = 6.95 Hz. Found: M^+ 340. Calculated: M 340.

3-N-(2′-Diethylaminoethyl)sulfonamido-6-nitroindole (Ib, $C_{14}H_{20}N_4O_4S$). Similarly to Ia from 6-nitro-3-indolesulfonyl chloride IIb to give sulfonamide Ib (1.5 g, 88%) with mp 190-192°C (from alcohol). IR spectrum: 3280, 3130 (NH), 1530 (NO_2), 1190, 1150 cm^{-1} ($-SO_2N=$). UV spectrum, λ_{max}(log ε): 209 (5.17), 258 (5.22), 312 nm (4.95). PMR spectrum: 8.3 (s, 2-H), 8.0 (d, 4-H), 8.09 (d, 5-H), 8.44 (s, 7-H), 2.79 (t, 1-CH_2), 2.36 (t, 2-CH_2), 2.32 (q, CH_2), 0.81 ppm (t, CH_3), $J_{4,5}$ = 9.03 Hz, $J_{5,7}$ = 2.2 Hz), $J_{4,7}$ = 0.74 Hz, $J_{2\text{-}CH2,3\text{-}CH2}$ = 7 Hz, $J_{CH2,CH3}$ = 7.08 Hz. Found: M^+ 340. Calculated: M 340.

4-N-(5-Nitroindole-3-sulfonyl)sulfanilamide (Ic, $C_{14}H_{12}N_4O_6S_2$). p-Aminobenzosulfonamide (0.9 g, 5 mmole) was added to a solution of 5-nitro-3-indolesulfonyl chloride (IIa, 1.3 g, 5 mmole) in dioxane (30 ml) and the product was stirred for 5 min at room temperature. Potassium carbonate (0.6 g, 5 mmole) in water (2 ml) was added, stirring continued for 5 min, and the product held at room temperature for 4 h. The reaction mixture was poured into water (100 ml) with vigorous stirring and the precipitate formed was filtered, washed with water, and dried to give product (1.2 g, 62%) with mp 285-286°C (from alcohol). IR spectrum: 3600, 3450, 3200 (NH, NH_2), 1540, 1390 (NO_2), 1360, 1160 cm^{-1} ($-SO_2N=$). UV spectrum, λ_{max}(log ε): 217 (4.426), 274 (3.790), 328 nm (3.700). PMR spectrum: 12.7 (s, 1-H), 8.41 (s, 2-H), 8.86 (s, 4-H), 8.12 (d, 6-H), 7.66 (d, 7-H), 11.0 (s, SO_2NH), 7.20 (s, NH_2), 7.25 (d, 2-H), 7.63 ppm (d, 3-H), $J_{4,6}$ = 2.35 Hz, $J_{6,7}$ = 9.0 Hz, $J_{2,3}$ = 9.0 Hz, $J_{CH,NH}$ = 2.74 Hz. Found: M^+ 396. Calculated: M 396.

4-N-(6-Nitroindole-3-sulfonyl)sulfanilamide (Id, $C_{14}H_{12}N_4O_6S_2$). Similarly to Ic from 6-nitro-3-indolesulfonyl chloride IIb to give sulfanilamide Id (1.2 g, 62%) with mp 235-237°C (from alcohol). IR spectrum: 3600, 3450, 3200 (NH, NH_2), 1540, 1350 (NO_2), 1380, 1160 cm^{-1} ($-SO_2N=$). UV spectrum, λ_{max}(log ε): 210 (4.460), 270 (4.235), 322 nm (3.760). PMR spectrum: 12.68 (s, 1-H), 8.47 (s, 2-H), 8.05 (d, 4-H), 8.16 (d, 5-H), 8.37 (s, 7-H), 10.9 (s, SO_2NH), 7.24 (d, 2-H), 7.62 (d, 3-H), 7.15 ppm (s, 4-SO_2NH_2), $J_{2,3}$ = 8.77 Hz. Found: M^+ 396. Calculated: M 396.

3-N,N-Dimethylsulfonamido-5-(2-hydroxynaphthyl-1-azo)indole (III, $C_{20}H_{17}N_4O_3S$). A solution of sodium nitrite (0.1 g, 1.5 mmole) in water (3 ml) was added with constant stirring to a solution of 3-N,N-dimethylsulfonamido-5-aminoindole (0.5 g, 2 mmole) in hydrochloric acid (4N, 5 ml) at a reaction temperature of 0°C. The diazonium salt obtained was added at 0°C with stirring to a solution of β-naphthol (0.2 g, 1.4 mmole) in sodium hydroxide (2N, 3 ml). Cold water (20 ml) was added to the mixture formed. The red precipitate was filtered, washed with cold water to neutrality, and dried to give product (0.5 g, 62%) with mp 185-187°C. IR spectrum: 3350 (OH), 3250 (NH), 1580 ($-N=N-$), 1380, 1150 cm^{-1} ($-SO_2N=$). UV spectrum, λ_{max}(log ε): 217 (4.510), 230 (4.520), 270 (4.170), 430 (3.890), 476 nm (3.890). PMR spectrum: 8.99 (s, 1-H), 7.79 (s, 2-H), 8.35 (s, 4-H), 8.68 (d, 6-H), 7.50 (d, 7-H), 10.60 (s, 2-H), 2.72 ppm (6H, $-NMe_2$), $J_{6,7}$ = 7.68 Hz, $J_{4,6}$ = 0.73 Hz, $J_{NH,CH}$ = 2.20 Hz. Found: M^+ 394. Calculated: M 394.

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