450. *The Chemistry of the Melanins. Part III.* The Synthesis of Hydroxyindoles from* p-*Benzoquinones.*

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Nenitzescu's method for the synthesis of hydroxyindoles has been examined and extended to the synthesis of 5-hydroxy-2 : 6-dimethyl-, 5-hydroxy-6-methoxy-2-methyl-, 5 : 6-dihydroxy-2-methyl-, and 5 : 6-dihydroxy-2 : 4 : 7-trimethyl-indole.

The following indoles have also been synthesised by the nitrostyrene method : 5-hydroxy-6-methoxy-2-methyl-, 6-hydroxy-5-methoxy-2-methyl-, 6-hydroxy-7-methoxy-, 7-hydroxy-6-methoxy-, 6-hydroxy-7-methoxy-2-methyl-, and 7-hydroxy-6-methoxy-2-methyl-indole.

IN addition to the methods for the synthesis of hydroxyindoles described in earlier papers (*J.*, 1948, 1605, 2223; 1949, 2061) two other routes are available which differ fundamentally from the previous procedures, *viz.*, (1) the conversion of 2-(3 : 4-dihydroxyphenyl)ethylamines into 5 : 6-dihydroxyindoles by oxidation and subsequent rearrangement of the product (cf. Bu'Lock and Harley-Mason, *Nature*, 1950, **166**, 1036), and (2) the method of Nenitzescu (*Bull. Soc. Chim. Roumania*, 1929, **11**, 37) which is the subject of the present communication. This author observed that *p*-benzoquinone reacted readily with ethyl β-aminocrotonate and certain of its *N*-monosubstituted derivatives to give hydroxyindole esters to which he assigned structures of type (I) without, however, presenting evidence regarding their configurations.

From the product (I; R = CO_2Et) Nenitzescu (*loc. cit.*) obtained a poor yield of the acid (I; R = CO_2H) which on decarboxylation afforded the indole (I; R = H), the identity of which has now been confirmed by comparison with authentic 5-hydroxy-2-methylindole (*J.*, 1948, 1609). The low yield of the acid (I; R = CO_2H) has now been found to be due to decarboxylation by the hot reagent, and in this respect the hydroxyindole-3-carboxylic acids appear to be considerably less stable than the analogous 2-carboxylic acids. High yields of 5-hydroxy- and 5-methoxy-2-methylindole have been obtained by hydrolytic decomposition of the ester (I; R = CO_2Et) and its methyl ether with boiling aqueous or aqueous-alcoholic sodium hydroxide in nitrogen. By essentially the same procedure 5-hydroxy-2 : 6-dimethyl- (II; R = Me), 5-hydroxy-6-methoxy-2-methyl- (II; R = OMe), 5 : 6-dihydroxy-2-methyl- (II; R = OH) (*J.*, 1948, 2225), and 5 : 6-dihydroxy-2 : 4 : 7-trimethyl-indole (III) have been prepared respectively from methyl-, methoxy-, hydroxy-, and 2-hydroxy-3 : 6-dimethyl-*p*-

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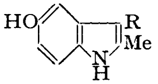
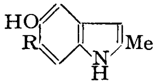
* Part II, *J.*, 1949, 2061.

benzoquinone. The orientation of (II; R = OMe) was established by its synthesis from 5-hydroxy-4-methoxy-2-nitrobenzaldehyde *via* the nitrostyrene (IV), a modification of the standard procedure being used. For comparison the isomeride, 6-hydroxy-5-methoxy-2-methylindole, was prepared from 4-hydroxy-5-methoxy-2-nitrobenzaldehyde.

In the preparation of 5-hydroxy-4-methoxy- and 4-hydroxy-5-methoxy-2-nitrobenzaldehyde the isomerides, 3-hydroxy-4-methoxy- and 4-hydroxy-3-methoxy-2-nitrobenzaldehyde, were obtained and from these latter compounds 7-hydroxy-6-methoxy- (V) and 6-hydroxy-7-methoxy-indole (VI) and their 2-methyl derivatives respectively have been synthesised by the nitrostyrene method; (VI) was also prepared by the azlactone route. For the condensation of the nitroaldehydes with nitro-methane or -ethane, ammonium acetate in hot acetic acid (method of Raiford and Fox, *J. Org. Chem.*, 1944, **9**, 170) was employed as the condensing agent in preference to alcoholic potassium hydroxide which fails in the case of 4-hydroxy-3-methoxy-2-nitrobenzaldehyde.



(I.)



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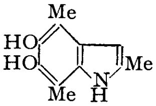

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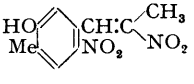

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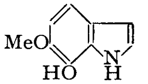

(V.)

(VI.)

EXPERIMENTAL.

5-*Hydroxy*-4-*methoxy*-β-*methyl*-β : 2-*dinitrostyrene*.—*iso*Vanillin (Robinson and Sugasawa, *J.*, 1931, 3167) was nitrated by Pschorr's method (*Ber.*, 1902, **35**, 4396), giving 3-hydroxy- and 5-hydroxy-4-methoxy-2-nitrobenzaldehyde. The latter compound (1 g.) was heated under reflux with acetic acid (5 ml.), nitroethane (0·6 ml.), and ammonium acetate (0·4 g.) for 2 hours. On dilution with water the resulting dark brown solution deposited a dirty yellow solid which was well washed with water and crystallised from dilute alcohol, giving 5-*hydroxy*-4-*methoxy*-β-*methyl*-β : 2-*dinitrostyrene* in brown prisms (0·8 g.), m. p. 188—189° (Found : N, 10·8. $C_{10}H_{10}O_6N_2$ requires N, 11·0%).

5-*Hydroxy*-6-*methoxy*-2-*methylindole*.—A mixture of the foregoing β : 2-dinitrostyrene (0·5 g.), alcohol (7 ml.), acetic acid (7 ml.), and iron powder (2 g.) was heated under reflux for 10 minutes and then filtered, and the filtrate diluted with water, neutralised with sodium hydrogen carbonate, and extracted several times with ether. Evaporation of the combined ethereal extracts left a brown gum from which 5-*hydroxy*-6-*methoxy*-2-*methylindole* was isolated by extraction with boiling light petroleum (b. p. 60—80°). Crystallised from this solvent, the indole formed long, colourless needles (0·2 g.), m. p. 129°, readily soluble in the usual organic solvents except light petroleum and having a magneta Ehrlich and a red ferric reaction in alcohol (Found : C, 68·1; H, 6·6; N, 7·5. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2; N, 7·9%).

6-*Hydroxy*-5-*methoxy*-2-*methylindole*.—The condensation of 4-hydroxy-5-methoxy-2-nitrobenzaldehyde (Raiford and Stoesser, *J. Amer. Chem. Soc.*, 1928, **50**, 2559) (1 g.) with nitroethane (0·6 ml.) by the method employed for 5-hydroxy-4-methoxy-2-nitrobenzaldehyde gave rise to 4-*hydroxy*-5-*methoxy*-β-*methyl*-β : 2-*dinitrostyrene*, which separated from alcohol and then benzene–light petroleum (b. p. 60—80°) in glistening yellow plates (0·8 g.), m. p. 97—98° (Found : N, 10·9. $C_{10}H_{10}O_6N_2$ requires N, 11·0%). Reduction of this compound (0·5 g.) with acetic acid–iron powder by the standard method gave a gum from which 6-*hydroxy*-5-*methoxy*-2-*methylindole* was extracted with boiling light petroleum (b. p. 60—80°), forming colourless slender needles (0·2 g.), m. p. 136° (Found : C, 67·9; H, 6·3; N, 7·8%). This compound, which is moderately soluble in benzene or carbon tetrachloride and readily soluble in alcohol, ethyl acetate, or chloroform, gave a deep magenta Ehrlich and a red ferric reaction.

6-*Hydroxy*-7-*methoxyindole*-2-*carboxylic Acid*.—An intimate mixture of 4-hydroxy-3-methoxy-2-nitrobenzaldehyde (Raiford and Stoesser, *loc. cit.*) (5 g.), aceturic acid (5 g.), acetic anhydride (25 ml.), and sodium acetate (5 g.) was heated until a clear brown solution was formed. After having been kept for 10 days this mixture was treated with water (25 ml.), and the solid disintegrated, isolated, washed, and crystallised from acetic acid, giving the 4-(4-*acetoxy*-3-*methoxy*-2-*nitrobenzylidene*)-2-*methyloxazol*-5-*one* in yellow prisms (4·4 g.), m. p. 215° (Found : N, 8·6. $C_{14}H_{12}O_7N_2$ requires N, 8·8%). Hydrolysis of this compound (5 g.) with dilute hydrochloric acid (50 ml.) on the steam-bath for 4½ hours afforded 4-*hydroxy*-3-*methoxy*-2-*nitrophenylpyruvic acid* which, on isolation with ether, formed yellow plates (3·7 g.), m. p. 182°, from acetic acid (Found : N, 5·3. $C_{10}H_9O_7N$ requires N, 5·5%). The *oxime* separated from benzene or ethyl acetate in colourless needles, m. p. 152° (Found : N, 10·6. $C_{10}H_{10}O_7N_2$ requires N, 10·4%).

A solution of the foregoing pyruvic acid (1 g.) in alcohol (15 ml.) and acetic acid (15 ml.) containing iron powder (5 g.) was gently heated, boiled for 15 minutes, filtered, diluted with water, cooled, and extracted several times with ether. Evaporation of the dried extracts left 6-*hydroxy*-7-*methoxyindole*-2-*carboxylic acid* which formed colourless needles (0·4 g.), m. p. 244—245° (decomp.), from ethyl acetate, having a green Ehrlich (with hot reagent) and a red-brown ferric reaction (Found : N, 6·8. $C_{10}H_9O_4N$ requires N, 6·8%).

6-*Hydroxy*-7-*methoxyindole*.—(*a*) 6-Hydroxy-7-methoxyindole-2-carboxylic acid (0·5 g.) was heated with glycerol (10 ml.) at 240° for 25 minutes, and the cooled solution diluted with water (50 ml.). On isolation with ether, the resulting 6-*hydroxy*-7-*methoxyindole* formed colourless prisms (100 mg.), m. p. 85°, from light petroleum (b. p. 60—80°) (Found : C, 66·4; H, 5·8; N, 8·5. $C_9H_9O_2N$ requires C, 66·3; H, 5·5; N, 8·6%). The yield of the compound was less satisfactory when the decarboxylation was effected with copper bronze in a vacuum at 240°. This indole, which is soluble in the usual organic solvents except light petroleum, gives a pale red Ehrlich and a greenish-brown ferric reaction.

(*b*) Prepared from 4-hydroxy-3-methoxy-β : 2-dinitrostyrene (Raiford and Fox, *J. Org. Chem.*, 1944, **9**, 170) (1 g.) by the pyridine method, the acetate formed yellow plates (1·1 g.), m. p. 101—102°, from dilute alcohol. On reduction by the acetic acid–iron powder method this compound (1 g.) gave 6-*acetoxy*-7-*methoxyindole*, which formed colourless plates (0·4 g.), m. p. 81°, from light petroleum (b. p. 60—80°) (Found : N, 7·2. $C_{11}H_{11}O_3N$ requires N, 6·8%). A solution of the acetate (0·1 g.) in methanol (3 ml.) was added to 2N-aqueous sodium hydroxide (3 ml.) containing sodium dithionite (hydrosulphite) (1 g.), and the mixture kept in a stoppered flask at 0° for 15 minutes, treated with excess of ice-cold dilute acetic acid, and extracted with ether. Evaporation of the ethereal extract gave 6-hydroxy-7-methoxyindole (70 mg.), m. p. and mixed m. p. 85—86°, after purification from light petroleum.

7-*Hydroxy*-6-*methoxyindole*.—The interaction of 3-hydroxy-4-methoxy-2-nitrobenzaldehyde (Pschorr, *loc. cit.*) (1 g.), nitromethane (0·5 ml.), and ammonium acetate (0·4 g.) in boiling acetic acid (5 ml.) for 2 hours gave 3-*hydroxy*-4-*methoxy*-β : 2-*dinitrostyrene*, which separated from dilute alcohol in pale brown needles (0·8 g.), m. p. 215° (Found : N, 11·7. $C_9H_8O_6N_2$ requires N, 11·7%). Reduction of this styrene (0·5 g.) by the acetic acid–iron powder method gave rise to 7-hydroxy-6-methoxyindole, which formed colourless needles (0·14 g.), m. p. 89°, from light petroleum (b. p. 60—80°) and had a green Ehrlich (blue with warm reagent) and a brown ferric reaction (Found : C, 66·5; H, 5·7; N, 8·5. $C_9H_9O_2N$ requires C, 66·3; H, 5·5; N, 8·6%).

6-*Hydroxy*-7-*methoxy*-2-*methylindole*.—Prepared from 4-hydroxy-3-methoxy-2-nitrobenzaldehyde (5 g.) and nitroethane (3·2 ml.) by the ammonium acetate method, 4-*hydroxy*-3-*methoxy*-β-*methyl*-β : 2-*dinitrostyrene* formed yellow needles (4 g.), m. p. 113—114°, from benzene (Found : N, 10·7. $C_{10}H_{10}O_6N_2$ requires N, 11·0%). By the acetic acid–iron powder reduction method this styrene (1 g.) was converted into 6-*hydroxy*-7-*methoxy*-2-*methylindole*, which separated from light petroleum (b. p. 60—80°) in colourless needles (0·4 g.), m. p. 114°, moderately soluble in benzene and readily soluble in alcohol, acetone, or ethyl acetate (Found : C, 68·0; H, 6·3; N, 8·2. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2; N, 7·9%). This compound gives a deep magenta Ehrlich and a red alcoholic ferric reaction. Formed by the reduction of the acetate of 4-hydroxy-3-methoxy-β-methyl-β : 2-dinitrostyrene, the acetate of 6-hydroxy-7-methoxy-2-methylindole crystallised from light petroleum in colourless needles, m. p. 118—119°, and on deacetylation by the sodium hydroxide–dithionite method gave the parent indole, m. p. and mixed m. p. 114°.

7-*Hydroxy*-6-*methoxy*-2-*methylindole*.—By the ammonium acetate–nitroethane method 3-hydroxy-4-methoxy-2-nitrobenzaldehyde (1 g.) furnished 3-*hydroxy*-4-*methoxy*-β-*methyl*-β : 2-*dinitrostyrene*, which crystallised from dilute alcohol in fine yellow needles (0·8 g.), m. p. 160° (Found : N, 11·4. $C_{10}H_{10}O_6N_2$ requires N, 11·0%). On reduction by the acetic acid–iron powder method during 10 minutes this compound (0·5 g.) gave 7-*hydroxy*-6-*methoxy*-2-*methylindole*, forming colourless needles (100 mg.), m. p. 93°, from light petroleum (b. p. 40—60°), readily soluble in the usual organic solvents except light petroleum (Found : C, 68·1; H, 6·2; N, 8·1. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2; N, 7·9%). This indole gives a deep violet Ehrlich and a bright red ferric reaction.

5-*Hydroxy*-2-*methylindole*.—Hydrolysed by Nenitzescu's method (*loc. cit.*), ethyl 5-hydroxy-2-methylindole-3-carboxylate (1 g.) gave a mixture of the acid (0·2 g.), m. p. 196°, and a little 5-hydroxy-2-methylindole (0·2 g.), m. p. 134°. When the ester (1 g.) was boiled with 2N-aqueous sodium hydroxide (20 ml.) for 1 hour in nitrogen 5-hydroxy-2-methylindole was obtained in almost theoretical yield on extraction of the acidified hydrolysate with ether. Crystallised from light petroleum, it formed colourless plates (0·6 g.), identical with an authentic specimen (Beer *et al.*, *J.*, 1948, 1609). The picrate separated from benzene in red needles, m. p. 158°.

Ethyl 5-methoxy-2-methylindole-3-carboxylate (Nenitzescu, *loc. cit.*) was similarly hydrolysed with aqueous-alcoholic alkali, giving 5-methoxy-2-methylindole, m. p. 89—90°, in good yield.

Ethyl 5-*Hydroxy*-6-*methoxy*-2-*methylindole*-3-*carboxylate*.—Ethyl β-aminocrotonate (Michaelis, *Annalen*, 1909, **366**, 337) (3 g.), dissolved in the minimum amount of alcohol, was added to a solution of methoxy-*p*-benzoquinone (Erdtmann, *Proc. Roy. Soc.*, 1934, *A*, **143**, 177) (3 g.) in warm alcohol (10 ml.). The mixture was refluxed for 1 hour and then on being kept at 0° slowly deposited *ethyl* 5-*hydroxy*-6-*methoxy*-2-*methylindole*-3-*carboxylate* (2·1 g.). Crystallised from alcohol, the ester formed colourless needles, m. p. 220°, which retained solvent of crystallisation (Found, in specimen dried in a high vacuum at 80° : C, 62·4; H, 6·1; N, 5·6. $C_{13}H_{15}O_4N$ requires C, 62·7; H, 6·0; N, 5·6%).

When the condensation of the methoxy-*p*-quinone (3 g.) and ethyl β-aminocrotonate (3 g.) was effected in acetone (100 ml.) at room temperature for 24 hours the resulting ethyl 5-hydroxy-6-methoxy-2-methylindole-3-carboxylate (2 g.) was mixed with a red by-product which was removed by extraction with boiling ligroin. Crystallised from this solvent the *substance* formed red needles, m. p. 150° (Found : C, 59·2, 59·4; H, 5·7, 5·6; N, 6·1, 6·2%).

Hydrolysis of the indole ester (1 g.) with boiling 2N-aqueous sodium hydroxide (40 ml.) in nitrogen gave 5-hydroxy-6-methoxy-2-methylindole (0·5 g.) which had m. p. and mixed m. p. 130°, after sublimation in a high vacuum followed by crystallisation from light petroleum (b. p. 80—100°). The rather unstable picrate formed red needles, m. p. 150°, from benzene.

5-*Hydroxy*-2 : 6-*dimethylindole*.—A solution of methyl-*p*-benzoquinone (Schniter, *Ber.*, 1887, **20**, 2283) and ethyl β-aminocrotonate (3 g.) in acetone (20 ml.) was boiled for 1 hour and concentrated by evaporation of part of the acetone 10 ml.) in a current of nitrogen. On being kept at 0° the residue deposited *ethyl* 5-*hydroxy*-2 : 6-*dimethylindole*-3-*carboxylate* (2·4 g.), which formed colourless needles, m. p. 220—221°, from alcohol (Found, in a specimen dried in a high vacuum at 80° : C, 66·8; H, 6·7; N, 6·2. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·4; N, 6·0%). Boiled with 2N-aqueous sodium hydroxide (50 ml.) for 1 hour, this ester (1 g.) gave rise to 5-*hydroxy*-2 : 6-*dimethylindole* (0·58 g.), which was purified by distillation in a vacuum at 130°/0·1 mm. followed by crystallisation from light petroleum (b. p. 80—100°), forming colourless plates and having an intense red Ehrlich reaction (Found : C, 74·6; H, 6·9; N, 8·5. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; N, 8·7%). The picrate separated from benzene in red needles, m. p. 162° (decomp.).

5 : 6-*Dihydroxy*-2-*methylindole*.—The interaction of hydroxy-*p*-benzoquinone (Willstätter and Müller, *Ber.*, 1911, **44**, 2180) (3 g.) and ethyl β-aminocrotonate (3 g.) in hot alcohol (20 ml.) for 1 hour gave *ethyl* 5 : 6-*dihydroxy*-2-*methylindole*-3-*carboxylate*, which formed colourless needles, blackening at 200°, from alcohol (Found : C, 61·1; H, 5·6; N, 6·1. $C_{12}H_{13}O_4N$ requires C, 61·3; H, 5·5; N, 6·0%). Hydrolysis of this ester (2 g.) with boiling 2N-aqueous sodium hydroxide and distillation of the product in a high vacuum furnished 5 : 6-dihydroxy-2-methylindole, which formed colourless plates (0·3 g.), becoming black at 200° (Found : C, 66·5; H, 5·7. Calc. for $C_9H_9O_2N$: C, 66·3; H, 5·5%). Obtained in poor yield by the acetic anhydride–pyridine method, the diacetate had m. p. and mixed m. p. 134° (cf. Beer *et al.*, *loc. cit.*).

3-*Hydroxy*-2 : 5-*dimethyl*-p-*benzoquinone*.—A mixture of triacetoxy-*p*-xylene (Erdtmann, *loc. cit.*) (30 g.), methanol (60 ml.), and concentrated hydrochloric acid (10 ml.) was heated under reflux for 1 hour, the solvent was removed in a vacuum, and the residual pale brown solid was crystallised from ethyl acetate–light petroleum (b. p. 60—80°), giving *trihydroxy*-p-*xylene* in colourless needles (12 g.), m. p. 156° (Found : C, 62·3; H, 6·4. $C_8H_{10}O_3$ requires C, 62·3; H, 6·5%). This hydroxyquinol (10 g.) was oxidised with silver oxide (16 g.) in anhydrous ether (200 ml.), containing sodium sulphate (50 g.), in the course of 15 minutes and on evaporation the filtered solution left 3-*hydroxy*-2 : 5-*dimethyl*-p-*benzoquinone* (8 g.), which separated from alcohol in orange plates, m. p. 135—137° (Found : C, 63·4; H, 5·5. $C_8H_8O_3$ requires C, 63·2; H, 5·3%).

5 : 6-*Dihydroxy*-2 : 4 : 7-*trimethylindole*.—Ethyl 5 : 6-dihydroxy-2 : 4 : 7-trimethylindole-3-carboxylate was prepared from 3-hydroxy-2 : 5-dimethyl-*p*-benzoquinone (1 g.) and ethyl β-aminocrotonate (1 g.) in boiling alcohol during 1 hour. On isolation the ester separated from alcohol as a *hydrate* in pale pink needles (0·85 g.), m. p. 174° (Found : C, 59·9; H, 6·9; N, 5·0. $C_{14}H_{17}O_4N,H_2O$ requires C, 59·8; H, 6·8; N, 5·0%). Hydrolysis of this compound (1 g.) followed by distillation of the product at 0·1 mm. (bath-temp. 200°) gave 5 : 6-*dihydroxy*-2 : 4 : 7-*trimethylindole* (0·6 g.), which formed colourless plates, m. p. 168°, from benzene–light petroleum (b. p. 60—80°) (Found : C, 69·0; H, 6·9; N, 7·2. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8; N, 7·3%). This compound, which blackens on exposure to air, gives an intense purple Ehrlich reaction. Its solution in dilute aqueous sodium hydrogen carbonate slowly acquires a brown colour, but no melanin-like precipitate is formed.

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