186. *Melanin and its Precursors. Part IV.* Synthesis of β-3 : 4-Dihydroxy-2- and -5-methylphenylalanine.*

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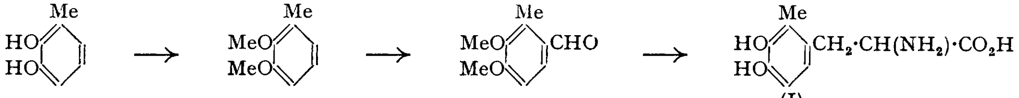
β-3 : 4-Dihydroxy-2- and -5-methylphenylalanine have been synthesised by conventional methods starting from 3-methylcatechol and *o*-vanillin respectively.

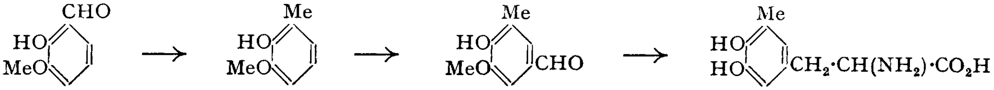
In Part III * the conversion of β-3 : 4-dihydroxyphenylalanine into 5 : 6-dihydroxyindole was described. In this paper the synthesis of β-3 : 4-dihydroxy-2- (I) and -5-methylphenylalanine (II) are described : their conversion into methylated 5 : 6-dihydroxyindoles will be recorded later.

3-Methylcatechol requires a large excess of methyl sulphate for conversion into the dimethyl ether, the hydroxyl group *ortho* to the methyl group apparently being sterically hindered. Treatment of the dimethyl ether with hydrogen cyanide and aluminium chloride gave 3 : 4-dimethoxy-2-methylbenzaldehyde, first obtained from cryptopine (Perkin, *J.*, 1916, **109**, 915); the derived azlactone was ring-opened by sodium hydroxide to give α-benzamido-3 : 4-dimethoxy-2-methylcinnamic acid, which with boiling hydriodic acid and red phosphorus afforded the amino-acid (I).



(I)

o-Vanillin was reduced to 3-methylcatechol 1-methyl ether by a modification of Koetschet's method (*Helv. Chim. Acta*, 1930, **13**, 476) and converted into 4-hydroxy-3-methoxy-5-methylbenzaldehyde as described by the same author. This aldehyde was converted into an azlactone with hippuric acid and acetic anhydride, the phenolic hydroxyl group being acetylated in the process. Treatment with sodium acetate in ethanol effected ring-opening and esterification, giving ethyl 4-acetoxy-α-benzamido-3-methoxy-5-methylcinnamate which with hydriodic acid and red phosphorus gave the amino-acid (II).



(II)

Experimental

2 : 3-*Dimethoxytoluene*.—To a boiling solution of 3-methylcatechol (62 g.) and sodium hydroxide (200 g.) in water (800 c.c.) methyl sulphate (266 g.) was added slowly under nitrogen. After the addition was complete, boiling was continued for 2 hours and then a further amount of methyl sulphate (266 g.) added as before. After a further 2 hours' boiling the mixture was cooled and extracted with ether, the extract dried, and the solvent removed. The residual 2 : 3-dimethoxytoluene (52 g.) distilled at 56—60°/1 mm.

3 : 4-*Dimethoxy*-2-*methylbenzaldehyde*.—Finely powdered aluminium chloride (28 g.) was covered with benzene (20 c.c.) and cooled in ice while 2 : 3-dimethoxytoluene (25 g.) was added slowly with stirring. A solution of anhydrous hydrogen cyanide (17·5 g.) in benzene (25 c.c.) was then added. A slow stream of hydrogen chloride was passed into the mixture, which was warmed under reflux in a thermostatic bath kept at 30°, for 8 hours. The mixture was decomposed with concentrated hydrochloric acid (100 c.c.) and ice (200 g.) and then boiled to remove excess of hydrocyanic acid. After cooling, the mixture was extracted with ether (2 × 250 c.c.), and the ethereal solution shaken with sodium hydrogen sulphite solution. When the sulphite solution was made alkaline, 3 : 4-dimethoxy-2-methylbenzaldehyde (20 g.) was precipitated. Recrystallisation from light petroleum (b. p. 40—60°) gave long colourless needles, m. p. 50° (Found : C, 67·1; H, 6·9. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%; Perkin (*loc. cit.*) gives m. p. 52—53°. The oxime formed colourless needles from light petroleum (b. p. 60—80°), m. p.

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96° (Found: C, 62·1; H, 6·9. Calc. for $C_{10}H_{13}O_3N$: C, 61·6; H, 6·7%); Perkin (*loc. cit.*) gives m. p. 98—99°.

β-3 : 4-*Dihydroxy-2-methylphenylalanine* (I).—3 : 4-Dimethoxy-2-methylbenzaldehyde (10 g.), hippuric acid (10·5 g.), anhydrous sodium acetate (4·8 g.), and acetic anhydride (18 c.c.) were mixed and heated at 100° for 2 hours. Ethanol (25 c.c.) was then added with stirring and the mixture kept overnight at 0°. The 4-(3 : 4-*dimethoxy-2-methylbenzylidene*)-2-*phenyloxazolone* (10·5 g.) which had separated was collected and washed with a little cold ethanol and then with boiling water. Recrystallisation from benzene–light petroleum afforded bright yellow prisms, m. p. 246° (Found: C, 70·8; H, 5·3. $C_{19}H_{17}O_4N$ requires C, 70·6; H, 5·3%).

To a solution of the oxazolone (9 g.) in warm ethanol (22 c.c.) 5% sodium hydroxide solution (22 c.c.) was added and the mixture heated for 15 minutes at 100°. After cooling, 20% hydrochloric acid was added until the solution was just acid to litmus and after 3 hours the precipitated α-*benzamido*-3 : 4-*dimethoxy-2-methylcinnamic* acid (7·5 g.) was collected and recrystallised from aqueous ethanol, giving colourless plates, m. p. 226—228° (decomp.) (Found: C, 67·3; H, 6·0. $C_{19}H_{19}O_5N$ requires C, 66·9; H, 5·6%).

The foregoing acid (11·2 g.) was boiled under reflux for 2½ hours with acetic anhydride (67 c.c.), hydriodic acid (*d* 1·7; 67 c.c.), and red phosphorus (6·7 g.). After cooling, water (120 c.c.) was added and the phosphorus filtered off. The solution was extracted with ether (3 × 100 c.c.) to remove benzoic acid and iodine and then evaporated to dryness in a vacuum. Water (200 c.c.) was added to the residue and the evaporation repeated. The last traces of hydriodic acid were removed at 100° in a high vacuum. The crystalline residue was dissolved in water (40 c.c.) and adjusted to pH 5 by addition of saturated sodium acetate solution. A little sodium dithionite was added to retard oxidation and after 4 hours a small amount of amorphous precipitate was filtered off. The filtrate was allowed to evaporate slowly in a vacuum-desiccator, β-3 : 4-*dihydroxy-2-methylphenylalanine* (3·5 g.) crystallising during several days. The acid recrystallised from water containing sulphur dioxide as small colourless plates, m. p. 186—192° (decomp.), containing a molecule of water of crystallisation not removed at 70°/1 mm. (24 hours) (Found: C, 52·5; H, 6·6; N, 6·2. $C_{10}H_{13}O_4N,H_2O$ requires C, 52·4; H, 6·55; N, 6·1%).

3-*Methylcatechol* 1-*Methyl Ether*.—Amalgamated zinc (150 g.) was placed in a flask fitted with a Vigreux column and condenser and two dropping funnels. The zinc was covered with a mixture of concentrated hydrochloric acid and water (2 : 1), and the mixture boiled so that slow distillation occurred. *o*-Vanillin (45 g.) heated to just above its m. p. was run in from one funnel at the same rate as the product distilled and hydrochloric acid of the same strength added from the other funnel as required. Distillation was continued until no more oily drops poured over (about 5 hours). The distillate was extracted with ether, the ethereal solution shaken with sodium hydrogen sulphite solution to remove *o*-vanillin, and dried, and the ether removed, leaving 3-methylcatechol 1-methyl ether (35 g.) as large prisms.

β-3 : 4-*Dihydroxy-5-methylphenylalanine* (II).—4-Hydroxy-3-methoxy-5-methylbenzaldehyde (Koetschet, *loc. cit.*) (8·5 g.), hippuric acid (10·3 g.), anhydrous sodium acetate (4·4 g.), and acetic anhydride (25 c.c.) were heated at 100° for 2 hours. Ethanol (25 c.c.) was then added and the whole kept overnight at 0°. 4-(4-*Acetoxy-3-methoxy-5-methylphenyl*)-2-*phenyloxazolone* (9·5 g.) which had separated was collected and washed with a little ethanol and then with boiling water. Recrystallisation from ethanol afforded yellow plates, m. p. 164—165° (Found: C, 68·2; H, 5·0. $C_{19}H_{17}O_5N$ requires C, 67·2; H, 5·0%).

The oxazolone (13·5 g.), fused sodium acetate (6 g.), and absolute ethanol (300 c.c.) were boiled under reflux for 3 hours. The cooled solution was poured into water (1 l.) and kept overnight at 0°. The *ethyl 4-acetoxy-α-benzamido-3-methoxy-5-methylcinnamate* (11·2 g.) which had separated was collected and formed colourless plates (from ethyl acetate–light petroleum), m. p. 142° (Found: C, 66·1; H, 6·0. $C_{22}H_{23}O_6N$ requires C, 66·5; H, 5·8%). The ester (8·7 g.), hydriodic acid (*d* 1·7; 53 c.c.), acetic anhydride (53 c.c.), and red phosphorus (5·3 g.) were refluxed for 2·5 hours and worked up as described above for the isomeric acid, to give β-3 : 4-*dihydroxy-5-methylphenylalanine* (2 g.) which decomposed without melting above 180° (Found: C, 52·7; H, 6·5; N, 5·8. $C_{10}H_{13}O_4N,H_2O$ requires C, 52·4; H, 6·55; N, 6·1%).

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