

790. Synthesis of the 3-2'-Aminopropyl- and 3-2'-Aminobutyl-derivatives of 5-Hydroxyindole, and an Alternative Synthesis of 5-Hydroxytryptamine.*

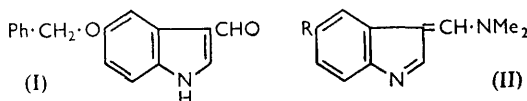
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5-Benzyloxy-3-formylindole (I), prepared from 5-benzyloxyindole, was condensed with nitromethane, nitroethane, and 1-nitropropane to give the respective 5-benzyloxy-3-2'-nitroalkenylindoles (III; R = C₆H₅·CH₂·O, R' = H, Me, or Et). The corresponding 5-hydroxytryptamines were then prepared by reduction with lithium aluminium hydride followed by catalytic debenzoylation. α -Methyltryptamine was similarly synthesised from 3-formylindole.

5-Benzyloxy- α -ethyltryptamine was also prepared by a less satisfactory route from 5-benzyloxygramine.

Boehme's synthesis¹ of 5-benzyloxyindole has been improved.

ALTHOUGH the true physiological significance of 5-hydroxytryptamine remains unknown,² interesting pharmacological properties may be expected in congeners of this compound, particularly since it may be a neurohormone.³ We decided to synthesise the α -methyl and α -ethyl derivatives because of their analogy to amphetamine. Moreover, it seemed possible that these substituents might inhibit attack by amine oxidase, which apparently initiates the normal metabolic degradation of 5-hydroxytryptamine to 5-hydroxy-3-indolylacetic acid.⁴



In the more practicable of the two routes to α -alkyl-5-hydroxytryptamines examined in this work, the key intermediate was 5-benzyloxy-3-formylindole (I). This was prepared by treating 5-benzyloxyindole with dimethylformamide and phosphorus oxychloride, a known method for formylating indole itself.^{5,6} The initial product, presumably a salt of 5-benzyloxy-3-dimethylaminomethyleneindolenine (II; R = Ph·CH₂·O), was hydrolysed to the aldehyde by dilute sodium carbonate solution. The unexpectedly low solubility of the aldehyde (I) in common solvents led us to enquire into its structure.

Molecular-weight determination confirmed that it was a monomer. Attempts to isolate the intermediate indolenine base (II; R = Ph·CH₂·O) at -5° gave only the aldehyde. By contrast, we were able to repeat the work of Smith⁶ who had no difficulty in isolating the corresponding unsubstituted indolenine base (II; R = H) under similar conditions. The aldehyde evidently had an indole structure since the ultraviolet spectrum of a solution in dioxan resembled that of indole and of 5-benzyloxyindole, in which the main peaks were all below 300 m μ . In particular it lacked the strong peak at 355 m μ which characterised the indolenine (II; R = H). The infrared spectrum of the aldehyde (I) and of 3-formylindole contained the expected strong carbonyl band.

The aldehyde (I) was condensed with nitroethane and 1-nitropropane by refluxing it in an excess of the nitroalkane in the presence of benzylamine, the catalyst selected in model experiments (see below). The products, 5-benzyloxy-3-2'-nitropropenyl- and -3-2'-nitrobutenyl-indole (III; R = Ph·CH₂·O, R' = Me and Et), obtained in yields of 60–80%, were reduced with lithium aluminium hydride in 40–50% yields to the corresponding

* Part of this work is the subject of B.P. Appl. No. 33141/55.

¹ Boehme, *J. Amer. Chem. Soc.*, 1953, **75**, 2502.

² Udenfriend, Shore, Bogdanski, Weissbach, and Brodie, *Recent Progr. Hormone Res.*, 1957, **12**, 1.

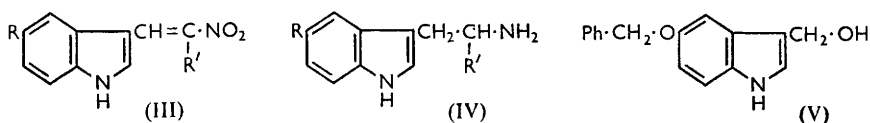
³ Woolley and Shaw, *Proc. Nat. Acad. Sci. U.S.A.*, 1954, **40**, 228; Himwich, *Science*, 1958, **127**, 59.

⁴ Sjoerdsma, Smith, Stevenson, and Udenfriend, *Proc. Soc. Exp. Biol. Med.*, 1955, **89**, 36.

⁵ Tyson and Shaw, *J. Amer. Chem. Soc.*, 1952, **74**, 2273.

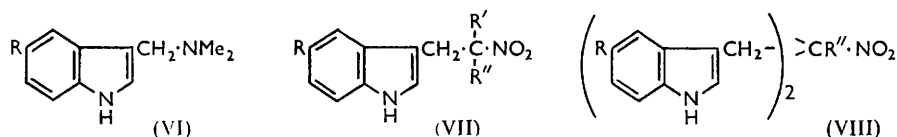
⁶ Smith, *J.*, 1954, 3842.

α -alkyltryptamines (IV; R = Ph·CH₂·O, R' = Me and Et). In these reductions a neutral by-product was formed, in spite of the use of an excess of lithium aluminium hydride: the infrared spectrum, analytical data, and neutral character indicated that it was 5-benzyloxy-3-hydroxymethylindole (V).



The α -alkyl-5-hydroxytryptamines (IV; R = OH, R' = Me and Et) were obtained by reductive debenzoylation, using a palladium catalyst. The overall yields, calculated on 5-benzyloxyindole, were 25% and 24% respectively.

A similar series of reactions provided another new synthetic route to 5-hydroxytryptamine (serotonin) (IV; R = OH, R' = H)⁷ which was obtained in 20% overall yield from the aldehyde (I), *via* 5-benzyloxy-3-2'-nitrovinylindole (III; R = Ph·CH₂·O, R' = H) and 5-benzyloxytryptamine (IV; R = Ph·CH₂·O, R' = H). This yield could no doubt be improved if the synthesis were studied in greater detail.



The other route to α -alkyl-5-hydroxytryptamines examined was condensation of 5-benzyloxygramine⁸ (VI; R = Ph·CH₂·O) with a nitroalkane and reduction of the resultant nitroalkylindoles (VII; R = Ph·CH₂·O, R' = H, R'' = Me and Et). In the preparation of unsubstituted α -alkyltryptamines, Snyder and Katz⁹ found that 1- and 2-nitropropane condensed with gramine (VI; R = H), in the presence of sodium hydroxide, to give the corresponding nitroalkylindoles (VII; R = R' = H, R'' = Et and R = H, R' = R'' = Me) but nitromethane, nitroethane, and ethyl nitroacetate gave mainly bis-substituted products of type (VIII; R = H, R'' = H, Me, and CO₂Et). Without sodium hydroxide, ethyl nitroacetate was, however, only monoalkylated by gramine.¹⁰

We found that treatment of 5-benzyloxygramine (VI; R = Ph·CH₂·O) with nitroethane resulted mainly in dialkylation, even in the absence of added catalyst. Although a little of the required 5-benzyloxy-3-2'-nitropropylindole (VII; R = Ph·CH₂·O, R' = H, R'' = Me) was isolated, this approach to 5-hydroxy- α -methyltryptamine was considered impracticable. 1-Nitropropane on the other hand gave a product which evidently consisted mainly of 5-benzyloxy-3-2'-nitrobutylindole (VII; R = Ph·CH₂·O, R' = H, R'' = Et) because hydrogenation of the crude material, with Raney nickel, gave the desired α -alkyltryptamine (IV; R = Ph·CH₂·O, R' = Et), isolated as the sulphate in 40% overall yield. The infrared spectrum of this sulphate was identical with that of the sample synthesised from 5-benzyloxy-3-formylindole (I).

Experiments to find suitable conditions for the condensation of 3-formylindoles with nitroalkanes led us to prepare α -methyltryptamine by a new route. 3-Formylindole failed to condense with nitroethane when the catalyst was (i) ethanolic potassium hydroxide, either at <0° or at reflux, (ii) alcoholic methylamine at room temperature, (iii) glacial acetic acid and sodium acetate, or (iv) acetic anhydride and sodium acetate, although similar conditions have been successfully employed in related nitrostyrene

⁷ (a) Harley-Mason and Jackson, *J.*, 1954, 1165 and references cited therein; (b) Bernini, *Ann. Chim. (Italy)*, 1953, **43**, 559; (c) Ek and Witkop, *J. Amer. Chem. Soc.*, 1954, **76**, 5579; (d) Speeter and Anthony, *ibid.*, p. 6209; (e) Justoni and Pessina, *Il Farmaco, Ed. Sc.*, 1955, **10**, 356.

⁸ Kuhn and Stein, *Ber.*, 1937, **70**, 567.

⁹ Snyder and Katz, *J. Amer. Chem. Soc.*, 1947, **69**, 3140.

¹⁰ Lyttle and Weisblat, *ibid.*, p. 2118.

preparations.^{7,11} A little 3-2'-nitropropenylindole (III; R = H, R' = Me) (9%) was formed in acetic acid in the presence of ammonium acetate, but a practicable yield (51%) was obtained only by the use of benzylamine as catalyst¹² and excess of refluxing nitromethane as solvent. These relatively drastic conditions contrast with the use of methylamine at room temperature for condensation of 3-formyl-2-methylindole with nitromethane.¹³

Reduction of the nitropropenyl compound (III; R = H, R' = Me) by lithium aluminium hydride, followed by distillation of the basic product, gave a sample of 3-2'-aminopropylindole, the melting point of which was 97—98°, not depressed when mixed with a sample synthesised from gramine *via* 3-2'-bromopropylindole.¹⁴ Snyder and Katz⁹ have given a melting point of 80—81° for this base when prepared by reduction of 3-2'-nitropropylindole.

For the preparation of substantial quantities of 5-benzyloxyindole, Boehme's synthesis¹ of this compound from *p*-acetamidophenol was modified in several respects. First, in preparing the intermediate ethyl 5-benzyloxyindole-2-carboxylate, sodium acetate was used instead of sodium hydroxide for the condensation of diazotised *p*-benzyloxyaniline with ethyl methylacetoacetate.¹⁵ This resulted in improved control of pH during the coupling reaction and ensured reproducible yields when the product was subsequently subjected to Fischer indole ring closure. Secondly, the decarboxylation of 5-benzyloxyindole-2-carboxylic acid was improved by using boiling quinoline as solvent and a copper chromite catalyst,¹⁶ instead of heating the solid acid alone. The 5-benzyloxyindole so produced occasionally contained a brown impurity which was not eliminated by several recrystallisations, with charcoal, from benzene–light petroleum or carbon tetrachloride. A single rapid passage through a short column of alumina, with benzene and chloroform as eluants, readily removed the coloured material. Concentration of the eluate gave almost colourless 5-benzyloxyindole of the high quality which we find is required for the preparation of 5-benzyloxygramine in satisfactory and reproducible yield.

EXPERIMENTAL

M. p.s determined in evacuated capillaries are designated: m. p. (e.c). All other m. p.s were determined in open capillaries.

Ethyl 5-Benzyloxyindole-2-carboxylate.—Sodium nitrite (147 g.) in water (320 ml.) was run in below the surface of an ice-cooled, stirred suspension of *p*-benzyloxyaniline hydrochloride¹ (471 g.) and ice (1720 g.) in concentrated hydrochloric acid (621 ml.) and water (1240 ml.). The temperature fell to –5° to –10°. After 1 hour's stirring, acid-washed charcoal was added and the mixture filtered through "Hyflo Supercel." The filtrate was added all at once to a stirred suspension of ethyl methylacetoacetate (320 g.), sodium acetate (1640 g.), and ice (1440 g.) in ethanol (2920 ml.), and the mixture was stirred for 2 hr. When the mixture had warmed to room temperature after 2 hr., it was extracted with benzene (2 × 1500; 3 × 800 ml.). The extract was washed with water (400 ml.), dried (MgSO₄), and evaporated, leaving crude ethyl pyruvate *p*-benzyloxyphenylhydrazone as a red oil.

The phenylhydrazone was dissolved in ethanol (350 ml.) at 0°. Ethanol saturated at 0° with hydrogen chloride (1050 ml.) was rapidly added to the stirred solution, which then refluxed vigorously. A solid separated and the mixture was stirred without heating for 1 hr. After cooling in ice (¾ hr.), the product was filtered off and washed with ice-cold ethanol (3 × 200 ml.) and hot water (3 × 500 ml.). Ethyl 5-benzyloxyindole-2-carboxylate was obtained as a yellow solid, m. p. 161—163° (352 g., 60%). Boehme¹ gives m. p. 110—117.5° (crude, yield 46—49%) and 162—164° (pure).

5-Benzyloxyindole.—A flask containing a stirred mixture of 5-benzyloxyindole-2-carboxylic

¹¹ Johnson and Hamilton, *J. Amer. Chem. Soc.*, 1941, **63**, 2864; Gairaud and Lappin, *J. Org. Chem.*, 1953, **18**, 1.

¹² Worrall, *J. Amer. Chem. Soc.*, 1934, **56**, 1556.

¹³ Seka, *Ber.*, 1924, **57**, 1868.

¹⁴ Dr. R. M. Jacob, personal communication.

¹⁵ Dr. K. Gaimster, personal communication.

¹⁶ Snyder and Beilfuss, *J. Amer. Chem. Soc.*, 1953, **75**, 4921.

acid ¹ (86 g.), freshly distilled quinoline (175 ml.), and copper chromite (0.9 g.) under nitrogen was immersed in a metal-bath at >200° and heated at 280° until carbon dioxide evolution was virtually complete (1½–2 hr.). The cooled brown syrup was poured into ether (900 ml.), stirred with charcoal, and filtered, and the filtrate extracted with 2*N*-hydrochloric acid (2 × 300; 2 × 200 ml.) and then with 2*N*-sodium hydroxide (2 × 200 ml.). The ether solution was washed with water (3 × 100 ml.), stirred with charcoal, and dried (Na₂SO₄). Removal of ether left an orange-yellow solid which was dissolved in hot carbon tetrachloride (500 ml.), boiled with charcoal, and filtered. 5-Benzyloxyindole separated as fawn needles, m. p. 99–101.5° (55.0 g., 77%).

Alternative Chromatographic Purification.—A solution of crude 5-benzyloxyindole (59.0 g.) in benzene (1 l.) was run on a column of alumina (15 cm. × 5 cm.) which was eluted with benzene (2 l.) and then with chloroform (3 l.). The combined eluates were evaporated, leaving an off-white solid (48.0 g.) which was crystallised from a mixture of benzene (250 ml.) and light petroleum (b. p. 60–80°; 1100 ml.) giving colourless or pale yellow needles, m. p. 100° (shrinks), 105–107° (44.0 g.) (Found: C, 80.5; H, 6.2; N, 6.0. Calc. for C₁₅H₁₃ON: C, 80.7; H, 5.9; N, 6.3%). Burton and Leong ¹⁷ give m. p. 107° and suggest that a m. p.^{1, 18} of about 96° is that of a metastable form.

5-Benzyloxy-3-formylindole.—Phosphorus oxychloride (66.8 g., 0.44 mole) was added dropwise with stirring to excess of dimethylformamide (116 g.) in a flask protected from moisture, the internal temperature being kept at 10–20°. 5-Benzyloxyindole (98 g., 0.44 mole) in dimethylformamide (70 g.) was then slowly added with stirring, the temperature being kept at 15–25°. The temperature was then held at 35° (±2°) for 45 min. The mixture was poured on ice; a pale yellow solid separated, presumably a salt of 5-benzyloxy-3-2'-dimethylaminomethyleneindolenine. The solid was collected and then hydrolysed for 2 min. by boiling 2*N*-sodium carbonate (500 ml.). The suspension, which now smelt strongly of dimethylamine, was cooled in ice and the buff-coloured granular precipitate filtered off and washed successively with water (1750 ml.), ice-cold methanol (200 ml.), and ether (750 ml.), to remove an ether-soluble brown impurity. The residual crude 5-benzyloxy-3-formylindole, m. p. 234–235° (94 g., 85%), crystallised from 4 : 1 dimethylformamide–water (500 ml.) as pale buff prismatic needles, m. p. 239–241° (83 g., 75%). An analytical sample, crystallised from pure dimethylformamide, had m. p. 241–242° (Found: C, 76.6; H, 5.7; N, 5.9. C₁₆H₁₃O₂N requires C, 76.5; H, 5.2; N, 5.6%). The 2 : 4-dinitrophenylhydrazone had m. p. 278–279°.

5-Benzyloxy-3-2'-nitropropenylindole.—A solution of 5-benzyloxy-3-formylindole (65 g., 0.26 mole) in nitroethane (1920 ml.), containing benzylamine (5.52 g., 0.05 mole), was refluxed for 1 hr. The glistening red plates, m. p. 192–194° (51 g.), which separated on cooling, were filtered off and washed with ether. Recrystallisation from ethanol (3.2 l.) gave pure 5-benzyloxy-3-2'-nitropropenylindole as prismatic red needles, m. p. 194–196° (47 g., 59%) (Found: C, 69.9; H, 5.5; N, 9.0. C₁₆H₁₆O₃N₂ requires C, 70.1; H, 5.2; N, 9.1%). A second crop (2.2 g.) had m. p. 193–195°. Evaporation of the mixture left a tar which was boiled with ethanol (1 l.) and charcoal and filtered. Further product was obtained on cooling as red needles, m. p. 192–195° (15 g.). The total yield of material suitable for the next stage was 64.2 g., 81%.

3-2'-Aminopropyl-5-benzyloxyindole.—A solution of 5-benzyloxy-3-2'-nitropropenylindole (7.7 g., 0.025 mole) in pure dry tetrahydrofuran (90 ml.) was added with stirring to a suspension of lithium aluminium hydride (3.0 g., 0.075 mole) in boiling tetrahydrofuran (100 ml.) at a rate sufficient to maintain reflux. The mixture was refluxed overnight, then cooled, and the excess of hydride decomposed by addition of wet ether (50 ml.) and then water (5 ml.). The complex was decomposed by stirring with 50% aqueous sodium hydroxide (25 ml.). The mixture was filtered through "Hyflo Supercel," and the filter-cake washed with ether (4 × 25 ml.). The organic layer (A) in the filtrate was separated, washed with water (3 × 50 ml.), and extracted with 2*N*-acetic acid (2 × 50 ml.). The acid solution was made alkaline with 2*N*-sodium hydroxide and extracted with ether (100; 50; 25 ml.). The ether extracts were washed with water (5 × 30 ml.), dried (Na₂SO₄), and evaporated under reduced pressure, leaving a straw-coloured oily base. This was triturated with *n*-sulphuric acid, and the crude hygroscopic salt filtered off. After being washed with acetone, 3-2'-aminopropyl-5-benzyloxyindole sulphate had m. p. (e.c.) 139–142° (decomp.) (4.4 g.). Crystallisation from methanol (50 ml.)–ether (450 ml.) raised the m. p. (e.c.) to 146–148° (decomp.) (3.5 g., 41%). A sample of the sulphate

¹⁷ Burton and Leong, *Chem. and Ind.*, 1953, 1035.

¹⁸ Burton and Stoves, *J.*, 1937, 1726.

recrystallised from the same solvents and equilibrated in air formed a *monohydrate* (Found: C, 62.0; H, 6.9; N, 7.8; H_2O , 5.2. $\text{C}_{18}\text{H}_{20}\text{ON}_2 \cdot \frac{1}{2}\text{H}_2\text{SO}_4 \cdot \text{H}_2\text{O}$ requires C, 62.2; H, 6.7; N, 8.1; H_2O , 5.2%). Another sample recrystallised from acetone-water (1:2) formed a *dihydrate* on equilibration. This had m. p. (e.c.) 128–131° (decomp.) (Found: C, 59.3; H, 7.1; N, 7.6; S, 4.6; H_2O , 9.2. $\text{C}_{18}\text{H}_{20}\text{ON}_2 \cdot \frac{1}{2}\text{H}_2\text{SO}_4 \cdot 2\text{H}_2\text{O}$ requires C, 59.2; H, 6.9; N, 7.7; S, 4.4; H_2O , 9.9%).

A sample of the neutral material left in the organic layer (A) was distilled at 115–120°/0.03 mm. The distillate partly solidified. Recrystallisation from chloroform–light petroleum (b. p. 60–80°) gave straw-coloured needles of 5-benzyloxy-3-hydroxymethylindole, m. p. 110–112° (Found: C, 75.8; H, 6.35; N, 5.6. $\text{C}_{16}\text{H}_{16}\text{O}_2\text{N}$ requires C, 75.9; H, 5.9; N, 5.5%).

3-2'-Aminopropyl-5-hydroxyindole.—Palladium chloride (0.2 g.) and acid-washed charcoal (1.0 g.) were suspended in water (60 ml.) and hydrogenated at room temperature and 1 atm. A suspension of 3-2'-aminopropyl-5-benzyloxyindole sulphate (3.5 g.) in ethanol (90 ml.) was added and the hydrogenation continued under similar conditions. A hydrogen uptake slightly in excess of theory was obtained. The suspension was filtered and the filtrate evaporated, under reduced pressure of hydrogen, leaving 3-2'-aminopropyl-5-hydroxyindole sulphate as a hygroscopic, straw-coloured syrup. After several days' drying over silica gel *in vacuo* at room temperature the syrup (2.5 g.) solidified to form flakes of the *monohydrate*, m. p. (e.c.) 130–133° (decomp.) (Found: C, 51.7; H, 6.8; N, 10.9. $\text{C}_{11}\text{H}_{14}\text{ON}_2 \cdot \frac{1}{2}\text{H}_2\text{SO}_4 \cdot \text{H}_2\text{O}$ requires C, 51.4; H, 6.6; N, 10.9%). Attempts to prepare a creatinine sulphate complex resulted in products containing varying proportions of creatinine sulphate. The picrate had m. p. 218–220° (decomp.).

5-Benzyloxy-3-2'-nitrobutenylindole.—A solution of 5-benzyloxy-3-formylindole (42 g.) in 1-nitropropane (1260 ml.) containing benzylamine (4.2 g.) was refluxed for 42 hr. The solution was concentrated by half under reduced pressure and set aside at 0°. The crystalline *product* (23 g.), m. p. 172–173°, was filtered off, washed with ether, combined with a second crop (7 g.; m. p. 171–172°), resulting from further concentration of the nitropropane, and recrystallised from ethanol (935 ml.). The prismatic red needles (23.1 g.) had m. p. 173–174° (Found: C, 70.8; H, 5.8; N, 8.7. $\text{C}_{19}\text{H}_{18}\text{O}_3\text{N}_2$ requires C, 70.8; H, 5.6; N, 8.7%). Further product was obtained by evaporating the reaction liquors to a syrup and after one recrystallisation was suitable for the next stage (7.4 g., m. p. 170–173°). The total yield of recrystallised material was 57%.

3-2'-Aminobutyl-5-benzyloxyindole.—A solution of 5-benzyloxy-3-2'-nitrobutenylindole (17.5 g.) in dry tetrahydrofuran (190 ml.) was reduced with lithium aluminium hydride as described for the nitropropenyl compound, except that the reaction time was reduced to 45 min. after completion of the addition. The resultant base was triturated with *n*-sulphuric acid, and the off-white hygroscopic sulphate (8.8 g.) washed with acetone. After crystallisation from ethanol, the m. p. (e.c.) was 185–187° (8.1 g., 41%). Recrystallisation from methanol (140 ml.)–ether (220 ml.) gave the pure *monohydrate*, m. p. (e.c.) 189–190° (Found: C, 62.8; H, 7.1; N, 7.5; S, 4.5. $\text{C}_{19}\text{H}_{22}\text{ON}_2 \cdot \frac{1}{2}\text{H}_2\text{SO}_4 \cdot \text{H}_2\text{O}$ requires C, 63.1; H, 6.7; N, 7.8; S, 4.4%).

Neutral material, isolated as in the reduction of the nitropropenyl compound, had m. p. 109–110°, undepressed on admixture with 5-benzyloxy-3-hydroxymethylindole.

3-2'-Aminobutyl-5-benzyloxyindole (from 5-Benzyloxygramine).—5-Benzyloxygramine⁸ (20 g.) was dissolved in 1-nitropropane (90 ml.) under nitrogen. The solution was stirred and refluxed for 5 hr. during which at least 70% of the theoretical quantity of dimethylamine was evolved. The cooled mixture was acidified with 10% aqueous acetic acid and extracted with ether (400 ml.). The extract was washed with water (5 × 100 ml.), dried (Na_2SO_4), and evaporated, leaving crude 5-benzyloxy-3-2'-nitrobutylindole as an orange-red oil (19.8 g.).

Part (16 g.) of the foregoing crude oil was hydrogenated in ethanol at 70° and 400 lb./sq. in. with a Raney nickel catalyst. After 100% hydrogen uptake the filtered solution was evaporated under reduced pressure, leaving an oil which was taken up in ether (150 ml.) and extracted with 2*N*-acetic acid (75; 50; 2 × 20 ml.). The acid extract was washed with ether (2 × 50 ml.) and basified to pH 10 with 2*N*-sodium hydroxide. The alkaline suspension was extracted with ether (100; 3 × 35 ml.) and the dried (Na_2SO_4) ether solution evaporated, leaving a sticky solid (9.5 g.). Trituration with an equivalent of 2*N*-sulphuric acid, and crystallisation from aqueous ethanol, gave 3-2'-aminobutyl-5-benzyloxyindole sulphate hydrate, m. p. (e.c.) 185–188° (8.5 g., 40% from 5-benzyloxygramine). Recrystallisation from methanol–ether gave the pure sulphate, m. p. (e.c.) 190–191°. This compound, although forming a *hydrate*

containing 1.6 H₂O, did not depress the m. p. of the sample prepared from 5-benzyloxy-3-2'-nitrobutenylindole (see above) and had an identical infrared spectrum (Found: C, 61.3; H, 7.8; N, 7.6; S, 4.7. C₁₉H₂₂ON₂·½H₂SO₄·1.6H₂O requires C, 61.5; H, 7.1; N, 7.6; S, 4.3%).

3-2'-Aminobutyl-5-hydroxyindole.—3-2'-Aminobutyl-5-benzyloxyindole sulphate (3.4 g.) in ethanol (115 ml.) was hydrogenated in the presence of palladium as described for the aminopropyl compound. Drying the product over silica gel *in vacuo* at room temperature gave flakes of 3-2'-aminobutyl-5-hydroxyindole sulphate monohydrate (2.4 g.), m. p. (e.c.) 148–150°, 155° (decomp.) (Found: C, 53.1; H, 6.9; N, 10.3; S, 5.9. C₁₂H₁₆ON₂·½H₂SO₄·H₂O requires C, 53.1; H, 7.1; N, 10.3; S, 5.9%). Treatment with ethanolic picric acid gave a *dipicrate*, m. p. 176–177° (Found: C, 43.8; H, 3.8; N, 16.5. C₁₂H₁₆ON₂·2C₆H₃O₇N₃ requires C, 43.5; H, 3.4; N, 16.9%).

5-Benzyloxy-3-2'-nitrovinylindole.—A suspension of 5-benzyloxy-3-formylindole (25 g.) in nitromethane (990 ml.) containing benzylamine (2.5 g.) was heated under reflux for 4 hr. The dark red solution was evaporated to ¼ volume under reduced pressure of nitrogen. On storage at 0°, 5-benzyloxy-3-2'-nitrovinylindole separated (m. p. 176–177°; 17.6 g., 60%). Recrystallisation from ethanol (900 ml.) gave red hexagonal plates, m. p. 179–180° (13.6 g.) (Found: C, 69.6; H, 5.2; N, 9.0. C₁₇H₁₄O₃N₂ requires C, 69.4; H, 4.8; N, 9.5%).

3-2'-Aminoethyl-5-benzyloxyindole.—A solution of 5-benzyloxy-3-2'-nitrovinylindole (7.3 g.) in dry tetrahydrofuran (90 ml.) was reduced with lithium aluminium hydride as described for the nitropropenyl compound except that the reaction time after addition was only an ½ hr. The straw-coloured oily base (4.4 g.) was triturated with N-sulphuric acid, and the sulphate, m. p. (e.c.) 230–232°, sintering at 178–181° (4.1 g., 51%), was filtered off and washed with ice-cold acetone. Recrystallisation from ethanol and equilibration in air gave the pure sulphate monohydrate, m. p. (e.c.) 230–232°, sintering at 187–189° (Found: C, 61.1; H, 6.1; N, 8.5; S, 5.1. Calc. for C₁₇H₁₈ON₂·½H₂SO₄·H₂O: C, 61.3; H, 6.3; N, 8.4; S, 4.8%).

3-2'-Aminoethyl-5-hydroxyindole (Serotonin).—5-Benzyloxy-3-2'-aminoethylindole sulphate monohydrate (10.0 g., 0.03 mole) in ethanol (180 ml.) was hydrogenated in the presence of palladium as described for the aminopropyl compound. The crude 5-hydroxytryptamine sulphate was dissolved in a solution of creatinine sulphate hemihydrate (5.13 g., 0.03 mole) in water (35 ml.), and hot acetone (200 ml.) was added. After storage at 0°, the resultant 5-hydroxytryptamine creatinine sulphate monohydrate, m. p. (e.c.) 217–219° (decomp.) (11.5 g., 94%), was filtered off and washed with acetone. Two recrystallisations, by dissolution in hot water (96 ml.), addition of charcoal, filtration, and addition of ethanol (64 ml.) to the filtrate, gave almost colourless prisms, m. p. (e.c.) 219–221° (decomp.) (7.5 g., 67%) (Found: C, 41.5; H, 5.7; S, 8.1; H₂O, 4.6. Calc. for C₁₄H₁₉O₂N₅·H₂SO₄·H₂O: C, 41.5; H, 5.7; S, 7.9; H₂O, 4.5%). Speeter and his collaborators¹⁹ give m. p. (Kofler) 214–216°.

3-2'-Nitropropenylindole.—3-Formylindole (2.5 g.), suspended in nitroethane (15 ml.) containing benzylamine (0.19 g.), was refluxed for 1 hr. The orange-red solid which separated on cooling recrystallised from methanol (70 ml.), giving 3-2'-nitropropenylindole as orange plates, m. p. 193–195° (1.8 g., 51%) (Found: N, 13.9. C₁₁H₁₀O₂N₂ requires N, 13.9%).

3-2'-Aminopropylindole.—A solution of 3-2'-nitropropenylindole (2.2 g.) in dry tetrahydrofuran was reduced with lithium aluminium hydride as described for the corresponding 5-benzyloxy-compound. Distillation of the waxy base at 125–130°/0.04 mm. gave 3-2'-aminopropylindole as a colourless solid, m. p. 94–96° (0.6 g.). Redistillation raised the m. p. to 97–98° (shrinkage at 96°) (Found: C, 76.1; H, 8.4; N, 16.2. Calc. for C₁₁H₁₄N₂: C, 75.8; H, 8.1; N, 16.1%).

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¹⁹ Speeter, Heinzelmann, and Weisblatt, *J. Amer. Chem. Soc.*, 1951, **73**, 5514.