Synthesis of 5,7- and 6,7-Disubstituted Tryptamines and Analogs (1)

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5,6-Dihydroxytryptamine has previously been shown by Baumgarten, *et al.* (3), to have a long lasting depletion effect on brain serotonin. More recently, 5,7-dihydroxytryptamine has been shown to have similar activity, but with less toxicity (4). This prompts us to report our synthesis of 5,7-dihydroxytryptamine and a series of its analogs as well as the synthesis of 6,7-dihydroxytryptamine, which represents another possible tool for the biological investigation of indoleamine neuron activity. We also want to report our synthesis of 5-hydroxy-7-chlorotryptamine.

The methods used to synthesize these compounds were based on combinations of several published methods for the synthesis of unsubstituted tryptamines. Of general importance to the syntheses was the development of a convenient route to the parent benzyloxyindoles.

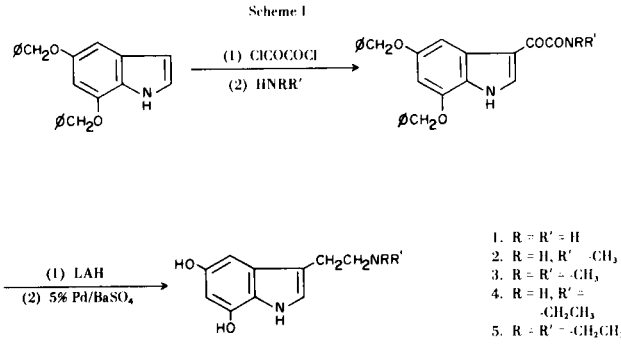
5-Benzyloxy-7-chloroindole was obtained by the Fisher indole ring closure of ethyl pyruvate 2-chloro-4-benzyloxyphenylhydrazone and subsequent hydrolysis and decarboxylation. However, the yield of the cyclization was low.

The Fisher indole cyclization of ethyl pyruvate *o*-substituted phenylhydrazones has been formerly shown to give rearrangement products and only a small percentage of the expected 7-substituted indoles (5). We observed this phenomenon also in the synthesis of ethyl 5-chloro-7-benzyloxyindole-2-carboxylate (6), where we obtained a very low percentage of product *via* this method. We, therefore, used the reductive cyclization of the appropriate dibenzyloxy-2,β-dinitrostyrenes to prepare 5,7- and 6,7-dibenzyloxyindoles.

3,5-Dibenzyloxy-2,β-dinitrostyrene was obtained by nitration of 3,5-dibenzyloxy-β-nitrostyrene with cupric nitrate at 70°, utilizing the method described in the synthesis of 5,7-dimethoxyindole (7). 3,4-Dibenzyloxy-2,β-dinitrostyrene was prepared by the condensation of 2-nitro-3,4-dibenzyloxybenzaldehyde with nitromethane. The dibenzyloxy-2,β-dinitrostyrenes were reduced with iron and acetic acid to yield the corresponding dibenzyloxyindoles.

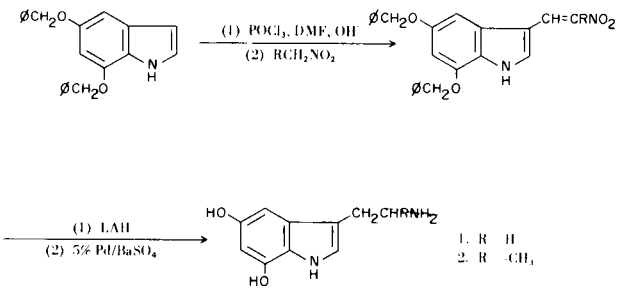
Two different routes were used for the introduction of the β-aminoethyl side chain at the 3-position of the indole nucleus. We found the route of Speeter and Anthony (8), which is shown in Scheme I, to be a good general synthetic method. According to this method, oxalyl chloride was allowed to react with 5,7- and 6,7-dibenzyloxyindoles to give the 5,7- and 6,7-dibenzyloxyindole-3-glyoxylyl chlorides. This intermediate was then treated with ammonia or a primary or secondary amine to give the appropriate glyoxylamide. This in turn was reduced with lithium aluminum hydride to the corresponding tryptamine. After some experimentation, we found that the best yields of the tryptamines were obtained when an excess of lithium aluminum hydride was used, tetrahydrofuran was used as solvent, and the mixture was refluxed for no more than 4.5 hours.

Scheme I



The second method of tryptamine synthesis, which was modeled after the synthesis of 5-methoxy-6-benzyloxytryptamine (9), is shown in Scheme II. It was used to prepare 5-benzyloxy-7-chlorotryptamine and 5,7-dibenzyloxytryptamine and its α-methyl analog. This method involved the synthesis of the substituted indole-3-carboxaldehydes which were converted to the appropriate nitrovinyl analogs by reaction with nitromethane or nitroethane. The nitrovinyl compounds were reduced to the corresponding tryptamines using lithium aluminum hydride. The carboxaldehydes were prepared analogously to the method described for 6-benzyloxyindole-3-carboxaldehyde (10) and 5,6-dibenzyloxyindole-3-carboxaldehyde (11).

Scheme II



The benzyloxytryptamines were converted to the corresponding hydroxytryptamines by catalytic hydrogenation using palladium catalyst. The 5,7- and 6,7-dihydroxytryptamines were isolated as their creatinine sulfate salts; the *N*-substituted amines as their oxalate salts; the methyl tryptamine as the hydrogen oxalate salt; and the 5-hydroxy-7-chlorotryptamine as its hydrochloride salt.

EXPERIMENTAL

Melting points are uncorrected. Spectral data in agreement with assigned structures. Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Illinois.

5,7-Dihydroxytryptamine and Analogs.

Benzyl 3,5-Dibenzyloxybenzoate.

A mixture of 300 g. (1.94 moles) of 3,5-dihydroxybenzoic acid, 860 g. (6.86 moles) of benzyl chloride, 1050 g. of potassium carbonate and 3.80 l. of *N,N*-dimethylformamide was stirred at 110-120° for 20 hours. The reaction mixture was cooled to room temperature, filtered and washed with *N,N*-dimethylformamide. The combined filtrates were concentrated under reduced pressure, then diluted with water and basified with dilute sodium hydroxide solution. The crude product was collected by suction filtration and crystallized from petroleum ether (b.p. 110-113°) to yield 569 g. (67.6%) of product, m.p. 63-66°. A portion was recrystallized from petroleum ether (b.p. 75-77°) to a constant, m.p. 71-72°.

Anal. Calcd. for $C_{28}H_{24}O_4$: C, 79.23; H, 5.70. Found: C, 79.46; H, 6.18.

3,5-Dibenzyloxybenzyl Alcohol.

A solution of 70.0 g. (0.164 mole) of benzyl 3,5-dibenzyloxybenzoate in 300 ml. of tetrahydrofuran was added dropwise with stirring to a suspension of 14.0 g. (0.37 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran. After the addition was complete, the mixture was heated under reflux with stirring for 3.5 hours, and allowed to stand at room temperature overnight. The work-up procedure was carried out as usual. After removal of the solvent under vacuum, the crude yellow viscous oil was treated with low boiling petroleum ether and the crude solid was recrystallized from benzene-hexane to yield 50.0 g. (95.0%) of colorless needles, m.p. 79.5-81°.

Anal. Calcd. for $C_{21}H_{20}O_3$: C, 78.73; H, 6.29. Found: C, 78.84; H, 6.20.

3,5-Dibenzyloxybenzaldehyde.

The oxidation was carried out according to Albright (12). A mixture of 90.0 g. (0.28 mole) of 3,5-dibenzyloxybenzyl alcohol, 950 g. of dimethylsulfoxide and 590 g. of acetic anhydride was stirred at room temperature for 24 hours, then added to 18.0 l. of water and the resulting mixture stirred for 2 hours. The water was decanted and the product extracted with 1.8 l. of benzene, washed with water and dried over sodium sulfate. After removal of the benzene, the residue was treated with *n*-hexane to give 65.0 g. (73.1%) of white, flaked crystals, m.p. 78-79°.

Anal. Calcd. for $C_{21}H_{18}O_3$: C, 79.23; H, 5.70. Found: C, 79.27; H, 5.73.

3,5-Dibenzyloxy-β-nitrostyrene.

To a stirred mixture of 8.50 g. (0.027 mole) of 3,5-dibenzyloxybenzaldehyde, 400 ml. of nitromethane, 5 ml. of acetic acid, and 200 ml. of toluene at a gentle reflux was added portionwise over 1.5 hours 6.0 g. of sodium acetate. The solvents were then removed under vacuum to leave an oil, which on trituration with methanol yielded a solid. It was filtered, washed with water and crystallized from ethanol (Darco) to yield 6.5 g. (66.8%) of product, m.p. 94-96°. On cooling, it remelted at 107-109°. A portion was crystallized from benzene-hexane to give a double m.p. 96-97°, then again 112-113°.

Anal. Calcd. for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.04; H, 5.37; N, 3.87.

3,5-Dibenzyloxy-2,β-dinitrostyrene.

To a solution of 150 g. (0.418 mole) of 3,5-dibenzyloxy-β-nitrostyrene in 1680 ml. of acetic anhydride was added with stirring 200 g. (0.83 mole) of powdered cupric nitrate portionwise over 3.5 hours at 70°. Red fumes were evolved and the temperature rose to 85°. Stirring was continued for 1 hour, the reaction mixture poured over ice and the crude product collected by decanting. Recrystallization from benzene-hexane yielded 94.0 g. (55.5%) of pale yellow crystals, m.p. 165-168°.

Anal. Calcd. for $C_{22}H_{18}N_2O_6$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.94; H, 4.42; N, 7.05.

5,7-Dibenzyloxyindole.

To a stirred mixture of 1 l. of acetic acid, 1.3 l. of ethanol, and 650 g. of iron powder at reflux was added dropwise over a period of 15 minutes a solution of 111 g. (0.272 mole) of 3,5-dibenzyloxy-2,β-dinitrostyrene in acetic acid. After the addition was complete, the mixture was stirred at reflux for 2 hours, and filtered into 5 l. of water containing 250 g. of sodium metabisulfite. The cake was washed with a little alcohol, then with 4 l. of methylene chloride, which was then used to extract the aqueous phase. The organic layer was washed with water, 5% sodium bicarbonate, then with water again, and dried. Removal of the solvent left an oil which was run over a silica column 6 x 85 cm., and eluted with benzene. It was necessary to run the compound again over the column to purify it, resulting in 47.6 g. (53.1%) of product, m.p. 85-87°. A portion was recrystallized from benzene-hexane to a constant, m.p. of 89-90° for analysis.

Anal. Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.15; H, 5.82; N, 4.12.

5,7-Dibenzyloxyindole-3-carboxaldehyde.

The reaction conditions for this preparation were identical to those of 5,6-dibenzyloxyindole-3-carboxaldehyde (10). From 15 g. (0.045 mole) of 5,7-dibenzyloxyindole, 9 g. (55%) of

product, recrystallized from ethanol, was obtained, m.p. 162-166°.

Anal. Calcd. for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.05; H, 5.24; N, 3.88.

5,7-Dibenzyloxy-3-(β-nitrovinyl)indole.

A mixture of 7 g. (0.0196 mole) of 5,7-dibenzyloxyindole-3-carboxaldehyde, 100 ml. of nitromethane, 150 ml. of toluene and 3 g. of ammonium acetate was heated under reflux with stirring for 2 hours. After the reaction period, the solvent and excess nitromethane were removed under vacuum. The crude residue was washed with hot water, then crystallized from ethanol to yield 6 g. (76.5%) of orange needles, m.p. 186-188°.

Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00. Found: C, 71.85; H, 5.10; N, 6.77.

5,7-Dibenzyloxy-3-(β-nitroallyl)indole Hemihydrate.

In a similar manner reaction of 5,7-dibenzyloxyindole-3-carboxaldehyde, 13.8 g. (0.038 mole) with nitroethane in benzene gave 7.1 g. (45%) of product, recrystallized from ethanol, m.p. 174-175°.

Anal. Calcd. for $C_{25}H_{22}N_2O_4 \cdot 0.5H_2O$: C, 70.95; H, 5.48; N, 6.62. Found: C, 70.85; H, 5.45; N, 6.50.

5,7-Dibenzyloxytryptamine Hydrogen Oxalate.

Method A.

A solution of 6 g. (0.015 mole) of 5,7-dibenzyloxy-3-(β-nitrovinyl)indole in 100 ml. of tetrahydrofuran was added dropwise to a stirred suspension of 7 g. of lithium aluminum hydride in 200 ml. of tetrahydrofuran and the mixture stirred for 2 hours at reflux and 3 hours at room temperature. The work-up was carried out as usual to give a semi-solid, which was converted to the hydrogen oxalate salt, and then crystallized from ethanol-water to yield 1.35 g. (19.5%) of product, m.p. 209-210° dec.

Anal. Calcd. for $C_{24}H_{24}N_2O_2 \cdot C_2H_2O_4$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.49; H, 5.84; N, 6.12.

5,7-Dibenzyloxy-α-methyltryptamine Hydrogen Oxalate.

Reduction of 7 g. (0.017 mole) of 5,7-dibenzyloxy-3-(β-nitroallyl)indole hemihydrate with lithium aluminum hydride, as in preparation of 5,7-dibenzyloxytryptamine hydrogen oxalate, gave, after recrystallization from methanol-ethanol, 1.8 g. (22%) of product, m.p. 224-225°.

Anal. Calcd. for $C_{25}H_{26}N_2O_2 \cdot C_2H_2O_4$: C, 68.05; H, 5.92; N, 5.88. Found: C, 68.01; H, 6.00; N, 5.89.

5,7-Dibenzyloxyindole-3-glyoxylamide.

To a stirred solution of 25 ml. of ammonia in 25 ml. of ether was added portionwise over 3 minutes 5,7-dibenzyloxyindole-3-glyoxylyl chloride made from 3.50 g. (0.0106 mole) of 5,7-dibenzyloxyindole. The mixture was stirred for 10 minutes, and the excess solvents were removed with the use of a warm water bath. The residue was stirred with water, filtered, and dried to yield 3.03 g. (72.3%) of product. A portion was crystallized from ether to a constant, m.p. 193-195° for analysis.

Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00. Found: C, 71.83; H, 4.94; N, 6.91.

The reaction conditions and work-up for the syntheses of the following compounds were identical with those just described.

N-Methyl-5,7-dibenzyloxyindole-3-glyoxylamide.

This compound was obtained in 63.2% yield, m.p. 197-199°.

Anal. Calcd. for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76. Found: C, 72.35; H, 5.29; N, 6.66.

N-Ethyl-5,7-dibenzyloxyindole-3-glyoxylamide.

This compound was obtained in 42.6% yield, m.p. 153-154°.

Anal. Calcd. for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 72.71; H, 5.74; N, 6.46.

N,N-Dimethyl-5,7-dibenzyloxyindole-3-glyoxylamide.

This compound was obtained in 70.1% yield, m.p. 204-206°.

Anal. Calcd. for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.65; N, 6.54. Found: C, 72.87; H, 5.52; N, 6.43.

N,N-Diethyl-5,7-dibenzyloxyindole-3-glyoxylamide.

This compound was obtained in 78.8% yield, m.p. 191-193°.

Anal. Calcd. for $C_{28}H_{28}N_2O_4$: C, 73.66; H, 6.18; N, 6.14. Found: C, 73.48; H, 6.24; N, 6.24.

5,7-Dibenzyloxytryptamine Hydrogen Oxalate.

Method B.

To a stirred suspension of 24.0 g. of lithium aluminum hydride in 3.0 l. of tetrahydrofuran was added dropwise over 20 minutes a solution of 17.0 g. (0.0425 mole) of 5,7-dibenzyloxyindole-3-glyoxylamide in 300 ml. of tetrahydrofuran. The mixture was heated to reflux and stirred for 1.5 hours, then stirred at room temperature for an additional 2 hours. The reaction mixture was decomposed with water in tetrahydrofuran, stirred at reflux for 15 minutes, and filtered hot. The residues were re-extracted with hot tetrahydrofuran, and the combined filtrates were taken to dryness to yield an oil, which was converted to the hydrogen oxalate salt (10.7 g., 53.6%), m.p. 198-200° dec. A single crystallization from ethanol gave a pure compound, m.p. 209-210° dec. identical in all respects to that obtained in Method A.

N-Methyl-5,7-dibenzyloxytryptamine Oxalate.

To a stirred suspension of 3.50 g. of lithium aluminum hydride in 200 ml. of tetrahydrofuran was added dropwise over 5 minutes a solution of 2.80 g. (0.0067 mole) of *N*-methyl-5,7-dibenzyloxyindole-3-gloxylamide in 50 ml. of tetrahydrofuran. After the addition was complete, the mixture was stirred at reflux for 4.5 hours, and decomposed with 7 ml. of water in tetrahydrofuran. The mixture was stirred at reflux for 15 minutes, filtered hot, the residues extracted with hot tetrahydrofuran, and the combined filtrates taken to dryness to leave an oil. The oil was dissolved in 35 ml. of ethanol, and to the stirred solution was added dropwise over 5 minutes a solution of 0.242 g. (0.0027 mole) of oxalic acid in 35 ml. of ethanol. The suspension was cooled and filtered to yield a solid, which was crystallized from 600 ml. of methanol to yield in 3 crops 1.35 g. (58.0%) of product, m.p. 213-214° dec.

Anal. Calcd. for $(C_{25}H_{26}N_2O_2)_2 \cdot C_2H_2O_4$: C, 72.36; H, 6.31; N, 6.49. Found: C, 72.65; H, 6.25; N, 6.34.

The reaction conditions and work-up for the syntheses of the following compounds were identical with those just described.

N-Ethyl-5,7-dibenzyloxytryptamine Oxalate.

This compound was obtained in 35.1% yield, m.p. 246-248° dec.

Anal. Calcd. for $(C_{26}H_{28}N_2O_2)_2 \cdot C_2H_2O_4$: C, 72.78; H, 6.56; N, 6.29. Found: C, 72.62; H, 6.58; N, 6.14.

N,N-Dimethyl-5,7-dibenzyloxytryptamine Oxalate.

This compound was obtained in 75.0% yield, m.p. 204-205.5°.

Anal. Calcd. for $(C_{26}H_{28}N_2O_2)_2 \cdot C_2H_2O_4$: C, 72.78; H, 6.56; N, 6.29. Found: C, 72.53; H, 6.66; N, 6.13.

N,N-Diethyl-5,7-dibenzyloxytryptamine Oxalate.

This compound was obtained in 70.3% yield, m.p. 166-167°.

Anal. Calcd. for $(C_{28}H_{32}N_2O_2)_2 \cdot C_2H_2O_4$: C, 73.55; H, 7.02; N, 5.92. Found: C, 73.47; H, 7.06; N, 5.82.

5,7-Dihydroxytryptamine Creatinine Sulfate.

A mixture of 2.71 g. (0.00585 mole) of 5,7-dibenzyloxytryptamine hydrogen oxalate, 370 ml. of methanol and 2.70 g. of 5% palladium-barium sulfate was stirred under an atmosphere of hydrogen for 6 hours. The catalyst was filtered and the filtrate taken to dryness to leave an oil, which was dissolved in 6.0 ml. (0.00608 mole) of 2*N* sulfuric acid. After stirring for a few minutes, 0.688 g. (0.00608 mole) of creatinine was added as a solid all at once. The solution was stirred for several minutes and acetone was added to the cloud point. After a few minutes, a precipitate formed. The suspension was cooled and filtered to yield 1.20 g. (51.5%) of product, m.p. 245-246° dec.

Anal. Calcd. for $C_{10}H_{12}N_2O_2 \cdot C_4H_7N_3O \cdot H_2SO_4$: C, 41.68; H, 5.25; N, 17.36. Found: C, 41.40; H, 5.29; N, 17.54.

5,7-Dihydroxy-α-methyltryptamine Hydrogen Oxalate.

A mixture of 0.7 g. (0.0015 mole) of 5,7-dibenzyloxy-α-methyltryptamine hydrogen oxalate, 0.35 g. of 5% palladium-barium sulfate, 0.05 g. of oxalic acid and 100 ml. of methanol was stirred under an atmosphere of hydrogen for 3 hours and left overnight. The catalyst was filtered in a nitrogen atmosphere and the filtrate concentrated to 10 ml. It was diluted with 15 ml. of ethanol (Norite), and concentrated to 15 ml., then 20 ml. of ether was added and the solution was cooled. The crude product, m.p. 244-249° was recrystallized repeatedly from ethanol-ether to give the analytical sample, m.p. 258-259° dec.

Anal. Calcd. for $C_{11}H_{14}N_2O_2 \cdot C_2H_2O_4$: C, 52.70; H, 5.44; N, 9.45. Found: C, 52.50; H, 6.00; N, 8.97.

N-Methyl-5,7-dihydroxytryptamine Oxalate Monohydrate.

A mixture of 1.10 g. (0.0126 mole) of *N*-methyl-5,7-dibenzyloxytryptamine oxalate, 0.55 g. of 5% palladium-barium sulfate, 130 ml. of water and 70 ml. of methanol was stirred under an atmosphere of hydrogen for 4 hours. The hydrogen was replaced with nitrogen, and the mixture was stirred and heated to 60° for a few minutes, the catalyst filtered and taken to dryness to leave an oil, which changed to a solid, when triturated with acetone. The product was dried under vacuum at 80° for 2 hours to yield 0.135 g. (20.8%), m.p. 197-199° dec.

Anal. Calcd. for $(C_{11}H_{14}N_2O_2)_2 \cdot C_2H_2O_4 \cdot H_2O$: C, 55.38; H, 6.20; N, 10.76. Found: C, 55.32; H, 5.78; N, 10.48.

The reaction conditions and work-up for the synthesis of the following compounds were identical with those just described.

N-Ethyl-5,7-dihydroxytryptamine Oxalate Hemihydrate.

This compound was obtained in 50.9% yield, m.p. 250-251° dec.

Anal. Calcd. for $(C_{12}H_{16}N_2O_2)_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$: C, 57.87; H, 6.53; N, 10.38. Found: C, 58.08; H, 6.54; N, 10.45.

N,N-Dimethyl-5,7-dihydroxytryptamine Oxalate.

This compound was obtained in 49.8% yield, m.p. 232-235° dec.

Anal. Calcd. for $(C_{12}H_{16}N_2O_2)_2 \cdot C_2H_2O_4$: C, 58.86; H, 6.46; N, 10.56. Found: C, 58.70; H, 6.55; N, 10.52.

N,N-Diethyl-5,7-dihydroxytryptamine Oxalate.

This compound was obtained in 54.0% yield, m.p. 249-250° dec.

Anal. Calcd. for $(C_{14}H_{20}N_2O_2)_2 \cdot C_2H_2O_4$: C, 61.42; H, 7.22; N, 9.55. Found: C, 61.25; H, 7.20; N, 9.51.

6,7-Dihydroxytryptamine.

3,4-Dihydroxy-2-nitrobenzaldehyde.

This compound was made according to the method of Lange (13). To a stirred mixture of 352 g. (1.80 moles) of 2-nitrovanillin (14), 2600 ml. of methylene chloride and 264 g. of anhydrous aluminum chloride was added 630 g. (8.00 moles) of pyridine over 0.5 hour. The mixture was stirred for 4 days, then poured into a mixture of 12 l. of water and 900 ml. of concentrated hydrochloric acid. The methylene chloride layer was separated and discarded, and the aqueous layer was stirred at 50-55° for 1 hour. The suspension was filtered hot to yield 50.0 g. of crude product. On cooling to room temperature, there was obtained in several crops 185.0 g. of pure product, m.p. 175-178°. Recrystallization of the 50.0 g. described above gave 25.0 g. of pure product, making the total yield 210 g. (63.8%), m.p. 175-178° dec. A portion was recrystallized from water to a constant, m.p. 178-179° dec. for analysis.

Anal. Calcd. for $C_7H_5NO_5$: C, 45.91; H, 2.75; N, 7.65. Found: C, 46.01; H, 2.70; N, 7.57.

3,4-Dibenzyloxy-2-nitrobenzaldehyde.

A mixture of 116 g. (0.63 mole) of 3,4-dihydroxy-2-nitrobenzaldehyde, 230 g. of potassium carbonate, 174 g. (1.37 moles) of benzyl chloride and 1500 ml. of *N,N*-dimethylformamide was stirred and heated at 115-117° for 1.5 hours, cooled and poured into 6 l. of cold water with stirring. The product was extracted with 2 x 7 l. of ether, the ether washed several times with water and concentrated to 400 ml. to yield in two crops 89.0 g. (38.6%) of product, m.p. 107-109°. A portion was recrystallized from propanol-2 to a constant, m.p. 109-110° for analysis.

Anal. Calcd. for $C_{21}H_{17}NO_5$: C, 69.41; H, 4.72; N, 3.85. Found: C, 69.21; H, 4.61; N, 4.05.

3,4-Dibenzyloxy-2,β-dinitrostyrene.

To a stirred mixture of 45.0 g. (0.124 mole) of 3,4-dibenzyloxy-2-nitrobenzaldehyde and 12.8 g. (0.21 mole) of nitromethane in 500 ml. of ethanol and 310 ml. of *N,N*-dimethylformamide at -2 to -1° was added a solution of 13.8 g. (0.25 mole) of potassium hydroxide in 26 ml. of water and 260 ml. of ethanol dropwise over 0.5 hour. Stirring was continued for 45 minutes, and the temperature lowered to -20 to -10°, and carefully acidified with 22.5 ml. of hydrochloric acid in 200 ml. of water. An additional 6 l. of water was added, the mixture was stirred for 1 hour at 0°, and the crude nitroalcohol filtered and dried. The resulting solid was heated to reflux for 10 minutes in 190 ml. of acetic anhydride with 19.0 g. of sodium acetate, cooled, poured into water and stirred for 0.5 hour. The product was triturated with hot alcohol and filtered to yield 44.0 g. (86.5%) of pure product, m.p. 160-162°. A portion was crystallized from alcohol to a constant, m.p. 162-164° for analysis.

Anal. Calcd. for $C_{22}H_{18}N_2O_6$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.04; H, 4.35; N, 6.80.

6,7-Dibenzyloxyindole.

This compound was prepared in the same manner as 5,7-dibenzyloxyindole described previously. From 73.0 g. (0.18 mole) of 3,4-dibenzyloxy-2,β-dinitrostyrene was obtained 38.0 g. (64.8%) of product, m.p. 37-39°.

Anal. Calcd. for $C_{22}H_{19}N_2O_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.26; H, 5.98; N, 4.23.

6,7-Dibenzyloxyindole-3-glyoxylamide.

The compound was prepared in the same manner as 5,7-dibenzyloxyindole-3-glyoxylamide. From 3.5 g. (0.0107 mole) of 6,7-dibenzyloxyindole was obtained 3.50 g. (81.6%) of product,

m.p. 195-197°. A portion was recrystallized from ether to a constant, m.p. 196-198° for analysis.

Anal. Calcd. for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00. Found: C, 72.06; H, 5.00; N, 7.02.

6,7-Dibenzyloxytryptamine.

The compound was prepared in the same manner as 5,7-dibenzyloxytryptamine (Method B). From 32.4 g. (0.081 mole) of 6,7-dibenzyloxyindole-3-glyoxylamide was obtained 8.20 g. (27.4%) of white powder, m.p. 105-107°, crystallized from benzene-hexane. It was not purified further for the next step. The compound was identified as its oxalate salt, m.p. 189-191°, dec. from ethanol.

Anal. Calcd. for $(C_{24}H_{26}N_2O_2)_2 \cdot C_2H_2O_4$: C, 71.57; H, 6.48; N, 6.67. Found: C, 71.41; H, 6.01; N, 6.69.

6,7-Dihydroxytryptamine Creatinine Sulfate Monohydrate.

A mixture of 4.58 g. (0.0123 mole) of 6,7-dibenzyloxytryptamine, 4.0 g. of 5% palladium-barium sulfate and 420 ml. of methanol was stirred under an atmosphere of hydrogen for 4 hours. The catalyst was filtered under nitrogen, the filtrate taken to dryness and mixed with 1.61 g. (0.00499 mole) of creatinine sulfate. After the addition of 19.7 ml. (0.00477 mole) of 0.5 *N* sulfuric acid, the resulting solution was heated to 40° for 2 minutes. Acetone was added to the cloud point, and after cooling the resulting solid was filtered to yield 2.30 g. (44.1%) of product, m.p. 196-198° dec.

Anal. Calcd. for $C_{10}H_{12}N_2O_2 \cdot C_4H_7N_3O \cdot H_2SO_4 \cdot H_2O$: C, 39.90; H, 5.50; N, 16.62. Found: C, 39.86; H, 5.38; N, 16.67.

5-Hydroxy-7-chlorotryptamine.

2-Chloro-4-benzyloxynitrobenzene.

A mixture of 59 g. (0.34 mole) of 3-chloro-4-nitrophenol (15), 48 g. (0.38 mole) of benzyl chloride, 79 g. (0.57 mole) of anhydrous potassium carbonate, and 900 ml. of *N,N*-dimethylformamide was heated and stirred at 110° for 6 hours. After pouring into 2.5 l. of ice and water, the resulting mixture was filtered and the solid washed with water, dried, and crystallized from benzene-hexane (charcoal) to yield 65.6 g. (72.5%) of product, m.p. 84-85°.

Anal. Calcd. for $C_{13}H_{10}ClNO_3$: C, 59.22; H, 3.82; N, 5.31. Found: C, 59.18; H, 3.73; N, 5.31.

2-Chloro-4-benzyloxyaniline Hydrochloride.

The reduction to 2-chloro-4-benzyloxyaniline hydrochloride was carried out in two runs, each containing 33.5 g. of 2-chloro-4-benzyloxynitrobenzene, 6.7 g. 5% Rh/C, and 200 ml. of ethyl acetate. After shaking for 6 hours in a Parr hydrogenation apparatus, the catalyst was filtered, the filtrate stripped and the residue treated with gaseous hydrogen chloride in ether solution. The precipitate was collected and crystallized from ether-absolute ethanol to yield in two crops 44.3 g. (65%) of product, m.p. 208.5-210° dec.

Anal. Calcd. for $C_{13}H_{12}ClNO \cdot HCl$: C, 57.80; H, 4.85; N, 5.19. Found: C, 57.89; H, 4.78; N, 5.19.

Ethyl Pyruvate 2-Chloro-4-benzyloxyphenylhydrazone.

A suspension of 65 g. (0.24 mole) of 2-chloro-4-benzyloxyaniline hydrochloride in 110 ml. of concentrated hydrochloric acid, 145 ml. of water, and 200 ml. of ethanol was stirred and cooled by the addition of ice as 35.7 g. (0.52 mole) of sodium nitrite in 165 ml. of water was added at 5-10°. The resulting diazonium salt solution was added rapidly to a stirred mixture of 48.5 g. (0.24 mole) of ethyl α-ethoxalylpropionate, 240 ml. of ethanol, 480 ml. of ice water, and 197 g. (2.4 moles) of anhydrous sodium acetate at 5-10°. After 2.5 hours of additional stirring, the mixture was extracted with ether, and the extract washed with 10% potassium carbonate and then with water, dried over sodium sulfate and stripped to a dark oil, crude weight, 93 g. (theory 83 g.). The latter contained a mixture of two phenylhydrazone isomers which was used as such or could be separated by passing through a silica gel column with benzene. Isomer A, m.p. 81-82°; isomer B, m.p. 95-96.5°.

Anal. Calcd. for $C_{18}H_{19}ClN_2O_3$: C, 62.33; H, 5.52; N, 8.08. Found (isomer A): C, 62.06; H, 5.49; N, 7.90. Found (isomer B) C, 62.17; H, 5.52; N, 7.86.

Ethyl 5-Benzyloxy-7-chloroindole-2-carboxylate.

To a solution of 102 g. (0.28 mole) of ethyl pyruvate 2-chloro-4-benzyloxyphenylhydrazone in absolute ethanol was added 320 ml. of concentrated sulfuric acid in 15 minutes. The resulting reaction mixture was stirred and refluxed under nitrogen for 1.75 hours, cooled and poured into 5 l. of ice and water with stirring. The product was extracted with benzene, washed with water, dried and stripped to give a crude oil which was applied to a silica gel column and eluted with benzene. Like fractions were combined and stripped to a mushy solid which, after washing with petroleum ether, gave 22.8 g. (24.6%) of product. An analytical sample was obtained from ethanol, m.p. 121.8-122.5°.

Anal. Calcd. for $C_{18}H_{16}ClNO_3$: C, 65.55; H, 4.89; N, 4.25. Found: C, 65.57; H, 5.00; N, 4.26.

5-Benzyloxy-7-chloroindole-2-carboxylic Acid.

A mixture of 14.4 g. (0.0438 mole) of ethyl 5-benzyloxy-7-chloroindole-2-carboxylate, 200 ml. of ethanol, and 51 ml. of aqueous potassium hydroxide (18 g. of potassium hydroxide in 45 ml. of water) was refluxed and stirred for 45 minutes, cooled, and poured into 1 l. of ice and water containing 100 ml. of concentrated hydrochloric acid. The precipitate was collected, washed with water and dried at 70° overnight to give 12.9 g. (97.5%) of product, m.p. 160.5-162°. An analytical sample was crystallized from ethanol (charcoal), m.p. 161-161.5°.

Anal. Calcd. for $C_{16}H_{12}ClNO_3$: C, 63.69; H, 4.01; N, 4.64. Found: C, 63.86; H, 3.98; N, 4.70.

5-Benzyloxy-7-chloroindole.

A mixture of 12.9 g. (0.0428 mole) of 5-benzyloxy-7-chloroindole-2-carboxylic acid, 190 ml. of quinoline, and 1.29 g. of copper chromite catalyst was heated and stirred at reflux for 0.5 hour when evolution of carbon dioxide ceased. Quinoline was largely removed by distillation at reduced pressure leaving a residue which was applied to a 300 g. silica gel column and eluted with benzene. Product fractions were stripped to a brown oil which eventually converted to a solid weighing 8.5 g. (78%), m.p. 59.5-61.5°. Crystallization from benzene-hexane (charcoal) gave an analytical sample, m.p. 61.8-62.8°.

Anal. Calcd. for $C_{15}H_{12}ClNO$: C, 69.90; H, 4.70; N, 5.44. Found: C, 70.08; H, 4.61; N, 5.51.

5-Benzyloxy-7-chloroindole-3-carboxaldehyde.

A formylating reagent was prepared by the dropwise addition of 1.6 ml. of phosphorus oxychloride to 5.5 ml. of *N,N*-dimethylformamide at 0-10°. A solution of 4 g. (0.0156 mole) of 5-benzyloxy-7-chloroindole in 7 ml. of *N,N*-dimethylformamide was added to the above at 20-34° over 15 minutes. The reaction mixture was then kept at 34-41° for 40 minutes after which it was poured into 2 volumes of ice and water and stirred for 1.5 hours in an ice bath. The addition of a solution of 3 g. of sodium

hydroxide in 15 ml. of water at 15-27° was followed by 15 ml. of water and the resulting mixture boiled for 4 minutes. After cooling, a yellow solid was collected, washed well with water and crystallized from ethanol to give 2.81 g. (65.5%), m.p. 170-171° in the first crop and an additional 1.20 g. (28%), m.p. 168.5-170° from the mother liquor.

Anal. Calcd. for $C_{16}H_{12}ClNO$: C, 67.25; H, 4.24; N, 4.90. Found: C, 67.12; H, 4.36; N, 5.00.

5-Benzyloxy-7-chloro-3-(β-nitrovinyl)indole.

A mixture of 3.9 g. (0.0137 mole) of 5-benzyloxy-7-chloroindole-3-carboxaldehyde, 50 ml. of nitromethane, and 1 g. of ammonium acetate was stirred and refluxed for 1 hour during which time 5 ml. of condensate was removed through a Dean-Stark trap. Cooling in an ice bath gave a rust colored solid which was collected, washed with water, and crystallized from methanol-ethyl acetate with charcoal treatment. Red needles were obtained weighing 1.69 g. (37.5%), m.p. 195-196° dec. Concentration of the mother liquor gave another 0.63 g. (14%), m.p. 193-194° dec.

Anal. Calcd. for $C_{17}H_{12}ClN_2O_3$: C, 62.11; H, 3.98; N, 8.52. Found: C, 62.29; H, 3.93; N, 8.63.

5-Benzyloxy-7-chlorotryptamine Hydrochloride.

A suspension of 1.75 g. (0.046 mole) of lithium aluminum hydride in 300 ml. of anhydrous ether was refluxed through a Soxhlet extractor containing 1.06 g. (0.0032 mole) of 5-benzyloxy-7-chloro-3-(β-nitrovinyl)indole for 40 hours. After cooling, the reaction mixture was decomposed with 15 ml. of water, and the precipitate filtered and washed well with ether. The filtrate was dried and stripped to a solid which was redissolved in ether and ethanol and treated with ethanolic hydrogen chloride. Dilution with ether and chilling yielded a precipitate which was collected and washed with ether to give 0.79 g. (74%) of product, m.p. 238-238.8°.

Anal. Calcd. for $C_{17}H_{17}ClN_2O{\cdot}HCl$: C, 60.54; H, 5.38; N, 8.31. Found: C, 60.63; H, 5.43; N, 8.36.

The free base was crystallized from ether-chloroform, m.p. 135-137°.

Anal. Calcd. for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 9.32. Found: C, 67.98; H, 5.70; N, 9.29.

5-Hydroxy-7-chlorotryptamine Hydrochloride.

A mixture of 0.50 g. (0.00148 mole) of 5-benzyloxy-7-chlorotryptamine hydrochloride, 100 mg. of 5% palladium-barium sulfate and 50 ml. of absolute ethanol was shaken under hydrogen in a Parr apparatus for 3 hours. The catalyst was filtered, washed with ethanol and the filtrate stripped to an oily residue which was triturated with ether to give an amorphous solid. After drying the latter weighed 0.177 g. (48.5%) and "melted" at 220-223°.

Anal. Calcd. for $C_{10}H_{11}ClN_2O{\cdot}HCl$: C, 48.60; H, 4.88; N, 11.34. Found: C, 48.88; H, 4.97; N, 11.45.

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