42. *Melanin and Its Precursors. Part VI.* Further Syntheses of 5 : 6-Dihydroxyindole and its Derivatives.*

By John Harley-Mason.

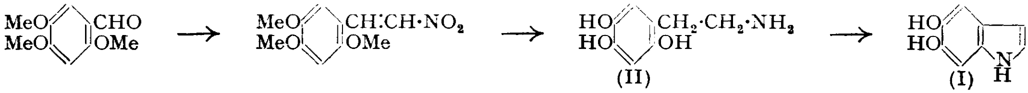
5 : 6-Dihydroxyindole is obtained in good yield by autoxidation of 2-(6-amino-3 : 4-dihydroxyphenyl)ethylamine and by ferricyanide oxidation of 2-(2 : 4 : 5-trihydroxyphenyl)ethylamine.

5 : 6-Dihydroxy-2-methyl- and -2 : 3-dimethyl-indole are readily obtained by demethylation of the corresponding 5 : 6-dimethoxyindoles with hydrobromic acid. In the reduction of 4 : 5-dimethoxy-2-nitro-1-2′-nitropropenylbenzene a 3 : 3′-di-indolyl derivative is obtained in addition to the expected 5 : 6-dimethoxy-2-methylindole.

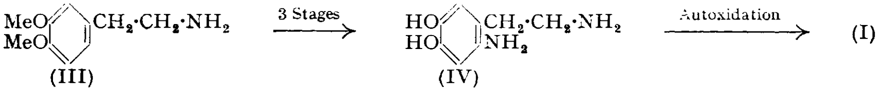
Ferricyanide oxidation of *N*-3 : 4-dihydroxybenzyl-2-(3 : 4-dihydroxyphenyl)ethylamine gives 1-(3 : 4-dihydroxybenzyl)-5 : 6-dihydroxyindole, but attempts to oxidise this further to a tetracyclic phenanthridine derivative were unsuccessful.

Methods at present available for the synthesis of 5 : 6-dihydroxyindole (I) include the oxidation of 3 : 4-dihydroxyphenylalanine and subsequent rearrangement of the quinonoid-product (Bu'Lock and Harley-Mason, *J.*, 1951, 2248), and the reduction of 4 : 5-diacetoxy-β : 2-dinitrostyrene and subsequent hydrolysis of the diacetoxyindole thus obtained (Beer, Clarke, Khorana, and Robertson, *J.*, 1948, 2223). The first method gives low and erratic yields whilst the second requires as starting product 6-nitroprotocatechualdehyde which is difficult to prepare on a considerable scale. Accordingly a search was made for a more convenient synthesis.

It had earlier been shown (Part V, *loc. cit.*) that oxidation of 2-(2 : 5-dihydroxyphenyl)-ethylamine gave 5-hydroxyindole in good yield and this approach has now been extended to the oxidation of 2-(2 : 4 : 5-trihydroxyphenyl)ethylamine (II), readily obtained from 2 : 4 : 5-trimethoxybenzaldehyde *via* the nitrostyrene. On oxidation with potassium ferricyanide (II) gave a good yield of (I).



The starting product in this case is, however, not commercially available and an alternative rather similar synthesis was then developed starting from the readily available 2-(3 : 4-dimethoxyphenyl)ethylamine (III). This material on nitration gave the 4 : 5-dimethoxy-2-nitro-derivative which was reduced catalytically to the corresponding amino-compound. On demethylation this afforded 2-(2-amino-4 : 5-dihydroxyphenyl)ethylamine (IV) as dihydrobromide, the overall yield up to this point being 70%. The diamine, on liberation from its salt, which was quite stable, autoxidised in aqueous solution extremely readily to give (I), the reaction presumably proceeding *via* a quinone-imine intermediate and resembling the synthesis described above except that ammonia instead of water is liberated in the cyclisation. Quite good yields were obtained and the synthesis is the simplest available for 5 : 6-dihydroxyindole. Oxidation of (IV) with potassium ferricyanide was unsatisfactory owing to the formation of a very sparingly soluble amine ferricyanide.



One further synthesis of (I) was examined : bromination of 2-(3 : 4-dimethoxyphenyl)-ethylamine gave the bromo-derivative which was then demethylated to 2-(2-bromo-4 : 5-dihydroxyphenyl)ethylamine. Oxidation with potassium ferricyanide gave 5 : 6-dihydr-

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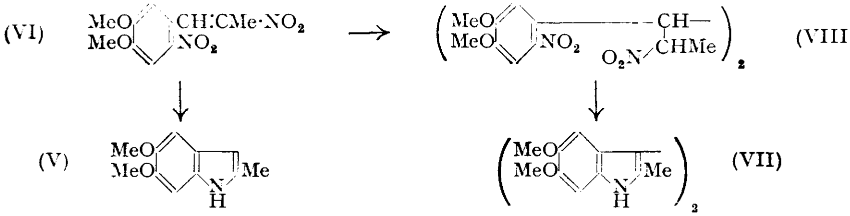
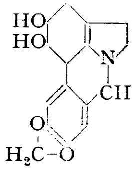
* Part V, *J.*, 1952, 2525.

oxyindole by cyclisation with elimination of hydrogen bromide, but much amorphous insoluble by-product was formed and the yield was very low.

5 : 6-Dihydroxy-2 : 3-dimethylindole was prepared by Beer, McGrath, Robertson, and Woodier (*J.*, 1949, 2061) by demethylation of the corresponding dimethoxy-compound with aluminium bromide. It has now been found that demethylation is effected more easily by short boiling with hydrobromic acid. 5 : 6-Dihydroxy-2-methylindole was similarly obtained from 5 : 6-dimethoxy-2-methylindole (V). The latter, which had earlier been obtained by Lions (*J. Proc. Roy. Soc. N.S.W.*, 1930, **63**, 168), was prepared more conveniently by reduction of 4 : 5-dimethoxy-2-nitro-1-2′-nitropropenylbenzene (VI) with iron powder and acetic acid (cf. Beer *et al.*, *loc. cit.*). From this reduction a considerable amount of a sparingly soluble by-product was obtained in addition to (V) : analysis indicated a molecular formula approximately twice that of (V), so the compound is regarded as 5 : 6 : 5′ : 6′-tetramethoxy-2 : 2′-dimethyl-3 : 3′-di-indolyl (VII), arising from reduction of the dimeric intermediate (VIII). It has been shown (Sonn and Schellenberg, *Ber.*, 1917, **50**, 1513; Kohler and Drake, *J. Amer. Chem. Soc.*, 1923, **45**, 1281) that hydrogenation of β-nitrostyrenes over platinum affords " hydrodimers " (1 : 4-dinitro-2 : 3-diarylbutanes) of the type of (VIII), and it seems probable that a reductive dimerisation of this kind occurs to some extent in the reduction of (VI) described above. Hydrobromic acid caused extensive decomposition of (VII), with a small amount of 5 : 6-dihydroxy-2-methylindole as sole isolable product.

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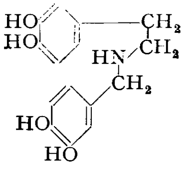
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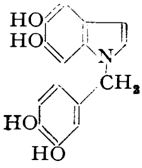
(XI)

A further and more complex case of 5 : 6-dihydroxyindole formation was next examined. The structure (IX) has been advanced for the alkaloid lycorine (isolated from several species of *Amaryllidacaea*) on the basis of degradative studies (Kondo and Uyeo, *Ber.*, 1937, **70**, 1087, 1094; 1938, **71**, 1529: Kondo and Katsura, *Ber.*, 1939, **72**, 2083; 1940, **73**, 112, 1424). An attempt was made to synthesise a tetracyclic structure of this kind, but with only partial success. The amine (X) was prepared by a method similar to that of Buck (*J. Amer. Chem. Soc.*, 1931, **53**, 2192), and oxidised with potassium ferricyanide. The product, obtained in 40% yield was, however, 1-(3 : 4-dihydroxybenzyl)-5 : 6-dihydroxyindole (XI) and attempts at further oxidation, to the tetracyclic system of lycorine, were unsuccessful.

EXPERIMENTAL.

2-(2 : 4 : 5-*Trihydroxyphenyl*)*ethylamine*.—2 : 4 : 5-Trimethoxybenzaldehyde (4 g.), nitromethane (1·5 g.), and ammonium acetate (1 g.) were refluxed in acetic acid (30 c.c.) for 3 hours. After cooling, dilution with water precipitated the product which was recrystallised from ethanol. 2 : 4 : 5-*Trimethoxy*-β-*nitrostyrene* (3·5 g.) formed orange-red prisms, m. p. 131—132° (Found : C, 55·0; H, 5·4. $C_{11}H_{13}O_5N$ requires C, 55·1; H, 5·4%).

The nitrostyrene (3 g.) was extracted (Soxhlet) into a solution of lithium aluminium hydride (2 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 (KOH), and the solvent removed, leaving 2-(2 : 4 : 5-trimethoxyphenyl)-ethylamine as a waxy solid. A portion was converted into the *hydrochloride*, plates (from ethanol–ether), m. p. 187—188° (decomp.) (Found: C, 53·1; H, 7·4. $C_{11}H_{18}O_3NCl$ requires C, 53·3; H, 7·3%).

The amine (2 g.) was refluxed for 1 hour with hydrobromic acid (*d* 1·49; 15 c.c.). On cooling, 2-(2 : 4 : *5-trihydroxyphenyl)ethylamine hydrobromide* separated and recrystallised from ethanol–ether, forming needles, m. p. 216—218° (Found, on a sample dried at 80°/0·1 mm.: C, 38·9; H, 5·0. $C_8H_{12}O_3NBr$ requires C, 38·4; H, 4·8%).

2-(2-*Amino*-4 : 5-*dihydroxyphenyl)ethylamine*.—An ice-cold solution of 3 : 4-dimethoxyphenylethylamine (5 g.) in water (15 c.c.) and concentrated nitric acid (5 c.c.) was added slowly with stirring to nitric acid (free from nitrous acid; *d* 1·4; 35 c.c.), at 10—15° (cooling). Separation of the sparingly soluble nitro-amine nitrate soon commenced, and after 2 hours the mixture was diluted with ice-water and the crystalline precipitate collected. It was dissolved in boiling water, basified hot with sodium hydroxide, and then cooled, whereupon the nitro-amine crystallised. Recrystallisation from water gave 2-(4 : 5-*dimethoxy*-2-*nitrophenyl)ethylamine* (4·8 g.) as pale yellow plates, m. p. 110—111° (Found: C, 53·2; H, 6·2. $C_{10}H_{14}O_4N_2$ requires C, 53·0; H, 6·2%). The *hydrochloride* formed plates (from ethanol), m. p. 228—230° (Found: C, 45·25; H, 5·9. $C_{10}H_{15}O_4N_2Cl$ requires C, 45·6; H, 5·7%).

A solution of the amine (5 g.) in ethanol (50 c.c.) was hydrogenated over Raney nickel at 50°/50 atm. Hydrogen chloride was passed into the resulting solution, whereupon the diamine dihydrochloride was precipitated, and a further quantity was obtained by addition of ether to the filtrate. 2-(2-*Amino*-4 : 5-*dimethoxyphenyl)ethylamine dihydrochloride* formed plates (from 95% ethanol), m. p. 247—248° (decomp.) (Found: C, 44·2; H, 6·8; N, 10·4. $C_{10}H_{18}O_4N_2Cl_2$ requires C, 44·6; H, 6·7; N, 10·4%).

The dihydrochloride (4 g.) was refluxed for an hour with hydrobromic acid (*d* 1·49; 30 c.c.). On cooling, 2-(2-*amino*-4 : 5-*dihydroxyphenyl)ethylamine dihydrobromide* crystallised and was recrystallised from ethanol–ether, forming plates, m. p. 239—241° (decomp.) (Found: C, 28·8; H, 4·4. $C_8H_{14}O_4N_2Br_2$ requires C, 29·0; H, 4·1%). Addition of ammonia to a concentrated aqueous solution precipitated the crystalline free base but this proved too unstable for characterisation.

2-(2-*Bromo*-4 : 5-*dihydroxyphenyl)ethylamine*.—To a cooled solution of 3 : 4-dimethoxyphenylethylamine (5·4 g.) in acetic acid (20 c.c.), bromine (4·8 g.) in acetic acid (15 c.c.) was added slowly with stirring. Separation of the product soon commenced, and after being kept overnight the crystals were collected and twice recrystallised from ethanol. 2-(2-*Bromo*-4 : 5-*dimethoxyphenyl)ethylamine hydrobromide* (7 g.) formed prisms, m. p. 202—204° (Found: C, 35·6; H, 4·5. $C_{10}H_{11}O_2NBr_2$ requires C, 35·1; H, 4·4%). Addition of sodium hydroxide to an aqueous solution precipitated the free base as white plates.

The hydrobromide (5 g.) was refluxed with hydrobromic acid (*d* 1·49; 35 c.c.) for 45 mins. (longer boiling caused darkening and decomposition), and the excess of acid removed under reduced pressure. The dihydroxy-amine hydrobromide formed a pale yellow glass.

5 : 6-*Dihydroxyindole*.—(*a*) To a solution of 2 : 4 : 5-trihydroxyphenylethylamine hydrobromide (1·0 g.) in water (25 c.c.), potassium ferricyanide (2·5 g.) and sodium hydrogen carbonate (1·0 g.) in water (25 c.c.) were added with stirring. The intensely red solution was kept under hydrogen for 24 hours, the colour changing to dirty brown, and was then extracted with ethyl acetate (3 × 30 c.c.). The extract was dried (Na_2SO_4), the solvent removed under hydrogen, and the residue sublimed at 150°/0·01 mm., giving 5 : 6-dihydroxyindole, m. p. 140° (decomp.) (0·3 g., 50%).

(*b*) A rapid stream of air was passed through a solution of 2-(2-amino-4 : 5-dihydroxyphenyl)-ethylamine dihydrobromide (1·7 g.) and sodium hydrogen carbonate (0·5 g.) in water (75 c.c.), which rapidly became deep violet-red as oxidation proceeded. When the colour had attained a maximum intensity (about 10 mins.) the current of air was stopped, the solution kept under hydrogen for 12 hours and then extracted with ethyl acetate (3 × 30 c.c.), and the extract worked up as in (*a*). In several experiments the yield of 5 : 6-dihydroxyindole varied from 0·25 to 0·4 g. (30—50%). The duration of the oxidation is critical, and, if it is continued too long, much 5 : 6-dihydroxyindole is further oxidised.

(*c*) To a solution of 2-(2-bromo-4 : 5-dihydroxyphenyl)ethylamine hydrobromide (1·6 g.) in water (30 c.c.), potassium ferricyanide (3·2 g.) and sodium hydrogen carbonate (1·7 g.) in water (30 c.c.) were added slowly with stirring. A voluminous dark blue-black precipitate was then filtered off. The filtrate was extracted with ethyl acetate and worked up as above, giving 5 : 6-dihydroxyindole (0·06 g., 8%).

5 : 6-*Dimethoxy*-2-*methylindole*.—To a solution of 3 : 4-dimethoxy-1-2′-nitropropenylbenzene (Bu'Lock and Harley-Mason, *loc. cit.*) (5 g.) in acetic acid (35 c.c.), concentrated nitric acid (*d* 1·5; 15 c.c.) was added dropwise with stirring, at < 15° (cooling). After an hour the mixture was poured into water and the precipitate recrystallised from ethanol. 4 : 5-*Dimethoxy*-2-*nitro*-1-2′-*nitropropenylbenzene* (VI) (5 g.) formed yellow plates, m. p. 133° (Found: C, 49·0; H, 4·6. $C_{11}H_{12}O_6N_2$ requires C, 49·3; H, 4·5%).

To a solution of the dinitro-compound (4 g.) in hot (not boiling) acetic acid (100 c.c.) and water (20 c.c.), iron powder (20 g.) was added in small portions. The mixture boiled vigorously after each addition, and when the reaction had subsided the solution was decanted as far as possible from undissolved residue and poured into water (500 c.c.). It was then extracted with ethyl acetate (4 × 100 c.c.), and the extract washed free from acetic acid with sodium hydrogen carbonate solution, dried, concentrated to 25 c.c., and kept at 0°. The pale brown crystalline solid (A) which had separated was filtered off and the filtrate diluted with light petroleum (b. p. 80—100°). 5 : 6-Dimethoxy-2-methylindole (1·8 g.) crystallised gradually at 0°, and was recrystallised (charcoal) from benzene–light petroleum, giving plates, m. p. 91°. Lions (*loc. cit.*) gives m. p. 91°.

The solid (A) above was recrystallised twice (charcoal) from acetone, giving 5 : 6 : 5′ : 6′-*tetramethoxy*-2 : 2′-*dimethyl*-3 : 3′-*di-indolyl* (VII) (0·8 g.) as white plates, m. p. 256—258° (Found: C, 69·9; H, 6·4; N, 7·4%; *M* (Rast), 365. $C_{22}H_{24}O_4N_2$ requires C, 69·5; H, 6·3; N, 7·35%; *M*, 380]. The product is sparingly soluble in the common organic solvents; with alcoholic hydrogen chloride (slowly) or Ehrlich's reagent a blue colour develops.

5 : 6-*Dihydroxy*-2-*methyl*- *and* -2 : 3-*dimethyl*-*indole*.—5 : 6-Dimethoxy-2-methylindole (0·5 g.) was refluxed for an hour with hydrobromic acid (*d*, 1·49; 10 c.c.). The solution, which had darkened considerably, was cooled, diluted with water (50 c.c.), and extracted with ethyl acetate (3 × 30 c.c.). The extract was dried (Na_2SO_4) and the solvent removed under hydrogen. Sublimation of the residue at 160°/0·005 mm. gave 5 : 6-dihydroxy-2-methylindole (0·25 g.), darkening at 180° and decomposing above this temperature as recorded by Beer *et al.* (*loc. cit.*) (Found: C, 66·0; H, 5·6. Calc. for $C_9H_9O_2N$: C, 66·3; H, 5·5%).

Similar treatment of 5 : 6-dimethoxy-2 : 3-dimethylindole gave the corresponding 5 : 6-dihydroxyindole, m. p. *ca.* 190° (decomp.).

1-3 : 4-*Dihydroxybenzyl*-5 : 6-*dihydroxyindole* (XI).—A mixture of veratraldehyde (8·4 g.) and 2-(3 : 4-dimethoxyphenyl)ethylamine (9 g.) was warmed at 100° for 0·5 hour and the resulting Schiff's base dissolved in ethanol (150 c.c.) and hydrogenated at 50°/50 atm. over Raney nickel. Hydrogen chloride was passed into the resulting solution and after addition of ether the precipitated amine hydrochloride (16 g.) was collected. The hydrochloride (10 g.) was demethylated by 2 hours' refluxing with hydrobromic acid (*d* 1·49; 80 c.c.). On cooling, *N*-3 : 4-dihydroxybenzyl-2-(3 : 4-dihydroxyphenyl)ethylamine hydrobromide (8·5 g.) crystallised.

To a solution of the hydrobromide (3·56 g.) in water (500 c.c.), potassium ferricyanide (13·1 g.) and sodium hydrogen carbonate (4·2 g.) in water (300 c.c.) were added during an hour with vigorous stirring. The solution became reddish-brown and a brown amorphous precipitate separated. Stirring was continued for a further hour and the precipitate was then filtered off and the filtrate extracted with ethyl acetate (4 × 100 c.c.). The extract was dried (Na_2SO_4) and concentrated to 20 c.c. Light petroleum (b. p. 60—80°; 20 c.c.) was added and the amorphous precipitate formed was filtered off. To the warmed filtrate, light petroleum (b. p. 40—60°; 100 c.c.) was added and, after storage overnight at 0°, the crystalline product was collected and recrystallised from water (20 c.c.). Dried at 70° in a vacuum, N-3 : 4-*dihydroxybenzyl*-5 : 6-*dihydroxyindole* (0·8 g.) formed prisms, m. p. 143—145°, sparingly soluble in cold water, readily soluble in the common organic solvents, and giving an intense purple colour with Ehrlich's reagent (Found: C, 66·15; H, 5·0; N, 5·2. $C_{15}H_{13}O_4N$ requires C, 66·2; H, 4·7; N, 5·2%). Acetylation (acetic anhydride–pyridine; 24 hours in the cold) gave a *tetra-acetate* which formed prisms (from ethanol), m. p. 194—195° (Found: C, 63·2; H, 4·9. $C_{23}H_{21}O_8N$ requires C, 63·0; H, 4·8%).

Attempts at further oxidation using potassium ferricyanide, ferric acetate or chloranil all led to intractable insoluble products, and no definite product could be isolated from the precipitate discarded in the course of the preparation.

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