880. *Tryptamines, Carbolines, and Related Compounds. Part II.* A Convenient Synthesis of Tryptamines and β-Carbolines.*

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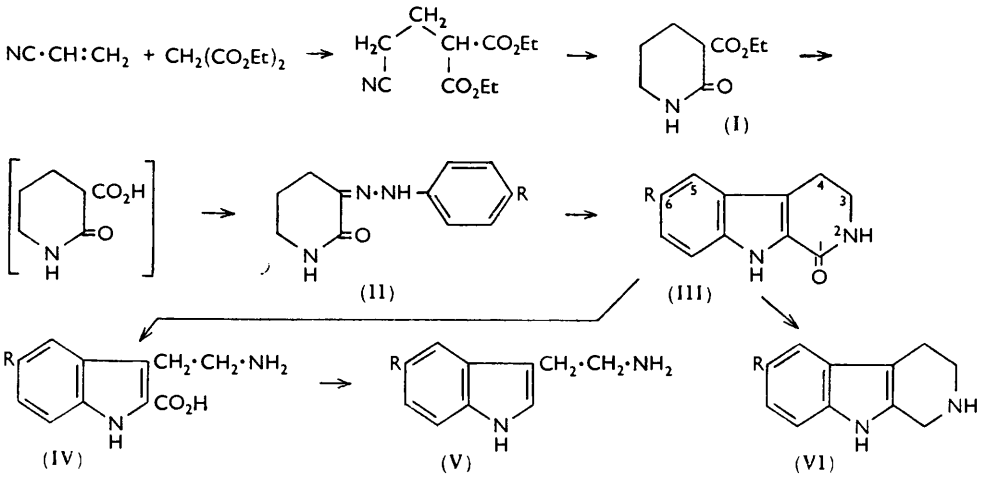
2 : 3-Dioxopiperidine 3-phenylhydrazone was cyclised under acid conditions to 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline. This was hydrolysed to tryptamine-2-carboxylic acid which was decarboxylated to tryptamine. The same reaction sequence with *p*-anisidine afforded a new route to serotonin. 5-Benzyloxytryptamine-2-carboxylic acid could not be decarboxylated to the base. The method also provides a route to the 1 : 2 : 3 : 4-tetrahydro-β-carbolines.

Interest in synthesis of tryptamines has been revived in connection with the synthesis of serotonin (5-hydroxytryptamine) and potential antimetabolites thereof, and a number of methods have been developed. Most of these start from a preformed substituted indole nucleus,[1-4] but preparation of the required precursors is difficult. Two methods [5] do not start from preformed indoles, but again are long or require starting materials which are not readily available. A relatively simple method of preparing tryptamines from tetrahydro-β-carbolines has now been developed.

2 : 3-Dioxopiperidine 3-phenylhydrazone (II; R = H), obtained [6] by a Japp–Klingemann reaction [7] from 2-oxopiperidine-3-carboxylic acid and benzenediazonium chloride, was cyclised to 1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline (III; R = H) by polyphosphoric



acid (already used [8] as a catalyst for the Fischer cyclisation). On scales larger than 1 g., however, this reagent caused extensive charring and milder conditions had to be used, *e.g.*, 70% formic acid. The ketocarboline (III; R = H), previously obtained less conveniently by Manske and Robinson [9] and by Keimatsu, Sugasawa, and Kasuya,[10] thus

* The paper on the α-carbolines by Abramovitch, Hey, and Mulley (*J.*, 1954, 4263) is considered to be Part I of this series.

[1] Hamlin and Fischer, *J. Amer. Chem. Soc.*, 1951, **73**, 5007.
[2] Speeter, Heinzelmann, and Weisblat, *ibid.*, p. 5514.
[3] Ek and Witkop, *ibid.*, 1954, **76**, 5579.
[4] (*a*) Asero, Colò, Erspamer, and Vorcellone, *Annalen*, 1952, **576**, 69; (*b*) Speeter and Anthony, *J. Amer. Chem. Soc.*, 1954, **76**, 6208; Noland and Hartman, *ibid.*, p. 3227.
[5] Harley-Mason and Jackson, *J.*, 1954, 1165; Ewins, *J.*, 1911, **99**, 270; Bernini, *Ann. Chim. appl. Roma*, 1953, **43**, 559; Shaw, *J. Amer. Chem. Soc.*, 1955, **77**, 4319.
[6] Shapiro and Abramovitch, *J. Amer. Chem. Soc.*, 1955, **77**, 6690.
[7] Japp and Klingemann, *Ber.*, 1887, **20**, 2942, 3284.
[8] Kissman, Farnsworth, and Witkop, *J. Amer. Chem. Soc.*, 1952, **74**, 3948.
[9] Manske and Robinson, *J.*, 1927, 240.
[10] Keimatsu, Sugasawa, and Kasuya, *J. Pharm. Soc. Japan*, 1928, **48**, 762; *Chem. Abs.*, 1929, **23**, 834.

becomes readily available; it was hydrolysed by aqueous-alcoholic alkali to tryptamine-2-carboxylic acid (IV; R = H), which was decarboxylated to tryptamine (V; R = H) by boiling 5% hydrochloric acid.[10] When absolute-ethanolic potassium hydroxide was used for hydrolysis of the amide, most of the amide was recovered: these or similar conditions may have been used by Nishikawa, Perkin, and Robinson,[11] who were unable to effect the ring opening of 1 : 2 : 3 : 4-tetrahydro-7-methoxy-1-oxo-β-carboline by alcoholic potassium hydroxide.

The same sequence of reactions was carried out with diazotised *p*-anisidine in the Japp–Klingemann reaction, to give the methoxyphenylhydrazone (II; R = OMe). The nature of the product obtained in this and similar Japp–Klingemann reactions was found to depend mainly on the pH of the reaction mixture. At pH >7 only a tar was formed, whereas at pH 6—7 a compound was obtained whose properties (instability on attempted purification, formation of a small amount of the phenylhydrazone accompanied by extensive decomposition on quick recrystallisation from water, and transformation into the carboline with ethanolic hydrogen chloride) point to a phenylazo-structure. At pH 3—4 and at 0—5° the required phenylhydrazone was obtained. This could not be cyclised with polyphosphoric acid as tar formation occurred, but 90% formic acid gave the required carboline (III; R = OMe) (previously prepared by Barrett, Perkin, and Robinson by a seven-stage synthesis [12]), which was hydrolysed and decarboxylated as above. Decarboxylation could also be effected with toluene-*p*-sulphonic acid. Since 5-methoxytryptamine has already been demethylated to serotonin [4a] this constitutes a new and convenient synthesis of this compound.

To avoid the final demethylation it was thought of interest to use the benzyloxy-derivative, as 5-benzyloxytryptamine can be smoothly debenzylated to serotonin.[1-3] Again, the success of the Japp–Klingemann reaction depended on the pH (optimum *ca.* 4·5). The product (II; R = O·CH_2Ph) was cyclised in 70% formic acid, and the amide (III; R = O·CH_2Ph) hydrolysed as before to the amino-acid (IV; R = O·CH_2Ph). The last, however, could not be decarboxylated to the required base under a variety of conditions, so that this route was abandoned.

The oxocarbolines (III) are convenient starting materials for the synthesis of 1 : 2 : 3 : 4-tetrahydro-β-carbolines. Attempts to reduce the amide linkage with lithium aluminium hydride failed, probably owing to formation of an insoluble complex before reduction, and the amide was recovered. Similar difficulties with secondary cyclic amides have been reported [13] in connection with the synthesis of morphine. 1 : 2 : 3 : 4-Tetrahydro-1-oxo-β-carboline had been reduced with sodium and butan-1-ol by Ashley and Robinson,[14] and substitution of propanol for butanol did not lead to an increased yield. 1 : 2 : 3 : 4-Tetrahydro-6-methoxy-1-oxo-β-carboline (III; R = OMe) was thus reduced to the corresponding tetrahydro-β-carboline (VI; R = OMe) which had previously been obtained by treating 5-methoxytryptamine with formaldehyde and sulphuric acid.[15]

Experimental

2 : 3-Dioxopiperidine 3-phenylhydrazone was prepared from diazotised aniline and ethyl 2-oxopiperidine-3-carboxylate [16] as described by Shapiro and Abramovitch.[6] The dried crude product was used directly for the next stage.

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxo*-β-*carboline*.—(i) *By use of polyphosphoric acid.* The phenylhydrazone (1 g.) and polyphosphoric acid (5 c.c.) were slowly heated in an oil bath with stirring. When the internal temperature reached *ca.* 105° the solid dissolved, and the internal temperature rose to 120—125° (bath-temp. 105°) and was kept there for 5 min. The cooled mixture was treated with water; the resulting oil solidified on trituration (0·85 g.; m. p. 183—185° after softening at 174°), was filtered off, washed with water, and recrystallised from very dilute alcohol, giving colourless needles, m. p. 183—185° (Found: C, 71·3; H, 5·5; N, 15·3. Calc.

[11] Nishikawa, Perkin, and Robinson, *J.*, 1924, **125**, 657.
[12] Barrett, Perkin, and Robinson, *J.*, 1929, 2942.
[13] Gates and Tschudi, *J. Amer. Chem. Soc.*, 1956, **78**, 1380.
[14] Ashley and Robinson, *J.*, 1928, 1376.
[15] Späth and Lederer, *Ber.*, 1930, **63**, 2102.
[16] Albertson and Fillman, *J. Amer. Chem. Soc.*, 1949, **71**, 2819.

for $C_{11}H_{10}ON_2$: C, 70·95; H, 5·4; N, 15·05%). Keimatsu, Sugasawa, and Kasuya [10] give m. p. 188—189°. The *picrate* separated from alcohol as orange-yellow plates, m. p. 195—197° (Found: C, 49·5; H, 3·5; N, 16·9. $C_{11}H_{10}ON_2,C_6H_3O_7N_3$ requires C, 49·2; H, 3·2; N, 16·9%).

(ii) *By use of* 70% *formic acid.* The phenylhydrazone (1 g.) was boiled under reflux with 70% formic acid (4 c.c.) for ½ hr., the hot solution was diluted with water, and the oil which separated just brought into solution by the dropwise addition of hot alcohol. The hot solution was seeded and allowed to cool, and the oxocarboline (0·7 g.), m. p. 183—185°, filtered off.

Tryptamine-2-carboxylic Acid.—The following are the optimum conditions found for this ring-opening. The carboline (0·5 g.) was boiled under reflux with 2N-potassium hydroxide in 50% ethanol (10 c.c.) for 5 hr. The solvent was evaporated (5 c.c.), water (5 c.c.) added, and the cooled solution filtered. Acidification with acetic acid gave the amino-acid as rosettes of needles (0·45 g.), m. p. 241—242° (decomp.) (from dilute alcohol) (Found: C, 64·8; H, 5·6. Calc. for $C_{11}H_{12}O_2N_2$: C, 64·7; H, 5·9%). Keimatsu, Sugasawa, and Kasuya [10] give m.p. 257°.

Tryptamine.—Tryptamine-2-carboxylic acid (0·33 g.) was boiled under reflux with 5% aqueous hydrochloric acid (5 c.c.) for 1 hr., then the evolution of carbon dioxide ceased. Making the solution alkaline gave tryptamine (0·2 g.), m. p. 115°. The picrate (from dilute acetone) had m. p. 245—246° (decomp.) (Found: C, 49·6; H, 3·8. Calc. for $C_{10}H_{12}N_2,C_6H_3O_7N_3$: C, 49·4; H, 3·9%).

1 : 2 : 3 : 4-*Tetrahydro-β-carboline.*[14]—1 : 2 : 3 : 4-Tetrahydro-β-carboline (0·30 g. from 1 g. of amide) was obtained as colourless plates, m. p. 200—202° (reported,[14] m. p. 204°), giving a picrate which on recrystallisation from alcohol–acetone had m. p. 253° (decomp.).

Action of Diazotised p-*Anisidine on* 2-*Oxopiperidine-3-carboxylic Acid.*—(i) *At* pH 6—7. *p*-Anisidine (2·5 g.) in water (30 c.c.) containing concentrated hydrochloric acid (5·5 c.c.) was diazotised at 0—5° with sodium nitrite (1·8 g.) in water (5 c.c.), and the diazonium solution added at 10—12° to one of ethyl 2-oxopiperidine-3-carboxylate (3·4 g.) in water (40 c.c.) containing potassium hydroxide (1·2 g.), which had been kept overnight at 30°. The stirred solution was brought to pH 6—7 by addition of saturated aqueous sodium acetate, and stirring was continued for 2 hr. The solution became cloudy when the temperature reached 15° and the precipitate (1·6 g.), m. p. 112·5° (decomp.), was filtered off and dried. This is probably the phenylazo-compound, for on attempted recrystallisation from most solvents it decomposed. Two quick recrystallisations from water (charcoal) gave a small amount of the phenylhydrazone (accompanied by extensive decomposition) as pale-yellow needles, m. p. 175—176°, undepressed on admixture with a sample obtained as under (ii).

(ii) *At* pH 3—4. *p*-Anisidine (5 g.) in water (60 c.c.) and concentrated hydrochloric acid (11 c.c.) was diazotised with sodium nitrite (3·6 g.) in water (10 c.c.). The excess of nitrous acid was decomposed with urea, and the solution neutralised below 0° with 10% aqueous sodium carbonate (45 c.c.) and filtered. The filtrate was added to an ice-cold solution of the ester (6·8 g.) in water (80 c.c.) containing potassium hydroxide (2·4 g.), which had been kept overnight at 30°, and the solution was brought to pH 3—4 with glacial acetic acid and stirred at 0—5° for 6 hr. The suspension was kept in the refrigerator overnight, then filtered, and the product washed with water and dried (6·7 g.). A sample, on recrystallisation from water (charcoal), gave 2 : 3-*dioxopiperidine* 3-p-*methoxyphenylhydrazone* as flat yellow needles, m. p. 176—177° (Found: C, 62·1; H, 6·7; N, 18·0. $C_{12}H_{15}O_2N_3$ requires C, 61·8; H, 6·5; N, 18·0%).

Cyclisation of the Phenylazo-derivative.—Dry hydrogen chloride was bubbled through the solid (1 g.) suspended in alcohol (40 c.c.). The solid dissolved and evolution of heat which was not controlled caused the solution to boil. The solution was then evaporated to a small volume and treated with water. The black precipitate (0·4 g.) was recrystallised from alcohol (charcoal), giving 1 : 2 : 3 : 4-tetrahydro-6-methoxy-1-oxo-β-carboline as colourless prisms, m. p. 275—277° (Found: C, 66·95; H, 5·7. Calc. for $C_{12}H_{12}O_2N_2$: C, 66·65; H, 5·6%). Barrett, Perkin, and Robinson [12] give m. p. 280°.

Cyclisation of the p-*Methoxyphenylhydrazone.*—The phenylhydrazone (5 g.) was boiled under reflux with 90% formic acid (20 c.c.) for ½ hr. and diluted with water (40 c.c.). The oxocarboline (3·1 g.), m. p. 271—273°, gave colourless crystals, m. p. 275—277°, on recrystallisation from alcohol.

5-*Methoxytryptamine-2-carboxylic Acid.*—1 : 2 : 3 : 4-Tetrahydro-6-methoxy-1-oxo-β-carboline (0·5 g.) was boiled under reflux with potassium hydroxide (1·1 g.) in 60% aqueous ethanol (12 c.c.) for 5 hr. The ethanol was evaporated and water (6 c.c.) added. The filtered cold solution was made just acid with acetic acid, giving 5-*methoxytryptamine-2-carboxylic acid* (0·53 g., 98%), m. p. 238—240° (decomp.). Recrystallisation from water containing a little

alcohol (charcoal) gave colourless plates, m. p. 246—248° (decomp.) (Found: C, 61·7; H, 5·8. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0%).

5-Methoxytryptamine.—(i) 5-Methoxytryptamine-2-carboxylic acid (2 g.) was boiled under reflux with 5% hydrochloric acid (30 c.c.) for 1 hr. The solid soon dissolved with evolution of carbon dioxide. The cooled solution was made alkaline with 30% aqueous sodium hydroxide, the colourless oil was extracted with ether, and the ether dried ($MgSO_4$) and evaporated, giving 5-methoxytryptamine (1·45 g.), m. p. 120—121°. The picrate (from alcohol) formed deep red flat prisms, m. p. 219° (decomp.) (Found: C, 49·2; H, 4·2; N, 16·3. Calc. for $C_{11}H_{14}ON_2,C_6H_3O_7N_3$: C, 48·7; H, 4·1; N, 16·7%). Wieland *et al.*[17] give m. p. 220° (decomp.).

(ii) The amino-acid (0·5 g.) and toluene-*p*-sulphonic acid (4·2 g.) in water (5 c.c.; 5N-solution) were boiled under reflux for 1 hr. The solution was made alkaline and extracted with ether, giving 5-methoxytryptamine (0·2 g.), m. p. 119—120°.

1 : 2 : 3 : 4-Tetrahydro-6-methoxy-β-carboline.—1 : 2 : 3 : 4-Tetrahydro-6-methoxy-1-oxo-β-carboline (1 g.) was suspended in boiling dry butanol (25 c.c.) and treated rapidly with pieces of sodium (2·5 g.), vigorous stirring and heating (oil-bath) being maintained (the external temperature should not be allowed to rise too much, otherwise considerable charring occurs). After ½ hr., when all the sodium had dissolved, the mixture was cooled and 90% ethanol (25 c.c.) followed by water (25 c.c.) was added, the mixture was steam-distilled, then cooled, and the product recrystallised from dilute methanol, giving 1 : 2 : 3 : 4-tetrahydro-6-methoxy-β-carboline (0·35 g.) as slightly brown needles, m. p. 221—222° (Späth and Lederer[15] give m. p. 223—224°). The *picrate* (from alcohol) had m. p. 240—241° (decomp.) (Found: C, 50·5; H, 4·3. $C_{12}H_{14}ON_2,C_6H_3O_7N_3$ requires C, 50·1; H, 3·9%).

2 : 3-Dioxopiperidine 3-p-Benzyloxyphenylhydrazone.—*p*-Benzyloxyaniline[18] (2 g.) was heated with concentrated hydrochloric acid (3 c.c.) in water (20 c.c.) until solution was complete. The solution was stirred, and diazotised at 0° with sodium nitrite (0·9 g.) in water (5 c.c.). After 30 min. the excess of nitrous acid was decomposed with urea, and the solution filtered and added at 0° to one of ethyl 2-oxopiperidine-3-carboxylate (1·7 g.) in water (20 c.c.) containing potassium hydroxide (0·6 g.), which had been kept at 30° overnight. After being stirred for ½ hr. at 0° the suspension was brought to pH 4·5 with saturated aqueous sodium acetate and stirring was continued at 12° for 5 hr. The precipitate was filtered off and the filtrate, whose pH had fallen to *ca.* 2, was brought to pH 4, stirred for another 2 hr., and kept in the refrigerator at 2° overnight. The solid was filtered off, washed with water, and dried. The combined solids (2·08 g.), m. p. 166—170°, were recrystallised from very dilute alcohol, giving the *3-p-benzyloxyphenylhydrazone* as small pale yellow plates, m. p. 185—186° (Found: C, 70·2; H, 5·8; N, 14·3. $C_{18}H_{19}O_2N_3$ requires C, 69·9; H, 6·2; N, 13·6%).

6-Benzyloxy-1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline.—The crude *p*-benzyloxyphenylhydrazone (8 g.) was boiled under reflux with 70% formic acid (30 c.c.) for ½ hr., then diluted with water. The product was triturated with a little cold 90% ethanol and collected, giving the colourless *carboline* (5·2 g.), which on recrystallisation from dilute ethanol gave colourless needles, m. p. 199—201° (Found: C, 73·95; H, 5·1. $C_{18}H_{16}O_2N_2$ requires C, 73·95; H, 5·5%).

5-Benzyloxytryptamine-2-carboxylic Acid.—The foregoing carboline (1 g.) was boiled under reflux for 5 hr. with 60% aqueous-ethanolic potassium hydroxide (2·2 g. in 20 c.c.). Working up as above gave the product (1 g.) which recrystallised from 90% ethanol, giving *5-benzyloxytryptamine-2-carboxylic acid* as colourless flat prisms, m. p. 243—244° (decomp.) (Found: C, 69·7; H, 5·75. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·85%).

The amino-acid (0·5 g.) was boiled under reflux with toluene-*p*-sulphonic acid (0·5 g.). An oil was formed which solidified on ½ hour's boiling. The suspension was diluted with water, cooled, and filtered, and the product (0·7 g.), m. p. 198° (effervescence, decomp.), was recrystallised from very dilute alcohol (charcoal), giving the *amino-acid toluene-p-sulphonate* as small colourless needles, m. p. 197—198° (effervescence) (mixed m. p. with 6-benzyloxy-1 : 2 : 3 : 4-tetrahydro-1-oxo-β-carboline, 165—180°) (Found: C, 62·3; H, 5·4. $C_{18}H_{18}O_3N_2,C_7H_8O_3S$ requires C, 62·2; H, 5·4%).

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[17] Wieland, Konz, and Mittasch, *Annalen*, 1934, **513**, 1.
[18] Boehme, *J. Amer. Chem. Soc.*, 1953, **75**, 2502.