INDOLE DERIVATIVES. XLIV. PREPARATIVE SYNTHESIS OF INDOPAN FROM INDOLE

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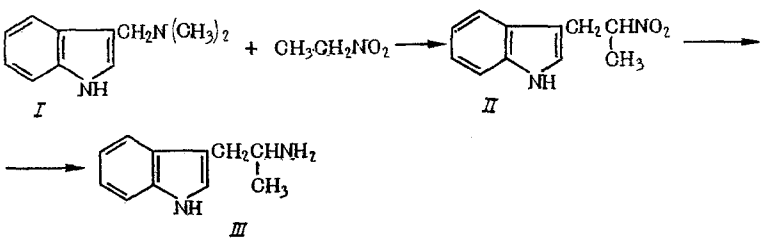
The high physiological activity of indopan (α-methyltryptamine hydrochloride) [1, 2] makes possible its use as a stimulator of the central nervous system in the treatment of certain forms of psychological sickness. However the method of obtaining indopan [3] by modification of Abramovich's scheme has many stages. A considerably simpler synthetic scheme is that based on the condensation of 3-dimethylaminomethylindole (gramine) (I) with nitroethane to 3-(2'-nitropropyl) indole (II) and its subsequent reduction to α-methyltryptamine (III).



The first attempt to carry out the condensation of (I) with nitroethane in an excess of nitroalkane, in the presence of a catalytic amount of solid sodium hydroxide, led to the condensation product which was isolated as a picrate in 20% yield. However, the condensation of nitroethane with (I) has recently [5] been successfully carried out in high yield in the presence of dimethyl sulfate (gramine reacts as the quaternary ammonium salt) and sodium ethoxide as catalysts in ethanolic medium.

We have shown that execution of the reaction under conditions of high dilution and the use of isopropyl alcohol as solvent in place of ethanol leads to a high yield of chromatographically pure (II) which makes possible its use in the subsequent stage without additional purification.

(III) was obtained in 67% yield by the catalytic hydrogenation of (II) under pressure in the presence of Raney nickel.

EXPERIMENTAL

3-Dimethylaminomethylindole (I) was obtained according to [6].

3-(2'-Nitropropyl) indole (II). Metallic sodium (0.42 g) was dissolved in 15 ml anhydrous ethanol, 95 ml anhydrous isopropyl alcohol added, then 4.1 g nitroethane was added dropwise with vigorous stirring and 2.9 g (I) was introduced. After 20 min a solution of 4.2 g dimethyl sulfate in 30 ml isopropyl alcohol was run in. At the end of the dimethyl sulfate addition the tempeature of the mixture had reached 26° and it had become clear. After stirring a further 1-2 h at room temperature, the mixture was poured into 300-500 ml water with vigorous stirring, the thick oil which precipitated was separated, the solution extracted with ether, the combined product and ether extract washed with 2 N acetic acid solution, with water, with 12% NH_4OH, and with water, and dried over anhydrous $MgSO_4$. After distilling off the ether there remained chromatographically pure reaction product. System: ether–petroleum ether (5:1); yield 3.1 g (91%). Thick light-yellow oil with bp 174-176°/1 mm (according to the literature [5], bp 142-144°/10^{-3} mm).

α-Methyltryptamine (III). The hydrogenation of (II) was carried out in ethanolic medium in the presence of Raney nickel at 60° and an initial autoclave pressure of 50 atm. At the end of hydrogen uptake (after 2-4 h), the catalyst was filtered off and the filtrate evaporated in vaccum. The residue, which crystallized,

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was treated with benzene and evaporated in vacuum once again. From 14.5 g (II), 7.7 g (67.2%) (III) was obtained as a white powder with mp 96-98° (according to literature [7], mp 97-100°).

α-Methyltryptamine hydrochloride (indopan) had mp 214-215° (according to literature [3], mp 206-207°).

α-Methyltryptamine adipate had mp 223-224° (lustrous crystals from ethanol). Found, %: C 68.09; H 7.78; N 11.21. $C_6H_{10}O_4 \cdot 2C_{11}H_{14}N_2$. Calculated, %: C 68.02; H 7.69; N 11.38.

α-Methyltryptamine picrate had mp 218-219° (carmine colored crystals from ethanol; according to literature [8], mp 216-218°).

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