708. *Melanin and Its Precursors. Part VII.* Synthesis of Methylated 5 : 6-Dihydroxyindoles, β-(4 : 5-Dihydroxy-2-methylphenyl)alanine, and Related Amines.*

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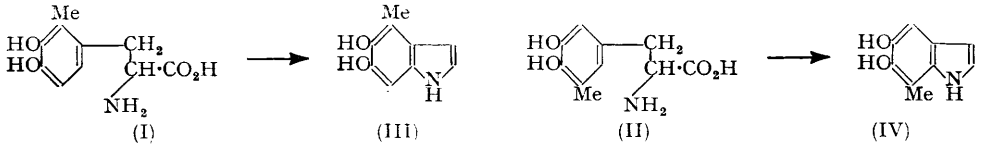
5 : 6-Dihydroxy-4- and -7-methylindole have been obtained by oxidation of 3 : 4-dihydroxy-2- and -5-methylphenylalanine. 5 : 6-Dihydroxy-4 : 7-dimethylindole has been prepared by a seven-stage synthesis from *p*-xyloquinone. β-(4 : 5-Dihydroxy-2-methylphenyl)alanine, 2-(4 : 5-dihydroxy-2-methylphenyl)ethylamine and its *N*-benzyl derivative have been prepared by conventional methods from 4 : 5-dimethoxy-2-methylbenzaldehyde.

In order to obtain information on the structure of tyrosine-melanin which is formed by the oxidative polymerisation of 5 : 6-dihydroxyindole, a comparative study of the oxidation of a series of 5 : 6-dihydroxyindoles substituted by methyl groups in each of the five available positions was envisaged. 5 : 6-Dihydroxy-1-, -2- and -3-methylindole have previously been prepared (Harley-Mason, *J.*, 1950, 1276; Beer, McGrath, Robertson, and Woodier, *J.*, 1949, 2061), and the syntheses of 5 : 6-dihydroxy-4- and -7-methyl- and -4 : 7-dimethyl-indole, now reported, complete the series.

Conversion of β-(3 : 4-dihydroxyphenyl)alanine into 5 : 6-dihydroxyindole was described by Bu'Lock and Harley-Mason (Part III; *J.*, 1951, 2248), though the yield was poor and erratic. With improved technique this reaction has now been applied to 3 : 4-dihydroxy-2- and -5-methylphenylalanine (I and II) (preparation, Cromartie and Harley-Mason Part IV, *J.*, 1952, 1052), giving 5 : 6-dihydroxy-4- and -7-methylindole (III and IV)

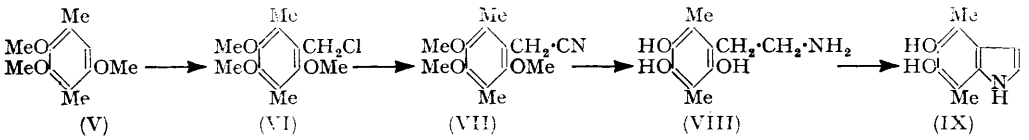
* Part VI, *J.*, 1953, 200.

respectively. For the preparation of 5 : 6-dihydroxy-4 : 7-dimethylindole the new dihydroxyindole synthesis described by Harley-Mason (Part VI *) was employed. Thiele acetylation of 2 : 5-dimethyl-*p*-benzoquinone gave triacetoxy-*p*-xylene which on treatment with a large excess of methyl sulphate and alkali gave trimethoxy-*p*-xylene (V). Chloromethylation then gave 2 : 4 : 5-trimethoxy-3 : 6-dimethylbenzyl chloride (VI), converted by



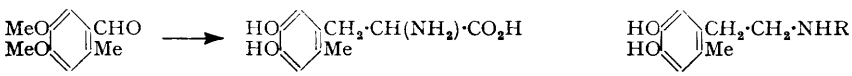
(I) (III) (II) (IV)

potassium cyanide into the corresponding cyanide (VII). Hydrogenation of (VII) gave 2-(2 : 4 : 5-trimethoxy-3 : 6-dimethylphenyl)ethylamine, demethylated by hydrobromic acid to the corresponding trihydroxy-amine (VIII). On oxidation with potassium ferricyanide this gave 5 : 6-dihydroxy-4 : 7-dimethylindole (IX) in good yield.



(V) (VI) (VII) (VIII) (IX)

The remaining monomethylated 3 : 4-dihydroxyphenylalanine, *i.e.*, β-(4 : 5-dihydroxy-2-methylphenyl)alanine (X) has now been prepared by a method similar to that employed for the other two, starting from 4 : 5-dimethoxy-2-methylbenzaldehyde. The corresponding amine, 2-(4 : 5-dihydroxy-2-methylphenyl)ethylamine (XI; R = H) and its *N*-benzyl derivative (XI; R = benzyl) have also been synthesised *via* 4 : 5-dimethoxy-2-methyl-β-



(X) (XI)

nitrostyrene. On oxidation with potassium ferricyanide or silver oxide none of the last three compounds gave any indole derivative : the methyl group of course prevents cyclisation to a 5 : 6-dihydroxyindole and it is particularly significant that the alternative cyclisation to give a 6 : 7-dihydroxyindole does not occur. This indicates that the product obtained by oxidation of (II) is in fact (IV) and not a 6 : 7-dihydroxyindole. Evidently the methyl group does not provide sufficient steric hindrance to prevent condensation at the position *ortho* to it, though it should be noted that the yield in this case is low.

Experimental

5 : 6-*Dihydroxy*-4-*methylindole* (III).—To a solution of β-(3 : 4-dihydroxy-2-methylphenyl)-alanine monohydrate (Cromartie and Harley-Mason, *J.*, 1952, 1052) (0·46 g., 0·002 mole) and sodium hydrogen carbonate (0·17 g., 0·002 mole) in water (8 c.c.), potassium ferricyanide (2·56 g., 0·008 mole), and sodium hydrogen carbonate (0·7 g., 0·008 mole) in water (30 c.c.) were added. A brisk evolution of carbon dioxide occurred and the solution became deep red. After 20 min. a solution of zinc sulphate (6 g.) in water (16 c.c.) was added and the mixture shaken until the red colour had faded to a greyish-brown (about 15 min.). After addition of a little sodium dithionite to prevent oxidation, the zinc ferrocyanide was filtered off and washed well with water. The combined filtrate and washings were extracted with ethyl acetate (3 × 30 c.c.), the extract was dried over alkali-free sodium sulphate, and the solvent removed under hydrogen. The residue was sublimed at 0·001 mm., most of the product coming over at 180—190°, though a further small fraction was obtained at 250°. Resublimation afforded 5 : 6-*dihydroxy*-4-*methylindole* (0·13 g., 40%) as colourless needles, m. p. 146—149° (decomp.) (Found : C, 66·6; H, 5·7; N, 8·7. $C_9H_9O_2N$ requires C, 66·3; H, 5·5; N, 8·6%). The material gave a violet Ehrlich reaction and slowly decomposed.

5 : 6-*Dihydroxy*-7-*methylindole* (IV).—β-(3 : 4-Dihydroxy-5-methylphenyl)alanine monohydrate (0·46 g.) (Cromartie and Harley-Mason, Part IV, *loc. cit.*) was oxidised as described above, giving a deep violet solution, which was treated with zinc sulphate and worked up as above. 5 : 6-*Dihydroxy*-7-*methylindole* (0·04 g., 12%) formed colourless needles, m. p. 108—109°, giving a violet Ehrlich reaction (Found : C, 66·1; H, 5·3; N, 8·7%). The material was less stable than the 4-methyl isomer and rapidly decomposed to a black mass.

2 : 4 : 5-*Trimethoxy*-3 : 6-*dimethylbenzyl Cyanide*.—Triacetoxy-*p*-xylene (Erdtman, *Proc. Roy. Soc.*, 1934, *A*, **143**, 177) (27 g., 0·1 mole) and 20% aqueous sodium hydroxide solution (200 c.c.) were boiled for 30 min. under nitrogen. Into the solution thus obtained were run alternately methyl sulphate (140 c.c., 1·5 mole) and 20% aqueous sodium hydroxide (300 c.c.) in small portions during 5 hr. After a further 2 hours' boiling the mixture was diluted with water and extracted with ether (2 × 500 c.c.). The extract was dried (Na_2SO_4) and the solvent removed, leaving an oil which was distilled under reduced pressure. *Trimethoxy*-p-*xylene* (10·5 g., 56%) formed an almost colourless oil, b. p. 135°/22 mm. (Found : C, 67·5; H, 8·5. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·1%).

Trimethoxy-*p*-xylene (7 g.), 40% formaldehyde solution (30 c.c.), and concentrated hydrochloric acid (50 c.c.) were mixed and saturated with hydrogen chloride at 0°. The homogeneous solution thus obtained was heated at 50—60° for 4 hr. and then kept overnight at 0°. The oil which separated solidified to a waxy mass of 2 : 4 : 5-trimethoxy-3 : 6-dimethylbenzyl chloride (8 g., 93%) which was collected and washed. The chloride (7·5 g.) was boiled for 3 hr. under reflux with potassium cyanide (22 g.) in water (40 c.c.) and ethanol (150 c.c.). The mixture was then poured on crushed ice, and the brownish solid collected and twice recrystallised (charcoal) from light petroleum (b. p. 40—60°), giving 2 : 4 : 5-*trimethoxy*-3 : 6-*dimethylbenzyl cyanide* (3·7 g., 52%), colourless prisms, m. p. 62° (Found : C, 66·1; H, 7·5; N, 6·0. $C_{13}H_{17}O_3N$ requires C, 66·3; H, 7·5; N, 6·0%).

5 : 6-*Dihydroxy*-4 : 7-*dimethylindole* (IX).—The foregoing cyanide (3·2 g.), dissolved in dry ethanol (70 c.c.) saturated with ammonia, was hydrogenated over Raney nickel at 75°/100 atm. for 10 hr. The filtered solution was evaporated to dryness, the residue dissolved in dry ethanol, and hydrogen chloride passed in, precipitating 2-(2 : 4 : 5-*trimethoxy*-3 : 6-*dimethylphenyl*)-*ethylamine hydrochloride* (2·5 g.), which after recrystallisation from ethanol–ether formed needles m. p. 266—267° (decomp.) (Found : C, 57·1; H, 8·4; N, 5·0. $C_{13}H_{22}O_3NCl$ requires C, 56·6; H, 8·0 : N, 5·1%).

The hydrochloride (1·5 g.) was refluxed for 1 hr. with hydrobromic acid (*d* 1·49; 10 c.c.). After being kept overnight at 0°, the dark solid was collected and twice recrystallised (charcoal) from ethanol–ether, giving 2-(2 : 4 : 5-*trihydroxy*-3 : 6-*dimethylphenyl*)*ethylamine hydrobromide* (1·1 g.) as small prisms, m. p. 227—228° (decomp.) (Found : C, 42·8; H, 5·6. $C_{10}H_{16}O_3NBr$ requires C, 43·2; H, 5·8%). To a solution of the hydrobromide (10·37 g.) in water (25 c.c.), a solution of potassium ferricyanide (0·8 g.) and sodium hydrogen carbonate (0·34 g.) in water (20 c.c.) was added. The intensely violet solution which resulted was kept for 24 hr. under hydrogen, the colour fadlng considerably. After addition of a little sodium dithionite, the solution was extracted with ethyl acetate (2 × 40 c.c.), the extract dried (Na_2SO_4), and the solvent removed.

The greyish solid residue was sublimed at 150°/0·01 mm. Resublimation of the product at 130°/0·001 mm. gave 5 : 6-*dihydroxy*-4 : 7-*dimethylindole* (0·14 g., 60%) as colourless needles, m. p. 170° (preheated bath; decomp.) (Found : C, 68·5; H, 6·6; N, 8·0. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·3; N, 7·9%). The solid was more stable than either of the monomethylated compounds; with Ehrlich's reagent a deep blue colour was given.

β-(4 : 5-*Dihydroxy*-2-*methylphenyl*)*alanine* (X).—4-(4 : 5-Dimethoxy-2-methylbenzylidene)-2-phenyloxazolone (Sugasawa and Shigehara, *Ber.*, 1941, **74**, 459) (12·5 g.) in ethanol (90 c.c.) was heated on a water-bath with 5% aqueous sodium hydroxide (90 c.c.). After cooling, the pale yellow solution was treated slowly with 20% hydrochloric acid until no more solid was precipitated. α-*Benzamido*-4 : 5-*dimethoxy*-2-*methylcinnamic acid* was collected and recrystallised from aqueous ethanol, giving cream-coloured needles (11·5, 87%), m. p. 212—214° (decomp.) (Found : C, 66·7; H, 5·8. $C_{19}H_{19}O_5N$ requires C, 66·9; H, 5·6%).

A solution of the foregoing acid (4·5 g.) in N-sodium hydroxide (160 c.c.) was diluted to 600 c.c. and hydrogenated over Raney nickel at room temperature and 80 atm. After filtration, the solution was acidified and kept overnight at 0°. The precipitate was collected and recrystallised from ethanol, giving α-*benzamido*-β-(4 : 5-*dimethoxy*-2-*methylphenyl*)*propionic acid* (3·8 g., 85%) as fine colourless needles, m. p. 203° (preheated bath) with decomposition to a bright yellow melt (Found : C, 66·2; H, 6·3. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·1%).

The foregoing acid (0·75 g.) was refluxed for 75 min. with hydrobromic acid (*d* 1·49; 10 c.c.). The cooled solution was diluted with water and extracted with ether to remove benzoic acid. The aqueous layer was evaporated to dryness under hydrogen, the residue dissolved in water, and the evaporation repeated to remove the last traces of hydrobromic acid. The pale buff crystalline residue was dissolved in water (8 c.c.) and brought to pH 5 by dropwise addition of pyridine. Evaporation at room temperature gave a syrup to which ethanol (10 c.c.) was added. Insoluble impurities were removed by filtration and the filtrate slowly deposited the amino-acid. Recrystallised from water containing sulphur dioxide, 4 : 5-*dihydroxy*-2-*methylphenyl*-*alanine* (0·23 g., 46%) formed colourless prisms, probably a hydrate, dehydrated at 100° in a vacuum to the anhydrous acid, m. p. 269° with effervescence (Found: C, 56·5; H, 6·0; N, 6·8. $C_{10}H_{13}O_4N$ requires C, 56·8; H, 6·2; N, 6·6%).

4 : 5-*Dihydroxy*-2-*methylphenylethylamine*.—A solution of 4 : 5-dimethoxy-2-methylbenzaldehyde (Gattermann, *Annalen*, 1907, **357**, 370) (12 g.), nitromethane (6 g.), and ammonium acetate (3 g.) in acetic acid (70 c.c.) was refluxed for 2 hr. and then poured into water. The precipitated product was collected and recrystallised from ethanol, giving 4 : 5-*dimethoxy*-2-*methyl*-β-*nitrostyrene* (8 g.) as deep golden-yellow needles, m. p. 155° (Found: C, 59·3; H, 5·9. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·8%). The nitrostyrene (8 g.) was placed in a Soxhlet thimble and extracted under reflux into a solution of lithium aluminium hydride (5·5 g.) in ether (400 c.c.) during 10 hr. The mixture was decomposed with sodium potassium tartrate solution, the ethereal layer separated and dried (KOH), and the solvent removed, leaving 4 : 5-dimethoxy-2-methylphenylethylamine (5·8 g., 83%) as a wax. A portion was converted into the *hydrochloride*, which formed prisms, m. p. 181—182·5°, from ethanol–ether (Found: C, 57·2; H, 7·9. $C_{11}H_{18}O_2NCl$ requires C, 57·0; H, 7·8%). The amine (1 g.) was refluxed with hydrobromic acid (*d* 1·49; 10 c.c.) for 1 hr., and the resulting solution kept overnight at 0°. The dark solid which had separated was collected and twice recrystallised (charcoal) from ethanol–ether, giving β-(4 : 5-*dihydroxy*-2-*methylphenyl*)*ethylamine hydrobromide* (0·75 g.) as pale brown needles m. p. 213—216° (decomp.) (Found: C, 43·5; H, 5·6. $C_9H_{14}O_2NBr$ requires C, 43·5; H, 5·6%).

N-*Benzyl*-β-(4 : 5-*dihydroxy*-2-*methylphenyl*)*ethylamine*.—A mixture of the above dimethoxy-amine (1·5 g.) and freshly distilled benzaldehyde (0·9 c.c.) was heated on the steam-bath for 45 min. and then kept overnight in a vacuum-desiccator. The resulting solid Schiff's base in ethanol (30 c.c.) was hydrogenated over Raney nickel at room temperature and 80 atm. for 5 hr. The filtered solution was concentrated and hydrogen chloride passed in. Addition of ether precipitated *N*-benzyl-β-(4 : 5-dimethoxy-2-methylphenyl)ethylamine hydrochloride. The crude hydrochloride (1 g.) was demethylated as in the preceding case. N-*Benzyl*-β-(4 : 5-*dihydroxy*-2-*methylphenyl*)*ethylamine hydrobromide* formed prisms, m. p. 152—153° (Found: C, 56·5; H, 5·9. $C_{16}H_{20}O_2NBr$ requires C, 56·8; H, 5·9%).

Oxidation Experiments.—4 : 5-Dihydroxy-2-methylphenylalanine was oxidised with potassium ferricyanide under the conditions described above for the other dihydroxyphenylalanines. An orange-red solution was obtained, which was, however, not decolorised on the addition of zinc sulphate. The ethyl acetate extract gave only a trace of solid on evaporation and gave a negative Ehrlich reaction. The dihydroxy-amines above behaved similarly and no trace of an indole derivative could be detected.

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