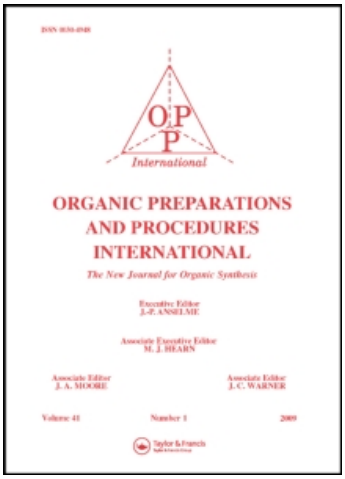

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THE SYNTHESIS OF β-HYDROXYTRYPTAMINES

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THE SYNTHESIS OF β-HYDROXYTRYPTAMINES

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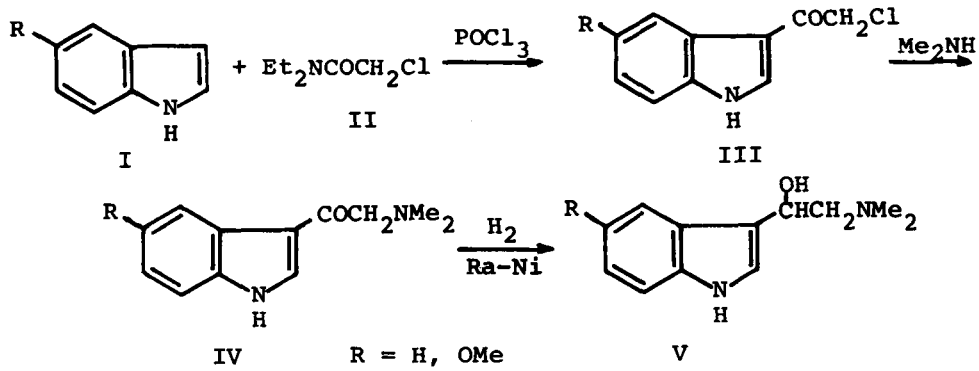
Dedicated to Professor C.G. Overberger on the Occasion of his 60th Birthday

Phenylethylamines such as phenethylamine itself, dopamine and related compounds, as well as indolethylamines such as tryptamine, 5-hydroxytryptamine and related compounds, are of importance in neurochemistry and are known to produce "abnormal" behavior in animals.[1] We recently found that hydroxylation of the side chain in the β-position of the phenylethylamine series reduces or abolishes the latter activity.[2] In order to determine whether or not β-hydroxylation of indolethylamines would also decrease or abolish activity, we decided to synthesize some of these β-hydroxylated compounds. This paper reports their chemical synthesis. Biological results will be presented elsewhere.



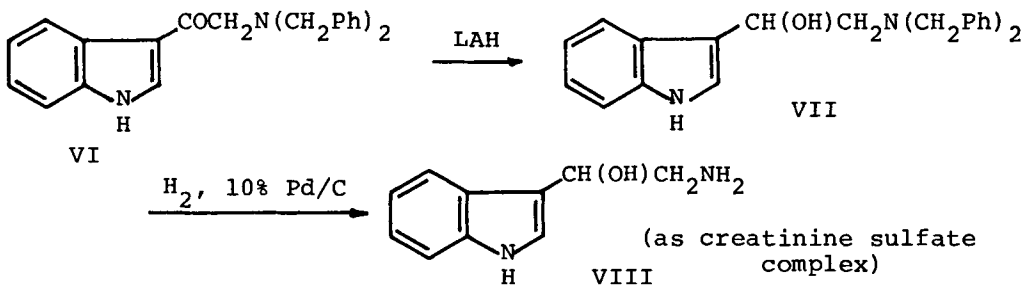
I III IV V

R = H, OMe

The reaction of N,N-diethylchloroacetamide (II) with either indole (Ia) or 5-methoxyindole (Ib) via the Vilsmeier reaction[9] afforded the corresponding chloroethyl ketones III by reaction with dimethylamine.

Lithium aluminum hydride has been reported to reduce 1-unsubstituted 3-acylindoles and 3-(1-hydroxyalkyl)indoles to the corresponding 3-alkylindoles.[3,4] Anthony and Szmuszkovicz[5] claimed that the reduction of the diethylamino analog of IVa with sodium borohydride afforded the diethylamino analog of Va. However, we were unable to reproduce these results. Ames et al.[6] were also unable to reduce ketone IVa with lithium borohydride. The reduction was accomplished by using the procedure of Preobrazhenskaya et al.[7] The 3-(1-hydroxyalkyl) derivatives Va and Vb were prepared by high pressure catalytic hydrogenation over Raney nickel catalyst.

The procedure of Plavsic et al.[8,9] was followed for the preparation of VIII. Reduction of the dibenzylamino ketone VI, prepared by the reaction of III with dibenzylamine, with lithium aluminum hydride stopped at the alcohol stage, presumably because of steric interference by the benzyl groups.[9] However, hydrogenolysis of compound VII to VIII did not proceed as reported[9] and VIII could not be isolated as a water soluble residue capable of being converted to its crystalline creatinine sulfate salt. Instead, an insoluble gum was obtained. A water soluble salt was isolated when the hydrogenolysis was performed in the presence of creatinine hemisulfate. This product could not be purified satisfactorily. It may be noted that the 3-hydroxymethylindoles may be considered as vinylogs of carbinolamines and are unstable, especially in the presence of acids.[10]



The structure of Va and Vb was confirmed by infrared and nuclear magnetic resonance spectroscopy. Compound Va exhibited a peak at 3200 cm^{-1} (broad) indicative of the hydroxyl strongly hydrogen bonded to the indole nitrogen. A complex multiplet at 6.8-7.2 ppm (5H) corresponding to positions 2,4,5,6,7 of the indole confirmed that the ring structure remained unsaturated. Compound Vb exhibited a peak at 3350 cm^{-1} (broad) and a complex multiplet at 6.5-7.2 ppm (4H) corresponding to positions 2,4,6,7 of the indole ring.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, TN 37921. Thin layer chromatograms were run on silica gel GF. Detection was by visualization in ultraviolet light against a fluorescent background.

N,N-Diethylchloroacetamide (II).- This procedure is a modification of that reported by Rohnert.[11] *WARNING! N,N-Diethylchloroacetamide is a powerful vesicant.*

A solution of chloroacetyl chloride (75 g, 0.66 mole) in 200 ml of anhydrous ether was added dropwise to a solution of diethylamine (97 g, 1.32 mole) previously dried and distilled over calcium hydride, in 200 ml of anhydrous ether. The reaction was very vigorous and exothermic and required efficient external cooling. The mixture was stirred for an additional hour at room temperature. The precipitate was filtered and washed with ether. The combined filtrate and washings was evaporated *in vacuo* and the residue fractionally distilled to give 50 g (50%) of II, bp. 127°/44 mm; $n_D^{25°}$ 1.4679.

3-Chloroacetylindole (IIIa).- *WARNING! Skin contact of IIIa causes sensitization reaction.* Phosphorus oxychloride (18.4 g) was added to II (36 g) at 0-5°. The solution was stirred at room temperature for an additional 20 minutes. To this solution cooled to 0-5° was added dropwise a solution of indole (9.9 g) dissolved in II(18 ml). The mixture was heated with stirring

for 1 hr. at 65-70°. After cooling, the resultant viscous purple solution was poured into 300 ml of ice-water with efficient stirring. The reaction flask was washed with a small amount of methanol and the washings were added to the water. The slurry was stirred for 30 minutes and refrigerated overnight. The light orange crystals were filtered and the dark residue in the flask was triturated with a small amount of hot methanol. The crystals thus formed were combined with the first crop. Further purification was accomplished by trituration with hot methanol to yield 11.0 g (67%) of product, mp. 234-235°, lit.[12,13] 232-233°, 233-234°.

3-Chloroacetyl-5-methoxyindole (IIIb).- *WARNING! Skin contact of IIIb causes sensitization reaction.* Phosphorus oxychloride (22.3 g) was added to II (43.5 g) at room temperature. The solution was stirred for an additional 20 minutes at room temperature during which time it darkened in color. A solution of 5-methoxyindole (15 g) in 22 ml of II at 0-5° was added in one portion to the previous solution and the mixture was heated for 1.5 hr. at 55-60°; higher temperatures had a detrimental effect on the yield. The dark viscous mixture was cooled and added to ice-water with efficient stirring. The residue in the flask was washed with a small amount of methanol and the washings added to the ice-water. Work up was as described for IIIa and the yield was 10.8 g (48%), mp. 259°, lit.[12] 271°. Trituration of the compound with hot methanol did not change the melting point.

Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26.

Found: C, 58.99; H, 4.56; N, 6.22.

N,N-Dimethylaminomethyl 3-indolyl ketone (IVa).- To a suspension of IIIa (5.0 g) in 35 ml of methanol was added 35 ml of 40% aqueous dimethylamine. The mixture was refluxed with stirring for 1 hr. The yield of product after filtering the precipitate from the cooled slurry and trituration with 95% ethanol was 5.0 g (96%), mp. 208-209°, lit.[7,5] 208-209°, 205-208°. IR (KBr): 1650 cm^{-1}.

N,N-Dimethylaminomethyl 3-(5-methoxy)indolyl ketone (IVb).- To a suspension of IIIb (10.0 g) in 70 ml of methanol was added 70 ml of 40% aqueous dimethylamine. The reaction conditions and work up were as described for IVa. and the yield was 8.6 g (86%), mp. 196-198°. IR (KBr): 1640 cm^{-1}.

N,N-Dimethyl-β-hydroxytryptamine (Va).- Compound IVa (7.0 g, 0.035 mole) in 200 ml of ethanol was hydrogenated over 10.5 g of Raney nickel at 30° and 60 atm. for 20 hrs. The solvent was evaporated and the residue repeatedly extracted with ether. Upon cooling the ethereal extracts, a gelatinous precipitate was isolated affording 1.1 g (16%) of product after air drying, mp. 118-120°, lit.[7,5] 118-120, 118-121°. Thin layer chromatography (methylene chloride-methanol 3:2) indicated an R_f of 0.31 for Vb along with two trace impurities which defied removal.

Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.55; H, 7.89; N, 13.71.

Found: C, 70.82; H, 8.01; N, 13.68.

N,N-Dimethyl-5-methoxy-β-hydroxytryptamine (Vb).- Compound IVb (4.0 g, 0.018 mole) in 150 ml of ethanol was hydrogenated over 5.0 g of Raney nickel at 30° and 60 atm for 18 hrs. Work up of the product as described for Va afforded 3.2 g (77%) of Vb which was air dried, mp. 113-115°. It was recrystallized from ether. Thin layer chromatography indicated trace amounts of starting material along with a second impurity. The R_f of Vb was 0.21.

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96.

Found: C, 66.77; H, 7.80; N, 11.98.

N,N-Dibenzylaminomethyl 3-indolyl ketone (VI).- IIIa (4.9 g, 0.025 mole) was treated with dibenzylamine (12.8 g, 0.065 mole) in 150 ml of absolute ethanol. The solution was stirred at reflux for 14 hrs. The solvent was evaporated and the residue was extracted with 4 x 40 ml of ether. The combined ethereal extracts were evaporated and the residue was extracted with petroleum ether affording 6.2 g (69%) of crude VI, mp. 153-162°. Recrystal-

lization from absolute ethanol containing Norit-A gave VI as a colorless solid, mp. 165-168°, lit.[9] 158-161°.

Instead of extraction with ether, VI can be separated from dibenzylamine hydrochloride by dissolution of the crude product in acetone leaving dibenzylamine hydrochloride behind. After evaporation of the acetone, the crude material is purified as described above.

N,N-Dibenzyl-β-hydroxytryptamine (VII).- To a stirred suspension of lithium aluminum hydride (1.2 g) in 40 ml of anhydrous ether, was added dropwise, VI (1.4 g, 0.04 mole) in 100 ml of anhydrous ether. The reaction mixture was cooled in an ice-bath. After completion of the addition, stirring was continued for 1.5 hr. with the mixture kept in an ice-bath.

Excess lithium aluminum hydride was decomposed by the dropwise addition of water (10 ml). The precipitate was filtered and the ethereal solution was dried over anhydrous magnesium sulfate. Evaporation of the ether afforded a viscous liquid which upon trituration with hot hexane afforded colorless crystals in a yield of 1.15 g (82%), mp. 114-116°, lit.[9] 114-116°.

β-Hydroxytryptamine Creatinine Sulfate Complex (VIII).- Compound VI (0.74 g, 0.02 mole) and creatinine hemisulfate (0.35 g, 0.002 mole) were dissolved in a mixture of 60 ml of methanol and 15 ml of water and was hydrogenated over 0.35 g of 10% Pd/C for 16 hrs. at 3 atm and room temperature. The catalyst was filtered and washed with methanol and water. The combined solution and washings were evaporated in vacuo. The residue was dissolved in 5 ml of water and precipitated by the slow addition of 50 ml of acetone. The process was repeated yielding a white powder which was dried in vacuo for 6 hrs. at room temperature to yield 0.4 g (48%), mp. 175-180° (dec.), lit.[9] 205°.

Anal. Calcd for $C_{14}H_{21}N_5SO_6 \cdot 3/4\ H_2O$: C, 41.95; H, 5.65; N, 17.46.

Found: C, 41.90; H, 5.72; N, 18.05.

Thin layer chromatography (methanol-water 4:1) indicated the product to have an R_f value of 0.56 with a second component corresponding to creatinine hemisulfate at 0.71; no starting material was detected.

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