RESEARCHES ON IMIDAZOLE DERIVATIVES

XL. Synthesis of Benzimidazole Derivatives of Psilocine

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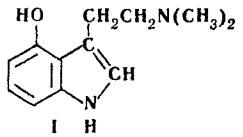
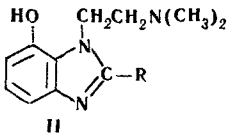
Reaction of 2, 3-dinitroanisole with N, N-dimethylethylenediamine leads to replacement of the nitro group in position 2. The resultant compound is used to synthesize benzimidazaole analogs of the naturally occuring halucinogenic drug psilocine.

Psilocibin, a naturally-occurring hallucinogenic drug, isolated from South American mushrooms, is the phosphoric acid ester of psilocine, which is 3-β-dimethylaminoethyl-4-hydroxyindole (I). It was of interest to prepare the benzimidazole analog of psilocine, and some of its derivatives of structure II, to compare their physiological activities.

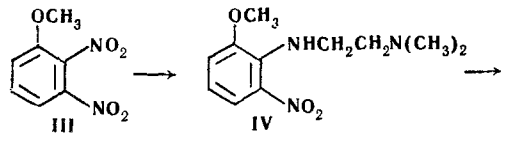


I



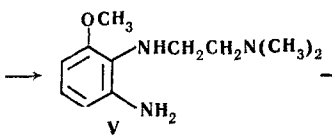
II

We synthesized these compounds starting from 2, 3-dinitroanisole (II), the route being

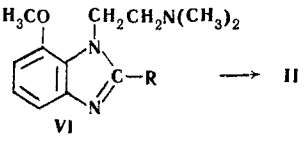


III

IV



V



VI → II

It should be mentioned that compounds IV, V, and VI (R=H) were previously obtained [1] by a similar route, starting from the very difficultly purifiable, and hence much contaminated 2-chloro-3-nitroanisole. Evidently IV and VI were isolated only as the perchlorates, and V was not characterized.

We were able to simplify considerably the preparation of 2,3-dinitroanisole (III) that is described in the literature [2,3]. It was condensed with N, N-dimethylethylenediamine in toluene, when an almost quantitative yield of compound IV was obtained, the latter being reduced with hydrogen and Raney nickel to the diamine V. Heating with formic or phenylacetic acid gave VI (R=H and $C_6H_5CH_2$ respectively), while Weidenhagen treatment with benzaldehyde gave VI ($R=C_6H_5$). Heating with hydrobromic acid effected hydrolysis of the methoxyl groups of all three products, giving compounds of structure II.

Preliminary pharmacological tests on compounds II, carried out by I. P. Lapin (Bekhterev Neuro-Psychological Institute) showed the products to be physiologically active, and to possess clearly marked action on the central nervous system.

EXPERIMENTAL

2,3-Dinitroanisole (III). 40 g (0.26 mole) m-nitroanisole was added in one lot to 100 ml HNO_3 (d 1.48) at 0°–20°, with stirring, when solution started immediately, and the mixture heated spontaneously to 50–55° above the starting temperature. After 15–20 min the products were cooled to –10°, and the colorless crystals filtered off, carefully pressed, washed with HNO_3 (2 × 15 ml, d 1.35), then with water until neutral, and dried at 100°, yield 22.0 g (42%) III, mp 119.0° [2, 3]. The acid spent could be used again.

2-Nitro-6-methoxy-N-(β-dimethylamino)ethylaniline (IV). In a flask fitted with a reflux condenser 19.8 g (0.1 mole) 2,3-dinitroanisole (III) and 17.6 g (0.2 mole) N, N-dimethylethylenediamine, were dissolved in 60 ml toluene, and the mixture heated for about 1 hr on a water bath. The products were cooled to room temperature, and the dark red toluene solution separated off from the lower layer. From the toluene solution the reaction product was extracted with 60 ml dilute (1:1) HCl, which was then neutralized, with cooling, by aqueous ammonia. The bright-red crystals of base IV which separated were filtered off, washed with a small amount of ice-water, and dried over P_2O_5 in a vacuum-desiccator. Yield 22.5 g (97%) IV, mp 32–34°, readily soluble in all organic solvents except low-boiling petrol ether. To purify it, the compound was dissolved in high-boiling petrol ether, filtered, and cooled in acetone-dry ice. IV crystallized as prisms, mp 32.5–34°. Found: N 17.32; 17.60%. Calculated for $C_{11}H_{17}N_3O_3$: N 17.55%. Perchlorate mp 130–132° [1].

Dihydrochloride of 2-amino-6-methoxy-N-(β-dimethylamino)ethylaniline (V). Prepared by reducing compound IV in EtOH solution over Raney Ni at atmospheric pressure. The catalyst was filtered off, 2 equivalents of hydrochloric acid added, the products evaporated almost to dryness under vacuum, acetone added, and the colorless crystals of V filtered off, yield 93–96% of theory. Compound V was very readily soluble in water, MeOH, EtOH, moist acetone, slightly soluble in PrOH, insoluble in dry acetone, dioxane, and ether. A salt containing 3 molecules of HCl can be formed, but it loses one molecule on recrystallizing or heating at 100–110°. Crystallized in thin needles, mp 208–210° (decomp) ex EtOH + PrOH (1:10). Found: Cl 24.85; 25.12; N

15.10; 15.29%. Calculated for $C_{11}H_{19}N_3O \cdot 2HCl$: Cl 25.10; N 14.90%.

Dihydrochloride of 1-(β-dimethylamino)ethyl-7-methoxybenzimidazole (VI, R=H). Prepared by 5 hr refluxing of V dihydrochloride with 80% HCOOH (1:10), yield ~ 98% theory. After treating with active carbon, the solution was evaporated almost to dryness under vacuum, the residue dissolved in PrOH, and the thin colorless crystals which separated on cooling filtered off, and washed with ether. The compound was very soluble in water, MeOH, EtOH, and moist acetone, insoluble in dioxane, dry acetone, and ether. Recrystallized from PrOH it had mp 245–247° (decomp). Adds two molecules of water, which it loses when heated at 105–110°. Found: Cl 21.50; 21.33; N 12.85; 12.88%. Calculated for $C_{12}H_{17}N_3O \cdot 2HCl \cdot 2H_2O$: Cl 21.60; N 12.80%. After drying at 105–110° found: Cl 24.25; 24.39; N 14.27; 14.45%. Calculated for $C_{12}H_{17}N_3O \cdot 2HCl$: Cl 24.25; N 14.33%.

1-(β-Dimethylamino)ethyl-2-phenyl-7-methoxybenzimidazole (VI, R=C_6H_5). 5.0 g (18 mmole) V dihydrochloride in 30 ml water and 2.0 ml benzaldehyde in 15 ml EtOH was added to a solution of 7.1 g (36 mmole) Cu acetate in 120 ml EtOH. After stirring for 1/2 hr, the mixture was refluxed for 1 hr. After cooling, the precipitate of Cu complex was filtered off, then washed with water and acetone. The Cu complex was decomposed by heating with 50 ml concentrated HCl. After cooling, 50 ml EtOH was added to the solution, which was then neutralized with aqueous ammonia until the precipitate formed dissolved completely. The resultant solution was greenish-blue, and removal of the EtOH from it under vacuum gave colorless needles of base VI, which were filtered off, and washed with a small amount of water, yield 4.2 g (80%), readily soluble in MeOH, EtOH, acetone, and hot water, slightly soluble in cold water. Recrystallized from water-EtOH (10:1), it formed colorless needles, mp 107°. Found: N 14.26; 14.26%. Calculated for $C_{18}H_{21}N_3O$: N 14.22%.

Dihydrochloride of 1-(β-dimethylamino)ethyl-2-benzyl-7-methoxybenzimidazole (VI, R=$C_6H_5CH_2$). Prepared as described in [4], by refluxing for 5 hr V with phenylacetic acid in 4 N HCl (1:1.25:5), yield 90–95%. When reaction was finished, the products were cooled, and carefully neutralized with aqueous ammonia and brought to pH 8–8.5, the colorless precipitate filtered off, and washed with a small amount of cold water. The compound was slightly soluble in cold water, and quite soluble in hot water, EtOH, acetone, and benzene. Recrystallized from aqueous EtOH, with water of crystallization which it lost, with melting, at 65–66°, or in a strongly alkaline medium. Anhydrous base VI was an oil. A salt with 2 molecules of HCl formed thin colorless needles, mp (decomp) 225–226°. Found: Cl 19.50; 19.68; N 11.35; 11.40%. Calculated for $C_{19}H_{23}N_3O \cdot 2HCl$: Cl 19.45; N 11.52%.

Dihydrobromides of 1-(β-dimethylamino)ethyl-2-R-7-hydroxybenzimidazoles (II) were obtained in 80–95% yield by refluxing for 4 hr compound VI with 7–10 times the weight of concentrated HBr, then evaporating almost to dryness under vacuum, and adding acetone or PrOH. The colorless crystals which came out were filtered off, and washed with dry acetone and ether. All hydroxy derivatives of benzimidazoles II were exceptionally readily soluble in water, MeOH, EtOH, moist acetone, moist PrOH, and alkalies, and insoluble in dry acetone, dioxane, benzene, and ether.

Dihydrobromide of 1-(β-dimethylamino)ethyl-7-hydroxybenzimidazole (II, R=H). Recrystallized ex PrOH + EtOH (10:1), forming colorless thin needles mp 240° (decomp). Found: Br 43.31; 43.39; N 11.41; 11.45%. Calculated for $C_{11}H_{15}N_3O \cdot 2HBr$: Br 43.50; N 11.45%.

Dihydrobromide of 1-(β-dimethylamino)ethyl-2-phenyl-7-hydroxybenzimidazole (II, R=C_6H_5). Recrystallized ex moist acetone. To accomplish this, the compound was put in acetone which was boiled, and water added dropwise, until the compound dissolved. When the solution cooled, thin colorless needless came out, mp 247–249° (decomp). Found: Br 35.42; 35.53; N 9.25; 9.17%. Calculated for $C_{17}H_{13}N_3O \cdot 2Hbr$: Br 35.95; N 9.43%.

Dihydrobromide of 1-(β-dimethylamino)ethyl-2-benzyl-7-hydroxybenzimidazole (II, R=$C_6H_5CH_2$). Recrystallized similarly to the above from moist acetone, when it formed thin colorless needles. When heated to 134° it began to contract, without melting, and gradually decomposed on further heating. Found: Br 34.71; 34.72; N 9.28; 9.42%. Calculated for $C_{18}H_{21}N_3O \cdot 2HBr$: Br 35.00; N 9.18%.

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