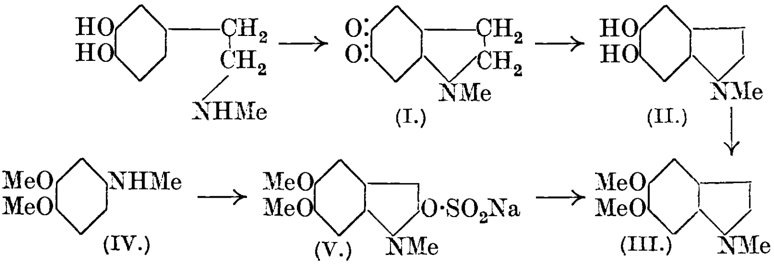
68. *The Oxidation of β-3 : 4-Dihydroxyphenylethylmethylamine with Silver Oxide. The Isolation of 5 : 6-Dihydroxy-1-methylindole and a Synthesis of 5 : 6-Dimethoxy-1-methylindole.*

By Harold Burton.

It was shown by Dulière and Raper (*Biochem. J.*, 1930, **24**, 239) that β-3 : 4-dihydroxyphenylethylmethylamine was oxidised in aqueous solution by tyrosinase to a deep red solution of a substance which was probably 1-methyl-2 : 3-dihydroindole-5 : 6-quinone (I). This solution was decolorised by treatment with sulphurous acid or by keeping in an atmosphere of hydrogen, with the production of 5 : 6-dihydroxy-1-methylindole (II), which was not isolated but was converted by methylation with methyl sulphate and alkali in an inert atmosphere into 5 : 6-dimethoxy-1-methylindole (III). The constitution of the dimethoxymethylindole was not proved by synthesis, but was inferred from the results of Raper's experiments (*ibid.*, 1927, **21**, 89) with tyrosine. The red solution of (I) was also obtained by oxidation of the dihydroxyphenylethylmethylamine with an aqueous suspension of silver oxide.

The oxidation with silver oxide has now been investigated further and the results, which amplify those of Dulière and Raper, substantially confirm Raper's view (*loc. cit.*) of the mechanism of the tyrosine–tyrosinase reaction.



When the red solution of (I) is treated with a solution of *o*-phenylenediamine in acetic acid, a reaction occurs but crystalline material could not be isolated. With phenylhydrazine acetate, however, a crystalline *monophenylhydrazone* is isolated in rather more than 50% of the theoretical yield, which has the correct analytical composition, and does not give the characteristic colour reaction of indole derivatives with *p*-dimethylaminobenzaldehyde and hydrochloric acid. Addition of a few drops of 5*N*-sodium hydroxide to the red solution causes immediate decolorisation; immediate acidification with a slight excess of acetic acid stabilises the almost colourless solution and the formation of the melanin-like pigment (compare Raper, *loc. cit.*) is completely suppressed. Extraction of the decolorised solution with ether affords 5 : 6-dihydroxy-1-methylindole (II), which has not been obtained crystalline but has been characterised as the *diacetyl* derivative. Methylation of the dihydroxymethylindole has given 5 : 6-*dimethoxy*-1-*methylindole* (III), which has now been synthesised by condensing 4-*methylaminoveratrole* (IV) with glyoxal sodium bisulphite in boiling aqueous alcohol (compare Pschorr and Karo, *Ber.*, 1906, **39**, 3142; Hinsberg, *Ber*, 1908, **41**, 1367) to give *sodium* 5 : 6-*dimethoxy*-1-*methylindolyl* 2-*sulphite* (V), from which the dimethoxymethylindole has been obtained by distillation with zinc dust.

Some interesting changes of the red solution are described in the experimental section, and further experiments regarding the production of a black pigment (melanin) from it are in progress.

EXPERIMENTAL.

1-*Methyl*-2 : 3-*dihydroindole*-5 : 6-*quinonemonophenylhydrazone*.—Silver oxide, precipitated from 9·4 g. of silver nitrate (5 mols. +

10% excess) with baryta and washed free from alkali with water, was suspended in 200 c.c. of water and mixed with a solution of β-3 : 4-dihydroxyphenylethylmethylamine hydrochloride (2 g.) in water (800 c.c.). An immediate red coloration was produced. After 15 minutes' vigorous stirring, the liquid was filtered repeatedly until free from admixed silver. Addition of an excess of phenylhydrazine acetate to the bright red solution (*A*) gave a *product* (1·3 g.), which crystallised from *iso*amyl alcohol, in which it was readily soluble when hot and almost insoluble when cold, in either deep orange-red plates or prisms or (occasionally) a mixture of both forms. Both forms, or a mixture, melt at 226—227° and then decompose (Found: C, 70·8, 71·0, 70·9; H, 6·0, 6·0, 6·0; N, —, 16·2, 16·0. $C_{15}H_{15}ON_3$ requires C, 71·15; H, 5·9; N, 16·55%).

5 : 6-*Dihydroxy*-1-*methylindole* (II).—The solution (*A*) was treated with a few drops of 5*N*-sodium hydroxide, and immediately the colour had faded to pale yellow a few drops of glacial acetic acid were added. Extraction with ether (until a test portion of the extract imparted little or no colour to an aqueous solution of sodium hydroxide when shaken) gave a solution having a beautiful blue fluorescence. 5 : 6-Dihydroxy-1-methylindole was obtained from the dried solution, by evaporation and drying in a vacuum desiccator over potassium hydroxide, as a glass (0·6 g.), which was very soluble in alcohol, insoluble in petroleum, and gave a reddish-purple coloration with *p*-dimethylaminobenzaldehyde and concentrated hydrochloric acid in alcohol, changing to brown on addition of a trace of sodium nitrite. Acetylation with acetic anhydride (5 c.c.) (boiled for 5 hours) gave a semi-solid product which, when dissolved in alcohol and treated with ice-water, separated as an amorphous solid. This *diacetyl* derivative, m. p. 95—100° after softening at 65° (Found: C, 62·75; H, 5·3; N, 5·4. $C_{13}H_{13}O_4N$ requires C, 63·5; H, 5·25; N, 5·65%), is insoluble in alkali hydroxide but is gradually hydrolysed with the production of a black solution. The diacetyl derivative appears to be partly polymerised, since it does not dissolve completely after 30 minutes' boiling with 10% sodium hydroxide solution in an atmosphere of nitrogen. The alkaline solution obtained turns black immediately it is in contact with air.

Solution (*A*) was decolorised by zinc dust. When air was bubbled through the colourless solution, a blue substance was precipitated, which changed to a brown insoluble substance on attempted crystallisation.

4-*Methylaminoveratrole* (IV).—A mixture of 4-acetamidoveratrole (40 g.), sodium wire (6·5 g.), and dry xylene (200 c.c.) was heated at 130° (bath) for 4 hours with frequent shaking. After cooling, methyl iodide (45 g.) was added, and the mixture heated from 110° to 150° during 6 hours. The major part of the xylene was distilled, and the residue hydrolysed by boiling with an excess of concentrated alcoholic potassium hydroxide solution for 24 hours. The alcohol and a small amount of residual xylene were distilled in steam; ether extracted from the residue 22 g. (65% of the theoretical) of 4-*methylaminoveratrole*. The base distils at 153—155°/12 mm. as a straw-coloured oil having a faint camphor-like odour (Found: C, 64·2; H, 7·5. $C_9H_{13}O_2N$ requires C, 64·7; H, 7·8%), gives Liebermann's nitroso-reaction, and darkens rapidly when it is exposed to the atmosphere.

Sodium 5:6-*Dimethoxy*-1-*methylindolyl* 2-*Sulphite* (V).—Solutions of glyoxal sodium bisulphite (32 g.) in water (250 c.c.) and of 4-methylaminoveratrole (20 g.) in alcohol (150 c.c.) were mixed and boiled under reflux for 48 hours. The greenish-yellow solution was filtered while hot and then cooled at about 0°. The *sodium* salt (19 g.) which separated crystallised from water in small prisms, m. p. 187° (decomp.) (Found: S, 10·1. $C_{11}H_{12}O_5NSNa,H_2O$ requires S, 10·3%).

When the sodium salt (5 g.) was boiled with 75 c.c. of a mixture of water (1 part) and hydrochloric acid (2 parts) for 30 minutes and the resulting solution neutralised, a small amount of insoluble material separated. Extraction of the basified solution with ether gave 5 : 6-*dimethoxy*-1-*methyloxindole* (?), which dissolved readily in water and crystallised from light petroleum (b. p. 100—120°) in clusters of needles, m. p. 120—121° (Found: C, 63·8; H, 6·3. $C_{11}H_{13}O_3N$ requires C, 63·65; H, 6·35%).

5 : 6-*Dimethoxy*-1-*methylindole* (III).—An intimate mixture of the above sodium salt and zinc dust (10 parts) was heated in a vacuum. The indole, which sublimed, was recrystallised from alcohol, the pure substance having m. p. 138—139° either alone or mixed with a specimen prepared from solution (*A*) by Dulière and Raper's procedure (Found: C, 68·7; H, 6·8. Calc. for $C_{11}H_{13}O_2N$: C, 69·1; H, 6·8%).

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