441. *The Chemistry of the Melanins. Part II. The Synthesis of 5 : 6-Dihydroxyindole-2-carboxylic Acid and Related Compounds.*

By R. J. S. Beer, L. McGrath, Alexander Robertson, and A. B. Woodier.

In continuation of studies on melanin and its precursors the syntheses of 5 : 6-dihydroxyindole-2-carboxylic acid, 6 : 7-dihydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole, and of 5 : 6-dihydroxy-3-phenyl-, 5 : 6-dihydroxy-3-methyl-, and 5 : 6-dihydroxy-2 : 3-dimethyl-indole are described. In faintly alkaline solution the behaviour of these compounds differs from that of 5 : 6-dihydroxyindole (Part I, *J.*, 1948, 2223).

The results of preliminary experiments on the autoxidation of 5 : 6-dihydroxyindole with the objective of defining the nature of the polymerisation process are recorded.

Both 5 : 6-dihydroxyindole and its 2-carboxylic acid have been regarded by Raper (*J.*, 1938, 125) as melanin precursors in the tyrosinase-catalysed oxidation of tyrosine. We have recently shown (Part I, *J.*, 1948, 2223) that the properties of authentic 5 : 6-dihydroxyindole, prepared by an unambiguous synthetical route, are consistent with this view and it seems probable from the spectrophotometric investigations of Mason (*J. Biol. Chem.*, 1948, **172**, 83) that the immediate melanin precursor in the conversion of tyrosine into melanin is the dihydroxyindole and not the carboxylic acid. In continuation of our synthetical approach to the melanin problem, we have now prepared 5 : 6-*dihydroxyindole*-2-*carboxylic acid* by a modification of the well-known general synthesis which proceeds through an *o*-nitrophenylpyruvic acid.


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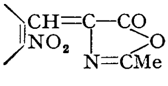
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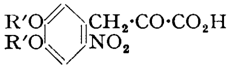
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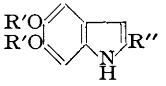
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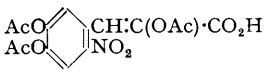
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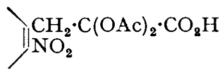

(V*a*.)

2-Nitroprotocatechualdehyde (I) was converted by way of a *monoacetate* of the azlactone (II) into 2-nitro-4 : 5-dihydroxyphenylpyruvic acid (III; $R' = H$), which was characterised by formation of the *oxime*. Attempts to acetylate this pyruvic acid with acetic anhydride and sodium acetate resulted in the formation of intractable products but with a mixture of acetic anhydride and sulphuric acid at room temperature the required 2-*nitro*-4 : 5-*diacetoxyphenylpyruvic acid* (III; $R' = Ac$) was obtained. When, however, the latter reaction was carried out at about 100° a different product was formed which, since it does not give the usual ferric reaction common to phenylpyruvic acids, may well be the triacetyl derivative (V) although the alternate possibility (V*a*) is not excluded.

Reductive cyclisation of the diacetate (III; $R' = Ac$) to 5 : 6-*diacetoxyindole*-2-*carboxylic acid* (IV; $R' = Ac$, $R'' = CO_2H$) was effected by treatment of the compound with iron powder and a mixture of acetic acid and ethanol, a modification of the normal procedure (first used by K. Clarke of this Department; unpublished work) which employs ferrous sulphate and aqueous ammonia. The reduction in acetic acid was preferred in order to avoid deacetylation of the initial compound and because of the marked sensitivity of the hydroxyindole derivatives already synthesised to alkaline reagents (Part I, *loc. cit.*). 5 : 6-Diacetoxyindole-2-carboxylic acid reacted normally with ethereal diazomethane to give the corresponding *methyl* ester.

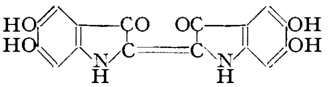
Prepared by deacetylation of the diacetate by the sodium hydroxide–sodium hydrosulphite (dithionite) method employed in the synthesis of dihydroxyindole (Part I, *loc. cit.*), 5 : 6-dihydroxyindole-2-carboxylic acid (IV; $R' = H$, $R'' = CO_2H$) proved to be a remarkably stable compound whose behaviour in faintly alkaline aqueous solution (*i.e.*, very dilute sodium hydrogen carbonate) is in striking contrast to that of 5 : 6-dihydroxyindole. With the acid, oxidation occurs only very slowly, giving in the course of 24 hours a dark brown solution but not an insoluble precipitate of the melanin type. Thus it seems unlikely that 5 : 6-dihydroxyindole-2-carboxylic acid is a melanin precursor, although it may be argued that in the presence of tyrosinase, oxidation to an insoluble melanin would occur. A study of the action of tyrosinase on this and other dihydroxyindoles will form the subject of a later paper in this series. In the meantime Professor C. E. H. Bawn and Mr. A. G. White of this University are engaged on a comprehensive quantitative study of the oxidative polymerisation of 5 : 6-dihydroxyindole. From their preliminary experiments they have reported the following observations :

" Preliminary experiments on the autoxidation of 5 : 6-dihydroxyindole in phosphate buffer solution have been carried out with the primary object of establishing the stoicheiometry of the process, and also to obtain information on the kinetics in the hope that this would be of some assistance in the elucidation of the mechanism of the polymeric reaction involved.

" The uptake of oxygen was found to be of the type usually associated with oxidative chain reactions. Initially there was an induction period during which no uptake of oxygen was observable, but once oxygen uptake had commenced the rate of absorption rapidly became constant until a large part of the total had been absorbed when it decreased rapidly to zero. On dissolving the dihydroxyindole in the phosphate buffer solution used as solvent there was no apparent change for some minutes, after which a violet coloration developed, rapidly deepening until eventually a black precipitate was formed. It was noted that the appearance of the violet coloration coincided approximately with the end of the induction period in the oxygen uptake experiments.

" From a study of the data so far obtained it is clear that the results are not readily reproducible and there is evidence of the reaction being susceptible to trace-metal catalysis."

In recent years a number of workers have speculated on the structure of melanin produced from 5 : 6-dihydroxyindole. Clemo and Weiss (*J.*, 1945, 702) have suggested, for example, that the oxidation involves the formation of tetrahydroxyindigotin (VI), but this now appears unlikely in view of the properties of the 5 : 6 : 5′ : 6′-tetrahydroxyindigotin prepared by Harley-Mason (*J.*, 1948, 1244). Cohen (*Bull. Soc. Chim. biol.*, 1946, **28**, 104, 107, 354) has indicated the possibility that the polymerising intermediate may be 3-hydroxyindole-5 : 6-quinone (VII), which would have a reactive methylene group and may therefore be capable of self-condensation. On the basis of analytical results obtained for melanins formed enzymically, Burton (*Chem. and Ind.*, 1947, 383) has proposed the empirical formula $C_{16}H_{10}O_5N_2$ for the melanin from tyrosine and in a later paper (*ibid.*, 1948, 313) this author has tried to account for his formula by postulating diphenylene oxide structures (*e.g.*, type VIII) as being possible intermediates, although it is admitted that further dehydrogenative coupling would lead to a polymer with a lower hydrogen content.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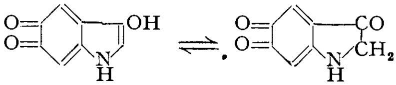
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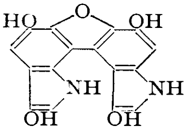
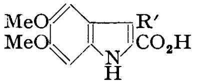

(VIII.)

The foregoing speculations involve the introduction of a hydroxyl-group into the β-position of the 5 : 6-dihydroxyindole nucleus, a process which is not altogether unlikely in view of the known tendency of indole itself to undergo oxidation in this position (compare Clemo and Weiss, *loc. cit.*). For this reason, it seemed to us a matter of some interest to study the properties and, in particular, the behaviour on oxidation of 5 : 6-dihydroxyindoles in which the β-position was already blocked by a substituent.

Since Hoshino and Shimodaira (*Bull. Chem. Soc. Japan*, 1936, **11**, 221) were able to demethylate bufotenin methyl ether (a β-substituted indole) with aluminium chloride, it appeared that this method might be applied to the preparation of the desired β-substituted 5 : 6-dihydroxyindoles, type (XI), from the corresponding dimethyl ethers (X).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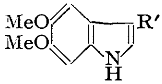
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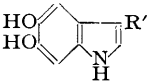

(XI.)

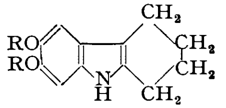
Both 5 : 6-*dimethoxy*-3-*phenyl*- (X; R′ = Ph) and 5 : 6-*dimethoxy*-3-*methyl-indole* (X; R′ = Me) were prepared by decarboxylation of the corresponding 2-carboxylic acids, which are readily available as a result of the work of Lions and Spruson (*J. Proc. Roy. Soc. N.S.W.*, 1932—1933, **66**, 171). The 3-phenylindole (X; R′ = Ph) was successfully demethylated by treatment with aluminium chloride in boiling benzene, giving 5 : 6-*dihydroxy*-3-*phenylindole* (XI; R′ = Ph) but when demethylation of the 3-methylindole (X; R′ = Me) was attempted, with either aluminium chloride or bromide under similar conditions, only traces of impure alkali-soluble products were isolated. It was subsequently found that 5 : 6-dimethoxy-3-methylindole-2-carboxylic acid (IX; R′ = Me) could be satisfactorily demethylated with aluminium bromide and on being heated in a high vacuum the resulting 5 : 6-dihydroxy-3-methylindole-2-carboxylic acid, which could not be satisfactorily purified, readily underwent decarboxylation yielding 5 : 6-*dihydroxy*-3-*methylindole* (XI; R′ = Me).

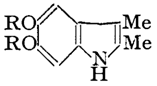
5 : 6-Dihydroxy-3-phenylindole proved to be so sparingly soluble in water that its sensitivity to aerial oxidation in faintly alkaline solution could not be satisfactorily determined. 5 : 6-Dihydroxy-3-methylindole, however, is more readily soluble, and when its aqueous solution is made faintly alkaline by addition of a trace of dilute sodium hydrogen carbonate solution rapid oxidation occurs, leading to the formation of a highly pigmented precipitate. This oxidation process, however, appears to differ from oxidations of 5 : 6-dihydroxyindole and 5 : 6-dihydroxy-2-methylindole (Part I, *loc. cit.*) carried out under comparative conditions in that the latter compounds give purple or brownish-red solutions in the early stages of the oxidation and later black precipitates, whereas the 3-methylindole gives a transient pure blue solution which soon deposits a blue precipitate. Whilst the precise significance of these differences is not clear at present, the results suggest that the oxidation of 5 : 6-dihydroxy-3-methylindole proceeds by a route which is different from that of 5 : 6-dihydroxyindole itself. This would be true if the latter oxidation involved attack at the 3-position of the indole nucleus.

The concept of studying the process of melanin formation by investigating the sensitivity of substituted dihydroxy-indoles towards oxidation is not a new one. Thus Clemo and Weiss (*loc. cit.*) attempted the preparation of 5 : 6-dihydroxy-2 : 3-dimethylindole, by demethylenation of the related methylenedioxy-compound, in order to test their theory that the production of melanin was preceded by indigotin-formation.

We have studied the demethylation of 6 : 7-dimethoxy-1 : 2 : 3 : 4-tetrahydrocarbazole (XII; R = Me) and, subsequently, of 5 : 6-*dimethoxy*-2 : 3-*dimethylindole* (XIII; R = Me).

(XII.)





(XIII.)

In the former case, demethylation was accomplished in good yield with aluminium chloride in boiling benzene and the same product, 6 : 7-*dihydroxy*-1 : 2 : 3 : 4-*tetrahydrocarbazole* (XII; R = H), was obtained by the action of aluminium bromide on 6 : 7-methylenedioxytetrahydrocarbazole. The dihydroxytetrahydrocarbazole oxidises only slowly in faintly alkaline aqueous solution, giving eventually a brown solution but not apparently an insoluble melanin-like product.

5 : 6-Dimethoxy-2 : 3-dimethylindole, obtained by an adaption of the Fischer method used by Clemo and Weiss (*loc. cit.*) for the preparation of the corresponding methylenedioxy-compound, was successfully demethylated with aluminium bromide in hot benzene. The resulting 5 : 6-*dihydroxy*-2 : 3-*dimethylindole* (XIII; R = H) oxidised more rapidly in alkaline media than the above dihydroxytetrahydrocarbazole but again a highly insoluble polymer was not formed.

In the course of this work it was observed that when the dimethoxytetrahydrocarbazole (XII; R = Me), prepared by the method of Lions *et al.* (*J. Proc. Roy. Soc. N.S.W.*, 1937—1938, **71**, 428), was recrystallised from light petroleum and subsequently from light petroleum–ethyl acetate, a change to a new compound of higher melting point and decreased solubility occurred. From the analytical results obtained the new compound was found to have the empirical formula $C_{14}H_{17}O_4N$, having been formed by the addition of a molecule of oxygen to the tetrahydrocarbazole, and, since it liberated iodine from an acidified aqueous solution of potassium iodide and decomposed vigorously when heated, this product is regarded as a *peroxide* or *hydroperoxide* of 6 : 7-dimethoxytetrahydrocarbazole. A more detailed account of the studies on this topic will be submitted when experiments now in progress have been completed.

EXPERIMENTAL.

2-*Nitro*-4 : 5-*dihydroxyphenylpyruvic Acid* (III; R′ = H).—An intimate mixture of 2-nitro-4 : 5-dihydroxybenzaldehyde (1·0 g., Part I, *loc. cit.*), aceturic acid (1·0 g.), acetic anhydride (3 ml.), and fused sodium acetate (1·0 g.)was heated on the steam-bath for ½ hour. Treatment of the cooled reaction mixture with water then afforded a slightly sticky solid which was triturated with a very small amount of ethyl alcohol, leaving a *monoacetate* of 4-(2′-nitro-4′ : 5′-dihydroxyphenyl)-2-methyloxazol-5-one as a granular yellow powder (m. p. 134—138°; 1·2 g.) sufficiently pure for use in the next stage of the synthesis. A pure sample was prepared by crystallisation from ethanol and formed elongated yellow needles, m. p. 140—142° (Found : N, 8·9, 9·1. $C_{13}H_{10}O_7N_2$ requires N, 9·15%). This compound was readily soluble in dilute aqueous sodium hydroxide, giving an intense purple solution.

The azlactone (1·0 g.) was heated on the steam-bath with 1% hydrochloric acid (60 ml.) for 4 hours and the resulting 2-nitro-4 : 5-dihydroxyphenylpyruvic acid was isolated from the cooled and filtered solution by means of ether, being obtained as a light yellow gum (0·6 g.) which slowly crystallised. This acid was characterised by the formation of the *oxime* which separated from acetic acid in hemispherical clusters of colourless needles, m. p. 178—179° (Found : N, 10·7. $C_9H_8O_7N_2$ requires N, 10·9%).

2-*Nitro*-4 : 5-*diacetoxyphenylpyruvic Acid* (III; R′ = Ac).—On the addition of a small drop of concentrated sulphuric acid to a solution of 2-nitro-4 : 5-dihydroxyphenylpyruvic acid (0·6 g.) in acetic anhydride (2 ml.), which had been prepared at about 50° and then cooled to room temperature, the mixture became warm and darkened. 10 Minutes later water (6 ml.) was introduced and the product triturated, with cooling, until it solidified. Collected after 24 hours, the *diacetyl* derivative (0·6 g.) was sufficiently pure for use in the next stage and on recrystallisation from the minimum quantity of hot 95% alcohol a sample was obtained in bright yellow prisms, m. p. 154—155°, giving a green ferric reaction in alcohol (Found : N, 4·2. $C_{13}H_{11}O_9N$ requires N, 4·3%).

When this acetylation was effected on the steam-bath for 10 minutes, a different product was obtained which is presumably the *triacetyl* derivative (V). This compound crystallised from alcohol in colourless prisms (0·6 g.), m. p. 152° (depressed by admixture with the foregoing diacetate), and did not give a coloration with ferric chloride in alcohol (Found : N, 3·8. $C_{15}H_{13}O_{10}N$ requires N, 3·8. $C_{17}H_{17}O_{12}N$ requires N, 3·5%).

5 : 6-*Diacetoxyindole*-2-*carboxylic Acid* (IV; R′ = Ac, R″ = CO_2H).—A solution of 2-nitro-4 : 5-diacetoxyphenylpyruvic acid (2·0 g.) in a mixture of acetic acid (40 ml.) and alcohol (50 ml.) was warmed with iron powder (10 g.) until a reaction set in which was then maintained by occasional heating over a period of 12 minutes. The mixture was then filtered, the solid residue was washed with several small portions of hot alcohol, and the combined filtrate and washings were diluted with water and extracted repeatedly with ether. The dark brown semi-solid obtained by evaporation of the combined dried

extracts was washed with a little cold methanol and then crystallised from the same solvent, giving 5 : 6-*diacetoxyindole*-2-*carboxylic acid* in buff squat prisms (0·83 g.), m. p. 256° (decomp.) (Found: C, 56·3; H, 3·9. $C_{13}H_{11}O_6N$ requires C, 56·3; H, 4·0%). It was sparingly soluble in ether and benzene but more soluble in alcohol, acetone, or chloroform, and gave a negative test with Ehrlich's reagent. Formed by the action of diazomethane on either a suspension of the acid in ether or a solution in dioxan, the *methyl ester* crystallised from alcohol in slender colourless needles, m. p. 179° (Found: C, 58·0; H, 4·4; N, 4·8. $C_{14}H_{13}O_6N$ requires C, 57·7; H, 4·5; N, 4·8%).

5 : 6-*Dihydroxyindole*-2-*carboxylic Acid* (IV; R′ = H, R″ = CO_2H).—Deacetylation of 5 : 6-diacetoxyindole-2-carboxylic acid (0·2 g.) was effected by application of the sodium hydroxide–sodium hydrosulphite (dithionite) method already described for the hydrolysis of 5 : 6-diacetoxyindole (Part I, *loc. cit.*), with the modification that a larger quantity of acetic acid (2 ml.) was used to acidify the alkaline reaction mixture. The crude *dihydroxy*-compound (70 mg.) was isolated with ether and purified from dilute acetic acid, forming almost white elongated prisms which on being heated darkened at about 225°, and then melted at 234° (decomp.) (Found: C, 55·3; H, 3·7; N, 7·1. $C_9H_7O_4N$ requires C, 55·9; H, 3·6; N, 7·2%). This acid is readily soluble in alcohol and in warm acetic acid, acetone, or water, but is sparingly soluble in hot ether, chloroform or carbon tetrachloride. In alcoholic solution, the compound gives an intense indigo-blue coloration with ferric chloride but does not give a coloration with Ehrlich's reagent. The addition of a drop of aqueous sodium hydroxide to an aqueous-alcoholic solution of the indolecarboxylic acid containing sodium nitroprusside produces an orange coloration, changing to greenish-blue on acidification with dilute acetic acid. In an aqueous solution made slightly alkaline by addition of a trace of sodium hydrogen carbonate, this dihydroxyindole derivative is very much more stable than 5 : 6-dihydroxyindole itself and does not appear to undergo the characteristic rapid oxidative polymerisation leading to melanin-like pigments.

An attempted purification of 5 : 6-dihyroxyindole-2-carboxylic acid by sublimation in a high vacuum afforded a colourless crystalline product, m. p. 140°, identified as 5 : 6-dihyrodroxyindole.

5 : 6-*Dimethoxy*-3-*phenylindole* (X; R′ = Ph).—5 : 6-Dimethoxy-3-phenylindole-2-carboxylic acid (Lions and Spruson, *J. Proc. Roy. Soc. N.S.W.*, 1932—1933, **66**, 171) (1·6 g.) was decarboxylated by being heated in a vacuum at 0·2 mm. Evolution of carbon dioxide commenced at a bath temperature of 150° and 5 : 6-*dimethoxy*-3-*phenylindole* sublimed as a hard glass which on crystallisation from ligroin afforded colourless feathery needles (1·0 g.), m. p. 137° (Found: C, 75·9; H, 5·8. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 5·9%). This compound, which darkens on prolonged exposure to air, gives a blue-green coloration, changing to blue, with Ehrlich's reagent at room temperature.

5 : 6-*Dihydroxy*-3-*phenylindole* (XI; R′ = Ph).—A solution of the foregoing dimethoxyindole (0·67 g.) in benzene (18 ml.) was heated under reflux with aluminium chloride (3·83 g.) for 10 hours, cooled in an ice-bath, and treated with ice-cold dilute hydrochloric acid followed by ether. The two layers were separated, the aqueous layer was extracted with further portions of ether, and the ether–benzene extracts were combined, dried, and concentrated by gentle warming in a stream of nitrogen until crystallisation commenced. The crude *dihydroxy*-compound (0·45 g.) was recrystallised from acetic acid, forming colourless plates, m. p. 256° (decomp.), which gave a strong violet coloration with Ehrlich's reagent, a purple ferric chloride reaction in alcohol, and a sticky red picrate in benzene solution (Found: C, 74·5; H, 5·1; N, 6·3. $C_{14}H_{11}O_2N$ requires: C, 74·7; H, 4·9; N, 6·2%).

5 : 6-*Dimethoxy*-3-*methylindole* (X; R′ = Me).—On being heated in a high vacuum 5 : 6-dimethoxy-3-methylindole-2-carboxylic acid (Lions and Spruson, *loc. cit.*) (1·6 g.) sublimed with only partial decomposition, and decarboxylation was best effected by subjecting the compound to distillation in a vacuum at 20 mm., thus affording 5 : 6-*dimethoxy*-3-*methylindole* (1·05 g.) which crystallised from ligroin in clusters of colourless needles, m. p. 150° (Found: C, 68·9; H, 7·0. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8%). With Ehrlich's reagent this indole gave a bluish-green coloration, changing to blue on being kept. Attempts to demethylate this compound by the aluminium bromide method gave only low yields of impure products.

5 : 6-*Dihydroxy*-3-*methylindole* (XI; R′ = Me).—A solution of 5 : 6-dimethoxyindole-2-carboxylic acid (1·6 g.) in benzene (125 ml.) was heated under reflux with aluminium bromide (9·1 g.) for 5 hours and the product isolated by the procedure described for the preparation of 5 : 6-dihydroxy-3-phenylindole. Thus prepared, 5 : 6-dihydroxy-3-methylindole-2-carboxylic acid (0·65 g.) separated as a grey solid, m. p. 158° (decomp.), which could not be recrystallised satisfactorily. Addition of benzene to an ether solution gave a greyish precipitate, m. p. 158° (decomp.) (Found: C, 57·1; H, 4·4. Calc. for $C_{10}H_9O_4N$: C, 58·0; H, 4·4%).

The foregoing acid (0·25 g.) was decarboxylated by being heated in a high vacuum [130—150° (bath)/0·001 mm.] and the resulting crystalline sublimate of 5 : 6-*dihydroxy*-3-*methylindole* dissolved in hot benzene–light petroleum. On cooling, the solution deposited the indole in colourless micaceous plates (0·16 g.), m. p. 152° (Found: C, 66·3; H, 5·3. $C_9H_9O_2N$ requires C, 66·3; H, 5·5%). This compound, which gives a bluish-violet Ehrlich reaction, a deep blue coloration with alcoholic ferric chloride, and a red crystalline picrate in benzene, is readily soluble in alcohol, ethyl acetate, acetic acid, or benzene, and moderately soluble in water. In very dilute aqueous sodium hydrogen carbonate, the 5 : 6-dihydroxy-3-methylindole oxidises rapidly, the solution acquiring a pure blue tint in a few minutes and subsequently depositing a blue precipitate which becomes darker on being kept further. This blue substance is insoluble in the usual organic solvents and in 2N-sodium hydroxide.

6 : 7-*Dimethoxy*-1 : 2 : 3 : 4-*tetrahydrocarbazole* (XII; R = Me) *and its Peroxide*.—The tetrahydrocarbazole was prepared from chloro*cyclo*hexanone and 4-aminoveratrole by the method of Lions *et al.* (*J. Proc. Roy. Soc. N.S.W.*, 1937, **71**, 428). The yellow glass obtained by the distillation of the crude product in a vacuum was triturated with a little alcohol and the resulting white solid recrystallised from dilute alcohol, giving the carbazole in long colourless needles, m. p. 105—106° (Found: C, 72·6; H, 7·6. Calc. for $C_{14}H_{17}O_2N$: C, 72·7; H, 7·4%) (Lions *et al.*, *loc. cit.*, record m. p. 98°). When the yellow glass was solidified by trituration with light petroleum, the colourless product had m. p. 99°. Successive recrystallisations of this material, first from light petroleum (b. p. 60—80°; an ordinary commerical sample was used) and, subsequently from ethyl acetate–light petroleum (b. p. 60—80°), brought about a rise in melting point and a marked decrease in solubility. The product, which was finally obtained in

almost colourless needles, m. p. 118° (with vigorous gas evolution), liberated iodine from an acidified aqueous solution of potassium iodide and is therefore regarded as a *peroxide* or, more probably, a *hydroperoxide* of the tetrahydrocarbazole (Found: C, 64·1, 64·0; H, 6·6, 6·3; N, 5·8, 6·0. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5; N, 5·3%).

6 : 7-*Dihydroxy*-1 : 2 : 3 : 4-*tetrahydrocarbazole* (XII; R = H).—A solution of 6 : 7-dimethoxytetrahydrocarbazole (1·0 g., m. p. 105°) in benzene (50 ml.) was heated with aluminium chloride (6·1 g.) for 11 hours and, on isolation by the procedure already described, the resulting 6 : 7-*dihydroxytetrahydrocarbazole* (0·8 g.) was crystallised from benzene (charcoal) in an atmosphere of nitrogen, forming almost white prisms, m. p. 175°. The same product (0·55 g.), m. p. and mixed m. p. 175°, was obtained when 6 : 7-methylenedioxy-1 : 2 : 3 : 4-tetrahydrocarbazole (1·0 g.) (Clemo and Weiss, *loc. cit.*) was heated in benzene with aluminium bromide (6·0 g.) for 4½ hours (Found: C, 70·9; H, 6·3; N, 6·9. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4; N, 6·9%). 6 : 7-Dihydroxy-1 : 2 : 3 : 4-tetrahydrocarbazole is sparingly soluble in water and more soluble in ethanol, acetone, ether, and warm benzene. In alcoholic solution the compound gave a sepia coloration with ferric chloride whilst in very dilute aqueous sodium hydrogen carbonate it oxidised slowly giving a brown solution, but an insoluble melanin-like product was not formed even after prolonged storage.

(WITH J. S. E. HOLKER.)

5 : 6-*Dimethoxy*-2 : 3-*dimethylindole* (XIII; R′ = Me).—The method used was an adaptation of the procedure of Clemo and Weiss (*loc. cit.*) for the preparation of the corresponding methylenedioxy-compound. Sodium nitrite (2·8 g.) in water (28 ml.) was added in the course of 20 minutes to a mechanically stirred solution of 4-aminoveratrole (6·2 g.) in a mixture of concentrated hydrochloric acid (30 ml.) and water (32 ml.) maintained at −5°. The diazotised solution was then cooled to −15° and a solution of stannous chloride (22·4 g.) in concentrated hydrochloric acid (18 ml.) added during ½ hour, the temperature being allowed to rise to −10°. After having been kept at −10° for a further ½ hour, the resulting phenylhydrazine hydrochloride was collected and crystallised from alcohol, forming pale buff plates (5·5 g.), m. p. 164—165° (decomp.) (compare Perkin and Rubenstein, *J.*, 1926, 357, who give m. p. 162°).

A mixture of methyl ethyl ketone (3·0 ml.) and acetic acid (6 drops) was added to a solution of the foregoing phenylhydrazine hydrochloride (5·5 g.) and fused sodium acetate (2·4 g.) in absolute alcohol (70 ml.), and the mixture (protected from extraneous moisture) heated under reflux for 1½ hours. The filtered reaction mixture was cooled to 0°, saturated with dry hydrogen chloride, kept at 0° for ½ hour, and then heated under reflux for 1½ hours. Next day the solvent was evaporated under reduced pressure and the residue was washed with 2N-aqueous sodium hydroxide and then with water. From this material 5 : 6-*dimethoxy*-2 : 3-*dimethylindole* (1·80 g.) was isolated by repeated extraction with hot light petroleum (b. p. 80—100°) and recrystallised twice from aqueous acetone, forming long colourless prisms, m. p. 110·5° (Found: C, 70·1; H, 7·5. $C_{12}H_{15}O_2N$ requires C, 70·2; H, 7·4%). This indole gave a red crystalline picrate but not an Ehrlich reaction.

5 : 6-*Dihydroxy*-2 : 3-*dimethylindole* (XIII; R = H).—A solution of 5 : 6-dimethoxy-2 : 3-dimethylindole (0·8 g.), in dry thiophen-free benzene (90 c.c.), was heated under reflux with powdered aluminium bromide (4·6 g.) for 4½ hours, cooled, treated with crushed ice and concentrated hydrochloric acid, and extracted with peroxide-free ether. The ether and most of the benzene were removed from the dried extract by evaporation in a stream of dry nitrogen and 5 : 6-*dihydroxy*-2 : 3-*dimethylindole*, which separated as an almost colourless solid (0·52 g.), was purified by sublimation at 150°/0·001 mm., being obtained in long colourless needles, m. p. *ca.* 189° (decomp.—preheated bath) (Found: C, 67·7; H, 6·4. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·3%). The compound gave a brown coloration with alcoholic ferric chloride and oxidised fairly rapidly in dilute sodium hydrogen carbonate solution, giving a brownish-purple solution but a precipitate did not separate even after a long time.

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