# 704. *The Synthesis of 5-Hydroxytryptamine (Serotonin) and Related Tryptamines.*

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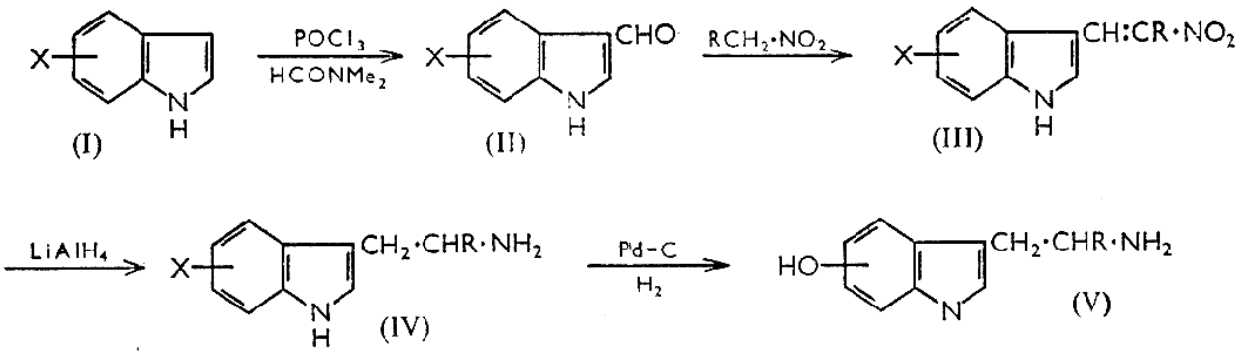
A new route to 5-hydroxytryptamine (serotonin) and related substituted tryptamines is described. 3-2′-Nitrovinylindoles, readily prepared by the condensation of substituted indole-3-aldehydes and nitroparaffins, are reduced with lithium aluminium hydride to the corresponding substituted tryptamines. An improved method of preparation of the indole-3-aldehydes, which are now obtained in 85—95% yield, is also described.

5-Hydroxytryptamine (serotonin, enteramine) is of interest because of its isolation from blood platelets and from the gastrointestinal tract of animals and its numerous physiological actions.[1]

Several syntheses have been described; some [2] involve formation of the indole nucleus with the side chain carbon skeleton already present, whilst others [3] introduce the side chain into a ready-formed indole nucleus. Substituted tryptamines have recently [4] been obtained by opening the piperidine ring in 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carbolines.

The synthesis here described [5] starts from 5-benzyloxyindole (I; X = 5-$PhCH_2$·O) and follows the reaction sequence, depicted below, that has been frequently used to introduce the 2-aminoethyl side chain into medicinal compounds, *e.g.*, mescaline.[6] Several *Bz*-substituted indole-3-aldehydes have been prepared previously [7] in low yield by the Reimer–Tiemann reaction. By treating the indoles (I; X = 5-Cl, 5-MeO, 5-Me,




5-$PhCH_2$·O, 6-$PhCH_2$·O, and 6-MeO) with dimethylformamide and phosphorus oxychloride [8] the corresponding aldehydes have been obtained in high yield (85—95%) and purity. Although phosphorus oxychloride was the most convenient reagent it could be replaced by other phosphorus halides, and the excess of dimethylformamide by dioxan without appreciably affecting the yield or quality of product.

The aldehydes were condensed with nitroparaffins to give 3-2′-nitrovinylindoles (III; X and R, as in Table 1). Few condensations of this kind have been reported [9] and

[1] Page, *Physiol. Reviews*, 1954, **34**, 563; Erspamer, *Pharmacol. Reviews*, 1954, 425.

[2] Harley-Mason and Jackson, *J.*, 1954, 1165; Justoni and Pessina, *Il Farmaco, Ed. Sci.*, 1955, **10**, 356; Bernini, *Ann. Chim. appl.* (*Rome*), 1953, **43**, 559; Vejdělek and Tůma, *Československ. farm.*, 1955, **4**, 510.

[3] Hamlin and Fisher, *J. Amer. Chem. Soc.*, 1951, **73**, 5007; Speeter, Heinzelmann, and Weisblat, *ibid.*, p. 5515; Asero, Colò, Erspamer, and Vercellone, *Annalen*, 1952, **577**, 69; Ek and Witkop, *J. Amer. Chem. Soc.*, 1954, **76**, 5579; Speeter and Anthony, *ibid.*, p. 6208; Pietra, *Il Farmaco, Ed. Sci.*, 1958, **13**, 75.

[4] Abramovitch and Shapiro, *J.*, 1956, 4589.

[5] B.P. Appln. Nos. 4404—4407/1956.

[6] Slotta and Szyszka, *J. prakt. Chem.*, 1933, **137**, 347.

[7] Kermack, Perkin, and Robinson, *J.*, 1922, **121**, 1882; Blaikie and Perkin, *J.*, 1924, **125**, 296; Boyd and Robson, *Biochem. J.*, 1935, **29**, 555; Harvey and Robson, *J.*, 1938, 97; Marchant and Harvey, *J.*, 1951, 1808.

[8] Smith, *J.*, 1954, 3842.

[9] Seka, *Ber.*, 1924, **57**, 1868; Majima and Kotake, *Ber.*, 1925, **58**, 2037; Onda, Kawanishi, and Sasamoto, *J. Pharm. Soc. Japan*, 1956, **76**, 472.

TABLE 1. *3-2′-Nitrovinylindoles* (III).

| X | R | Reaction Temp. | Reaction Time (min.) | M. p. | Formula | Analyses Found, % C | H | N | Reqd., % C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | 95—98° | 10 | 171—172° [a] | $C_{10}H_8O_2N_2$ | 64·4 | 4·7 | 14·9 | 63·8 | 4·25 | 14·9 |
| H | Me | 95—98 | 30 | 195—196 | $C_{11}H_{10}O_2N_2$ | 65·4 | 5·2 | 13·7 | 65·35 | 4·95 | 13·9 |
| H | Et | 95—98 | 180 | 134—136 | $C_{12}H_{12}O_2N_2$ | 66·6 | 5·5 | 13·2 | 66·7 | 5·55 | 13·0 |
| 5-Cl | H | 95—100 | 10 | 186—187 | $C_{10}H_7O_2N_2Cl$ | 54·1 | 3·5 | 12·5 | 53·9 | 3·1 | 12·6 |
| 5-MeO | Me | 105—108 | 10 | 182—184 | $C_{12}H_{12}O_3N_2$ | 61·6 | 5·4 | 11·7 | 62·1 | 5·2 | 12·1 |
| 5-Me | H | 100 | 10 | 160—161 | $C_{11}H_{10}O_2N_2$ | 65·9 | 5·3 | 13·6 | 65·35 | 4·95 | 13·9 |
| 5-Me | Me | 100 | 10 | 184—187 | $C_{12}H_{12}O_2N_2$ | 66·6 | 5·7 | 12·9 | 66·7 | 5·55 | 13·0 |
| 5-$PhCH_2$·O | H | 95—98 | 30 | 181—182 | $C_{17}H_{14}O_2N_2$ | 69·7 | 5·3 | 9·1 | 69·4 | 4·8 | 9·5 |
| 5-$PhCH_2$·O | Me | 105—108 | 30 | 195—196 | $C_{18}H_{16}O_3N_2$ | 70·0 | 5·2 | 9·6 | 70·1 | 5·2 | 9·1 |
| 5-$PhCH_2$·O | Et | 110 | 45 | 175—176 | $C_{19}H_{18}O_3N_2$ | 71·0 | 5·8 | 8·4 | 70·8 | 5·6 | 8·7 |
| 5-$PhCH_2$·O | $C_7H_{15}$ | 110—115 [b] | 10 | 128 | $C_{24}H_{28}O_3N_2$ | 73·9 | 7·1 | — | 73·5 | 7·1 | — |
| 6-$PhCH_2$·O | H | 95—98 | 15 | 186—187 | $C_{17}H_{14}O_3N_2$ | 69·5 | 4·9 | 9·5 | 69·9 | 4·8 | 9·6 |

[a] Ref. 24, m. p. 167—168° (decomp.); all other compounds are new. [b] Dimethylformamide was used as solvent.

TABLE 2. *3-2′-Aminoethylindoles* (IV).

| X | R | M. p. | Formula | Analyses Found, % C | H | N | Reqd., % C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| H | H | 249—250° [a] (dec.) | $C_{10}H_{12}N_2$,HCl | — | — | — | — | — | — |
| H | Me | 215—217 [b] | $C_{11}H_{14}N_2$,HCl | 62·9 | 7·1 | 13·1 | 62·7 | 7·1 | 13·3 |
| H | Et | 218—219 [b] | $C_{12}H_{16}N_2$,HCl | 63·6 | 7·5 | 12·6 | 64·1 | 7·6 | 12·5 |
| 5-Cl | H | 286—289 [c] (dec.) | $C_{10}H_{11}N_2Cl$,HCl | 51·9 | 5·1 | 12·0 | 51·9 | 5·2 | 12·1 |
| 5-MeO | Me | 220—221 | $C_{12}H_{16}ON_2$,HCl | 60·1 | 7·2 | 11·6 | 59·9 | 7·1 | 11·6 |
| 5-Me | H | 289—291 (dec.) | $C_{11}H_{14}N_2$,HCl | 62·8 | 6·9 | 13·4 | 62·7 | 7·1 | 13·3 |
| 5-Me | Me | 256—257 | $C_{12}H_{16}N_2$,HCl | 63·8 | 7·7 | 12·5 | 64·1 | 7·6 | 12·5 |
| 5-$PhCH_2$·O | H | 251—252 [d] (dec.) | $C_{17}H_{18}ON_2$,HCl | — | — | — | — | — | — |
| 5-$PhCH_2$·O | Me | 257—258 (dec.) | $C_{18}H_{20}ON_2$,HCl | 68·2 | 6·6 | 8·8 | 68·2 | 6·6 | 8·8 |
| 5-$PhCH_2$·O | Me | 181—182 | $(C_{18}H_{20}ON_2)_2$,$C_4H_6O_4$ | 70·7 | 6·8 | 8·4 | 70·8 | 6·8 | 8·3 |
| 5-$PhCH_2$·O | Et | 243—244 (dec.) | $C_{19}H_{22}ON_2$,HCl | 69·4 | 7·1 | 8·2 | 69·0 | 7·0 | 8·5 |
| 6-$PhCH_2$·O | H | 255—256 (dec.) | $C_{17}H_{18}ON_2$,HCl | 67·4 | 6·5 | 9·2 | 67·4 | 6·3 | 9·3 |
| 5-HO | H | 216—218 [d] (dec.) | $C_{10}H_{12}ON_2$,$C_4H_7ON_3$,$H_2SO_4$,$H_2O$ | 41·5 | 6·1 | 17·2 | 41·5 | 5·7 | 17·3 |
| 5-HO | Me | 208—209 | $C_{11}H_{14}ON_2$,$2C_6H_3O_7N_3$ | 42·8 | 3·0 | 17·3 | 42·6 | 3·1 | 17·3 |
| 5-HO | Et | 183—184 | $C_{12}H_{16}ON_2$,$2C_6H_3O_7N_3$ | 43·4 | 3·3 | 16·9 | 43·5 | 3·3 | 16·9 |
| 6-HO | H | 192 | $C_{10}H_{12}ON_2$,HCl,$H_2O$ | 51·6 | 6·0 | 12·7 | 52·1 | 6·5 | 12·1 |
| 6-HO | H | 226—227 (dec.) | $C_{10}H_{12}ON_2$,$C_6H_3O_7N_3$ | 47·3 | 3·9 | 17·2 | 47·4 | 3·7 | 17·3 |

[a] Majima and Hoshino, *Ber.*, 1925, **28**, 2042. [b] Snyder and Katz, *J. Amer. Chem. Soc.*, 1947, **69**, 3140, report m. p. of bases. [c] Abramovitch, *J.*, 1956, 4593. [d] Ref. 3*b*.

in all cases reaction was slow. The condensation, however, takes place in 10—30 min. at about 100° with excess of the nitroparaffin as solvent and ammonium acetate as catalyst, high yields of almost pure product being obtained. Other catalysts and solvents were tried and, although 3-2′-nitrovinylindoles were obtained, the results were generally poor. There was no evidence of appreciable reaction between the nitro-olefins formed and the excess of nitroparaffin used.[10]

The nitro-olefins were reduced to the corresponding aminoethylindoles (IV; R and X, as in Table 2) by lithium aluminium hydride.[11] Catalytic reduction of nitro-olefins is known to present difficulties [12] and attempts to reduce the 3-2′-nitrovinylindoles by means of hydrogen and a platinum catalyst were unsuccessful.

The benzyloxy-3-2′-aminoethylindoles (IV; X = 5-$PhCH_2$·O; R = H, Me, or Et; X = 6-$PhCH_2$·O, R = H) were debenzylated by catalytic reduction, palladium on carbon or barium sulphate being used as catalyst.

The indoles were prepared by literature methods, except for 5-chloroindole. Attempts

[10] Heim, *Ber.*, 1911, **44**, 2016.

[11] Nystrom and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3738; Hamlin and Weston, *ibid.*, 1949, **71**, 2210; Ramirez and Burger, *ibid.*, 1950, **72**, 2781.

[12] Sonn and Schellenburg, *Ber.*, 1917, **50**, 1513; Skita and Keil, *Ber.*, 1932, **65**, 424; Kohler and Drake, *J. Amer. Chem. Soc.*, 1923, **45**, 1281.

to prepare this compound by Rydon and Long's method [13] were unsuccessful, as ethyl pyruvate *p*-chlorophenylhydrazone did not cyclise in acetic acid or ethanolic hydrogen chloride. Rydon and Tweddle [14] have since described the cyclisation of this compound with polyphosphoric acid. 5-Chloroindole was prepared as described by Uhle [15] for the 4-chloro-compound.

## Experimental

*5-Chloro-2-nitrophenylpyruvic Acid.*—Potassium ethoxide [from potassium (8 g.) and ethanol (60 c.c.)] and anhydrous ether (300 c.c.) were treated dropwise, with stirring, with diethyl oxalate (29·2 c.c.). 5-Chloro-2-nitrotoluene (34·3 g.) was added gradually and the mixture gently refluxed for 3 hr., then cooled, and the potassium salt washed with ether. The dry salt (59 g.) was shaken with water (400 c.c.) at room temperature for 4 hr. and the solution then filtered. The filtrate was acidified (concentrated hydrochloric acid) and the *pyruvic acid* dried [37 g.; m. p. 180—182° (decomp.)]. The m. p. was not raised by crystallization from water (Found: C, 41·8; H, 1·8; N, 5·7. $C_9H_6O_5NCl,H_2O$ requires C, 41·3; H, 3·1; N, 5·35%).

*5-Chloroindole-2-carboxylic Acid.*—5-Chloro-2-nitropyruvic acid (10 g.) in ammonia (50 c.c.; *d* 0·88)–water (150 c.c.) was warmed (steam-bath) and a hot solution of ferrous sulphate ($FeSO_4,7H_2O$, 80 g.) in water (250 c.c.) added rapidly. The mixture was heated (steam-bath) for 1 hr. and then boiled for ½ hr. The iron residues were removed by filtration and washed with hot ammonia solution (5%; 50 c.c.). The hot filtrates were acidified (Congo Red) with concentrated hydrochloric acid and cooled to room temperature. The white solid was washed with a little cold water and dried (5·2 g.). 5-Chloroindole-2-carboxylic acid crystallized from aqueous ethanol in micro-needles, m. p. 291—292° (decomp.) (Found: C, 54·8; H, 2·9; N, 7·3. Calc. for $C_9H_6O_2NCl$: C, 55·1; H, 3·1; N, 7·2%).

*5-Chloroindole.*—5-Chloroindole-2-carboxylic acid (4·5 g.) was heated to 290° (bath temp.) until the solid began to fuse; the bath temperature was then reduced to 250—260° and kept there until evolution of carbon dioxide ceased (*ca.* 10 min.). The residue was distilled. Crystallization from light petroleum (25 c.c.; b. p. 80—100°) gave plates, m. p. 72—73° (1·48 g.) (Found: C, 63·4; H, 3·9; N, 8·9. Calc. for $C_8H_6NCl$: C, 63·3; H, 3·95; N, 9·2%).

*5-Benzyloxyindole-3-aldehyde.*—Phosphorus oxychloride (10 c.c.) was added dropwise, with stirring, at 10—20° to dimethylformamide (35 c.c.). A solution of 5-benzyloxyindole (22·3 g.) in dimethylformamide (25 c.c.) was then added gradually at 20—30°. The solution was then kept at 35—37° for 45 min. and finally poured into stirred ice (100 g.) and water (100 c.c.). Sodium hydroxide (19 g.) in water (100 c.c.) was added during ½ hr. at 20—30°, the rate of addition being such that when *ca.* 3/4 of the sodium hydroxide solution had been added the mixture was at pH 6. The remainder was then added at once. Water (200 c.c.) was added and the mixture boiled for 3 min. The *aldehyde* was washed with cold water (5 × 50 c.c.) and dried at 80° (21·6 g.). Crystallization from ethanol gave pale fawn needles, m. p. 237—238° (Found: C, 75·7; H, 5·3; N, 5·1. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%). Similarly the following indole-3-aldehydes were obtained: 5-*chloro*-, m. p. 215—216° (93%) (Found: C, 60·1; H, 3·1; N, 8·0. $C_9H_6ONCl$ requires C, 60·2; H, 3·3; N, 7·8%); 5-methoxy-, m. p. 181—182° (94%); 6-methoxy-, m. p. 187—189° (83%); 5-methyl-, m. p. 148—149° (92%).

*6-Benzyloxyindole-3-aldehyde.*—(*a*) By using 6-benzyloxyindole instead of the 5-compound in the above preparation, 6-*benzyloxyindole-3-aldehyde* was obtained in 90% yield; it formed needles, m. p. 215—216° from 2-ethoxyethanol (Found: C, 76·3; H, 5·5; N, 5·5. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%). (*b*) Phosphorus tribromide (5 c.c.) was added to stirred dimethylformamide (20 c.c.) at 10—20°. A solution of 6-benzyloxyindole (5 g.) in dimethylformamide (10 c.c.) was added gradually at 20—30°. The experiment was completed as described above for 5-benzyloxyindole-3-aldehyde, 4·6 g. of product, m. p. 211—212°, being obtained. The m. p. was raised by crystallization from 2-ethoxyethanol to 215—216°. (*c*) Phosphorus pentachloride (2 g.) was used in place of the tribromide with 6-benzyloxyindole (1·5 g.) in dimethylformamide (5 c.c.). The aldehyde (1·2 g., m. p. 209—211°) was again obtained. (*d*) Phosphorus oxychloride (5 c.c.) was added at 10—20° to stirred dimethylformamide (5 c.c.)–dioxan (20 c.c.). 6-Benzyloxyindole (5 g.) in dioxan (10 c.c.) was added gradually

[13] Rydon and Long, *Nature*, 1949, **164**, 575.
[14] Rydon and Tweddle, *J.*, 1955, 3499.
[15] Uhle, *J. Amer. Chem. Soc.*, 1949, **71**, 761.

at 20—30°, and the mixture worked up as before. The product (4·9 g.; m. p. 208—209°) was purified by crystallization from 2-ethoxyethanol; it then had m. p. 215—216°.

The following experiments are typical of the methods employed to obtain the compounds described in Tables 1 and 2.

*5-Benzyloxy-3-2′-nitrovinylindole.*—5-Benzyloxyindole-3-aldehyde (4·4 g.), nitromethane (25 c.c.), and ammonium acetate (1 g.) were heated gently under reflux for ½ hr. On cooling, dark ruby prisms slowly separated (3·4 g. which crystallized from benzene or methanol as red prisms,

*3-2′-Methyl-2′-nitrovinylindole.*—(*a*) Indole-3-aldehyde hydrate (5 g.), nitroethane (10 c.c.), and ammonium acetate (1 g.) were heated on the steam-bath with occasional shaking for ½ hr. On cooling the crystals were collected, washed with hot water (2 × 50 c.c.), and crystallized from methanol; the product (3·1 g., m. p. 195—196°) was then obtained as yellow prisms. (*b*) Replacing ammonium acetate by butylamine (0·25 c.c.) and heating the mixture on the steam-bath for 1 hr. gave 3-2′-methyl-2′-nitrovinylindole which after crystallization from methanol had m. p. 195—196°, not altered on admixture with a sample made by use of ammonium acetate.

*5-Benzyloxytryptamine Hydrochloride.*—Lithium aluminium hydride (5 g.) was added to ether (250 c.c.) in the flask of a Soxhlet extractor. Finely ground 5-benzyloxy-3-2′-nitrovinylindole (3 g.) was then extracted from the thimble with ether for 6 hr. The product was cooled, and water (30 c.c.) added dropwise to decompose the excess of lithium aluminium hydride and the addition complex. The solid was filtered off and washed with ether (2 × 25 c.c.), and the ethereal solution dried (KOH) and then saturated with dry hydrogen chloride. The hydrochloride was collected and washed with ether; it (2·7 g.) had m. p. 251—252° (decomp.).

*6-Benzyloxytryptamine Hydrochloride.*—(*a*) This *hydrochloride* was prepared as described for the 5-compound; it crystallized from methanol–ethyl acetate in prisms (2·1 g.), m. p. 255—256° (decomp.). (*b*) 6-Benzyloxy-3-2′-nitrovinylindole (4 g.) in tetrahydrofuran (50 c.c.) was added during 15 min. to a stirred suspension of lithium aluminium hydride (4 g.) in tetrahydrofuran (150 c.c.). The mixture was stirred for a further 30 min. and allowed to cool. Water (20 c.c.) was cautiously added and the tetrahydrofuran solution was then filtered. The residue was washed with tetrahydrofuran (20 c.c.) and the combined filtrates were evaporated. The residual 6-benzyloxytryptamine was dissolved in ether and the solution saturated with hydrogen chloride, giving the hydrochloride [2·4 g.; m. p. and mixed m. p. with sample (*a*) 254—256° (decomp.)].

*5-Hydroxytryptamine.*—5-Benzyloxytryptamine hydrochloride (10 g.) was suspended in methanol (150 c.c.) and shaken in an atmosphere of hydrogen in the presence of palladium–carbon (10%; 2 g.) until adsorption of hydrogen stopped. The methanolic solution was filtered and the solvent evaporated *in vacuo*. The residue was dissolved in hot dilute sulphuric acid (2 c.c. of concentrated acid + 20 c.c. of water). Creatinine (4 g.) was added and the hot solution was filtered. The residue was washed with water (5 c.c.) and the combined filtrates were treated with acetone (150 c.c.). After 1 hr. the solid was collected and washed with acetone (20 c.c.) containing a few drops of water. The 5-hydroxytryptamine–creatinine sulphate complex (serotonin) (6·6 g.) had m. p. 216—218° (Found: C, 41·5; H, 6·1; N, 17·2; S, 7·9. Calc. for $C_{14}H_{19}O_2N_5,H_2SO_4,H_2O$: C, 41·5; H, 5·7; N, 17·3; S, 7·9%).

*Tryptamine.*—3-2′-Nitrovinylindole (15 g.) in a Soxhlet thimble was extracted continuously with dry ether for 8 hr. The ethereal extract was returned to the extractor flask which contained ether (500 c.c.) and lithium aluminium hydride (15 g.). The mixture was cooled and the complex was decomposed by gradual addition of water (80 c.c.). The solid was filtered off and washed with ether (2 × 100 c.c.). The ethereal solution was dried ($Na_2SO_4$) and saturated with hydrogen chloride. The hydrochloride (12·7 g.) was collected and crystallized from methanol–ethyl acetate giving prisms, m. p. 249—250° (decomp.).