477. *Melanin and Its Precursors. Part V.* Synthesis of 5- and 7-Hydroxyindole from Dihydroxyphenylalanines.*

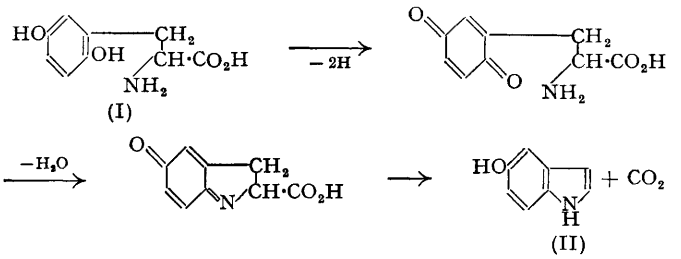
By R. I. T. Cromartie and John Harley-Mason.

Oxidation of 2 : 5-dihydroxyphenylalanine or 2-(2 : 5-dihydroxyphenyl)-ethylamine with potassium ferricyanide gives 5-hydroxyindole in high yield. Similar oxidation of 2 : 3-dihydroxyphenylalanine gives 7-hydroxyindole in lower yield, whereas the methyl ester gives methyl 7-hydroxyindole-2-carboxylate. Oxidation of 2-(2 : 3-dihydroxyphenyl)ethylamine gives only ill-defined products.

Oxidation of 3 : 4-dihydroxyphenylalanine at room temperature with potassium ferricyanide in the presence of sodium hydrogen carbonate gives 5 : 6-dihydroxyindole (Bu'Lock and Harley-Mason, *J.*, 1951, 2248). As previously reported briefly (Harley-Mason, *Chem.*

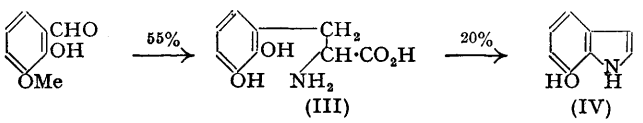
* Part IV, *J.*, 1952, 1052.

and Ind., 1952, 173) we have now found that similar oxidation of 2 : 5-dihydroxyphenylalanine (I) (Neuberger, *Biochem. J.*, 1948, **43**, 599) gives 5-hydroxyindole (II) in 85% yield. No intermediate could be isolated, but it seems probable that the reaction follows the course indicated in the scheme.



Oxidation of 2-(2 : 5-dihydroxyphenyl)ethylamine also gives (II) in good yield. This amine had earlier been prepared by Buck (*J. Amer. Chem. Soc.*, 1932, **54**, 3661) and by Leaf and Neuberger (*Biochem. J.*, 1948, **43**, 606). We adopted a more convenient synthesis in which 2 : 5-dimethoxy-β-nitrostyrene (Sugasawa and Shigehara, *Ber.*, 1941, **74**, 459) was reduced to the corresponding phenylethylamine with lithium aluminium hydride and this was then demethylated with hydrobromic acid.

Oxidation of 2 : 3-dihydroxyphenylalanine (III) (Clemo and Duxbury, *J.*, 1950, 1795) was next examined. In this case treatment with potassium ferricyanide and sodium hydrogen carbonate led to the formation of much dark insoluble material and it became apparent that the 7-hydroxyindole (IV) at first formed was very susceptible to further oxidation.



Addition of an organic solvent phase (ethyl acetate) to the aqueous solution and stirring vigorously during the addition of the ferricyanide resulted in the extraction of the indole as it was formed, thus protecting it to some extent from further oxidation. By this means, yields of 20% were obtained. Similar oxidation of 2 : 3-dihydroxyphenylalanine methyl ester gave methyl 7-hydroxyindole-2-carboxylate in slightly better yield. 2 : 3-Dihydroxy-β-phenylethylamine (Buck, *loc. cit.*) was prepared from 2 : 3-dimethoxy-β-nitrostyrene as described above for the 2 : 5-isomer. However, on oxidation, only traces of 7-hydroxyindole could be detected and the major product was insoluble amorphous material.

The syntheses of (II) and (IV) reported above give much higher yields than those described earlier (Bergel and Morrison, *J.*, 1943, 49; Beer, Clarke, Khorana, and Robertson, *J.*, 1948, 1605), particularly in the latter case in which an overall yield of 11% is obtained from the readily available *o*-vanillin. The difficulty in the earlier syntheses is the decarboxylation of the corresponding 2-carboxylic acids : this is avoided in our process, since decarboxylation of the quinonoid intermediates occurs spontaneously on rearrangement.

The biogenetic significance of the oxidation of 2 : 5-dihydroxyphenylalanine has been discussed elsewhere (Harley-Mason, *loc. cit.*).

Experimental

5-Hydroxyindole.—(*a*) To a solution of 2 : 5-dihydroxyphenylalanine monohydrate (0·43 g.) and sodium hydrogen carbonate (0·2 g.) in water (15 c.c.), a solution of potassium ferricyanide (1·3 g.) and sodium hydrogen carbonate (0·3 g.) in water (20 c.c.) was added with stirring during 10 minutes. The solution, which had at first darkened, subsequently became pale yellow and was then extracted with peroxide-free ether (3 × 20 c.c.), and the ethereal layer dried (Na_2SO_4) and freed from solvent. The residual 5-hydroxyindole (0·23 g., 85%) formed colourless needles,

m. p. 106—107°, from benzene–light petroleum (Found : C, 72·0; H, 5·4; N, 10·4. Calc. for C_8H_7ON : C, 72·2; H, 5·3; N, 10·5%). Beer *et al.* (*loc. cit.*) give m. p. 107°. Acetylation (acetic anhydride–pyridine in the cold) gave *5-acetoxyindole* which formed plates (from light petroleum), m. p. 116—117° (Found : C, 68·6; H, 5·3. $C_{10}H_9O_2N$ requires C, 68·3; H, 5·1%).

(*b*) 2 : 5-Dimethoxy-β-nitrostyrene (5·5 g.) was placed in a small Soxhlet thimble and extracted under reflux into a solution of lithium aluminium hydride (3·8 g.) in ether (200 c.c.), boiling being continued for 6 hours. The resulting suspension was decomposed with a concentrated solution of sodium potassium tartrate, the ethereal layer separated and dried, and the solvent removed. The residual oil, 2 : 5-dimethoxy-β-phenylethylamine (3·5 g., 87%), distilled at 140°/2 mm.

The amine (3 g.) was treated cautiously with hydrobromic acid (*d* 1·49; 20 c.c.) and the whole refluxed for 2 hours. The excess of acid was removed under reduced pressure and the residual gum crystallised on storage in a desiccator, giving the dihydroxy-amine hydrobromide which was recrystallised from ethanol–ether.

The hydrobromide (0·47 g.) in water (20 c.c.) was shaken for 0·5 hour with freshly precipitated silver chloride (2 g.). The mixed silver halides were filtered off and the solution was treated with potassium ferricyanide (1·3 g.) and sodium hydrogen carbonate (0·5 g.) and worked up as in (*a*) above, giving 5-hydroxyindole (0·19 g., 70%).

7-Hydroxyindole.—2 : 3-Dihydroxyphenylalanine (2 g.) and sodium hydrogen carbonate (0·8 g.) were dissolved in water (400 c.c.), and ethyl acetate (250 c.c.) was added. The mixture was vigorously stirred mechanically while a solution of potassium ferricyanide (6·0 g.) and sodium hydrogen carbonate (1·8 g.) in water (200 c.c.) was added dropwise during 0·5 hour. To the resulting reddish-violet emulsion a little sodium dithionite was added, the colour then changing to pale buff. On centrifugation the emulsion separated readily; the ethyl acetate layer was dried (Na_2SO_4) and the solvent removed. The residual brown gum was recrystallised from light petroleum (b. p. 100—120°), giving 7-hydroxyindole (0·25 g., 20%), m. p. 97—98° (Found : C, 71·6; H, 5·5; N, 10·3%). Beer *et al.* (*loc. cit.*) give m. p. 96°. Working in more concentrated solutions caused a lowering of the yield.

Acetylation (acetic anhydride–pyridine in the cold) gave *7-acetoxyindole* which formed needles, m. p. 55°, from light petroleum (b. p. 40—60°) (Found : C, 68·6; H, 5·1%).

Methyl 7-Hydroxyindole-2-carboxylate.—A suspension of 2 : 3-dihydroxyphenylalanine (1·0 g.) in dry methanol was saturated with hydrogen chloride and then refluxed for 0·5 hour. The solvent was removed, leaving the methyl ester hydrochloride as a glass which could not be crystallised. The product was dissolved in water (50 c.c.), ethyl acetate (100 c.c.) added, and then a solution of potassium ferricyanide (3·1 g.) and sodium hydrogen carbonate (1·25 g.) in water (50 c.c.) was added dropwise during 0·5 hour with vigorous stirring. The resulting emulsion was worked up as described above for 7-hydroxyindole except that the product was recrystallised from benzene. *Methyl 7-hydroxyindole-2-carboxylate* formed small pale yellow prisms, m. p. 218—220° (decomp.) (Found : C, 62·9; H, 5·0. $C_{10}H_9O_3N$ requires C, 62·8; H, 4·7%).

Hydrolysis of the ester with boiling 2N-sodium hydroxide under nitrogen, followed by acidification, gave the corresponding acid which sublimed unchanged in a high vacuum.

2-(2 : 3-*Dihydroxyphenyl*)*ethylamine.*—Reduction and demethylation of 2 : 3-dimethoxy-β-nitrostyrene (Lindenmann, *Helv. Chim. Acta*, 1949, **32**, 69) to the dihydroxy-amine were carried out as described above for the 2 : 5-compound.

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