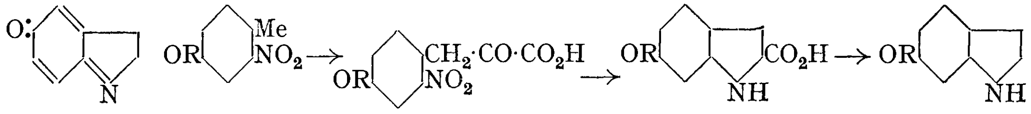
363. *The Synthesis of 5- and 6-Benzyloxyindoles and Attempts to prepare 5- and 6-Hydroxyindoles therefrom.*

By Harold Burton and John L. Stoves.

The synthesis of 5- and 6-benzyloxyindoles has been accomplished. Debenzylation gave, not the corresponding hydroxy-derivatives, but dark-coloured, complex, phenolic, amorphous substances, apparently formed by oxidative polymerisation.

The knowledge that 5 : 6-dihydroxyindole (Dulière and Raper, *Biochem. J.*, 1930, **24**, 239) and 5 : 6-dihydroxy-1-methylindole (Burton, J., 1932, 546) undergo atmospheric oxidation in weakly alkaline solution to yield black melanin-like pigments, coupled with the lack of knowledge concerning the mechanism of such oxidations, led us to attempt the preparation of the simpler 5- and 6-hydroxyindoles, in order to see if they could be similarly oxidised to analogous pigments. It was foreseen that 5-hydroxyindole might undergo preferential oxidation to the quinonoid derivative (I), and for that reason it was decided to investigate the isomeric 6-derivative, since its structure precludes such a change.

In view of the well-known fact that the benzyl group can be eliminated much more readily than the methyl group from the respective phenolic ethers, the procedure finally adopted was to synthesise the benzyloxyindoles by methods similar to those used by Blaikie and Perkin (J., 1924, **125**, 307) for the methoxyindoles. Thus, 2-*nitro*-4-*benzyloxytoluene* (II), condensed with ethyl oxalate in presence of potassium ethoxide, gave 2-*nitro*-4-*benzyloxyphenylpyruvic acid* (III) together with a considerable amount of 2 : 2'-*dinitro*-4 : 4'-*dibenzyloxydibenzyl* (for analogous results, compare Reissert, *Ber.*, 1897, **30**, 1052). Reduction of the pyruvic acid with ferrous hydroxide afforded 6-*benzyloxyindole*-2-*carboxylic acid* (IV), which was decarboxylated to 6-*benzyloxyindole* (V) by heating in glycerol. 2-Nitro-5-benzyloxyphenylpyruvic acid (Burton and Stoves, this vol., p. 403) similarly gave 5-*benzyloxyindole*-2-*carboxylic acid* and thence 5-*benzyloxyindole*, which, like its isomeride (V), has only feebly basic properties.



(I.) (II.) (III.) (IV.) (V.)

(R = CH_2Ph)

Attempts to debenzylate either benzyloxyindole with hydrobromic or hydriodic acid in the customary manner resulted in the formation of dark-coloured complex substances, which, however, usually had phenolic properties. Furthermore, since the nitrogen content was only 45—60% of the theoretical value for the simple hydroxyindole, it would appear that these complex substances were produced by oxidative polymerisation of the first-formed hydroxyindoles; their molecular weights could not be determined, owing either to insolubility or to decomposition (as, for example, in camphor). Oxidation could be suppressed to some extent during debenzylation by working as far as possible in an atmosphere of nitrogen, but even then polymeric products were obtained. The hydroxyindoles containing the hydroxy-group in the benzene ring are, as regards instability, in marked contrast to those substituted in the pyrrole nucleus.

Experimental.

2-*Nitro*-4-*benzyloxytoluene* (II).—A mixture of 2-nitro-*p*-cresol (100 g.), benzyl chloride (84 g.), sodium hydroxide solution (27·5 g. in 200 c.c. of water), and alcohol (600 c.c.) was boiled under reflux for 8 hours. Removal of the alcohol by distillation and addition of water to the residue gave an oil which gradually solidified. Recrystallisation from benzene–ligroin gave 100 g. of 2-*nitro*-4-*benzyloxytoluene* in nearly colourless, fine needles, m. p. 52° (Found : C, 69·1 ; H, 5·3 ; N, 5·9. $C_{14}H_{13}O_3N$ requires C, 69·1 ; H, 5·35 ; N, 5·8%).

2-*Nitro*-4-*benzyloxyphenylpyruvic Acid* (III).—Potassium ethoxide (from powdered potassium, 4·9 g., and sodium-dried alcohol, 5·7 g.) in ether (200 c.c.) was treated with ethyl oxalate (19·3 g.) and then with 2-nitro-4-benzyloxytoluene (30·3 g. in the minimum amount of ether). The mixture was heated under reflux for 18 hours and then treated with water. The yellow solid (*A*) obtained was collected and washed with a little ether, and the filtrate separated; evaporation of the dried (sodium sulphate) ethereal extract gave 8·4 g. of recovered nitrobenzyloxytoluene, and acidification of the aqueous extract with concentrated hydrochloric acid (Congo-red) afforded 14·1 g. of 2-*nitro*-4-*benzyloxyphenylpyruvic acid*, which separated from water in pale yellow needles, m. p. 89—90°, apparently containing water of crystallisation (Found: C, 57·3; H, 4·8; N, 4·3. $C_{16}H_{13}O_6N,H_2O$ requires C, 57·6; H, 4·5; N, 4·2%). The acid gave a deep green coloration with alcoholic ferric chloride.

Recrystallisation of (*A*) from glacial acetic acid afforded material, m. p. 162°, which gave a deep purple colour with aqueous potassium hydroxide; two further recrystallisations from the same solvent afforded pale yellow plates, m. p. 164—165° (unchanged by further recrystallisation), which did not give a colour with potassium hydroxide. The substance is probably 2 : 2′-*dinitro*-4 : 4′-*dibenzyloxydibenzyl* (Found: C, 69·1; H, 5·0; N, 6·0; *M*, in camphor, 507. $C_{28}H_{24}O_6N_2$ requires C, 69·4; H, 5·0; N, 5·8%; *M*, 484).

The use of sodium ethoxide as the condensing agent gave a tarry product from which the above acid could not be isolated.

6-*Benzyloxyindole*-2-*carboxylic Acid* (IV).—A hot solution of hydrated ferrous sulphate (156 g.) in water (300 c.c.) was added rapidly with stirring to a solution of 2-nitro-4-benzyloxypyruvic acid (26 g.) in sodium hydroxide (52 g. in 300 c.c. of water). The black mixture was heated (stirring) on the steam-bath for 1 hour and then boiled gently for ½ hour. Filtration of the iron oxide sludge and acidification of the concentrated filtrate with hydrochloric acid (Congo-red) gave 15 g. of 6-*benzyloxyindole*-2-*carboxylic acid*, which separated from benzene in nearly colourless, ill-defined crystals, m. p. 185—186° (decomp.) (Found: C, 71·9; H, 4·8; N, 5·8. $C_{16}H_{13}O_3N$ requires C, 71·9; H, 4·9; N, 5·2%). The acid gave a red colour when warmed with Ehrlich's reagent.

5-*Benzyloxyindole*-2-*carboxylic acid*, similarly prepared from 2-nitro-5-benzyloxypyruvic acid (this vol., p. 403), could not be obtained pure. It crystallised from benzene in nearly colourless prisms, m. p. 190° with darkening, containing approximately $1H_2O$ (Found: C, 68·4; H, 5·2; loss at 110°, 9·0. $C_{16}H_{13}O_3N,H_2O$ requires C, 67·4; H, 5·3; H_2O, 6·3%), and gave a deep pink colour with Ehrlich's reagent.

6-*Benzyloxyindole* (V).—Attempted decarboxylation of 6-benzyloxyindole-2-carboxylic acid by heating alone, or in quinoline with or without copper-bronze, resulted in the production of unworkable tars. The following method proved fairly satisfactory. The acid (2·5 g.), mixed with glycerol (20 c.c.), was heated at 210° until gas evolution ceased. The cooled mixture was poured into water and extracted three times with ether. The residue from the washed and dried (sodium sulphate) ethereal solution was a dark brown tar, which was repeatedly extracted with light petroleum. Concentration gave colourless plates of 6-*benzyloxyindole*, m. p. 111—112°, unchanged by further recrystallisation (Found: C, 80·9; H, 6·0; N, 6·0. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8; N, 6·3%), which gave with cold Ehrlich's reagent a transient red colour, becoming bluish-purple on heating. The yield was 4 g. from 15 g. of the acid.

5-*Benzyloxyindole*, similarly prepared (yield, 3 g. from 15 g. of 5-benzyloxyindole-2-carboxylic acid), separated from light petroleum in colourless fine needles, m. p. 96—97° (Found: C, 80·3; H, 6·0; N, 6·4. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8; N, 6·3%), which gave a reddish-purple colour with Ehrlich's reagent (cold or hot). Both benzyloxyindoles darkened gradually when kept. They did not yield picrates, but formed unstable hydriodides.

5-*Benzyloxy*-1-*acetylindole*, obtained when the indole (3 g.) was boiled with acetic anhydride (40 c.c.) and sodium acetate (10 g.) for 3 hours, separated from methyl alcohol in nearly colourless, prismatic needles, m. p. 129—130° (Found: C, 77·3; H, 5·6. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7%).

Attempts to prepare 6-*Hydroxyindole*.—(i) 6-Benzyloxyindole (1 g.), acetic acid (10 c.c.), and 48% hydrobromic acid (10 c.c.) were heated on the steam-bath for 5 hours, the colour of the mixture changing through red to green; volatile products were then removed as far as possible by steam-distillation. Filtration of the residue removed a small amount of brown solid (insoluble in sodium hydroxide solution), and neutralisation of the filtrate with sodium bicarbonate precipitated a dark red solid (Found: N, 6·4. C_8H_7ON requires N, 10·5%), which was soluble in alcohol and sodium hydroxide solution.

(ii) A mixture of the benzyl ether (1 g.), acetic acid (20 c.c.), and hydriodic acid (*d* 1·7;

20 c.c.) was kept at room temperature for 24 hours, then diluted with water, and finally neutralised with sodium bicarbonate, whereupon considerable darkening occurred. Extraction with ether and subsequent filtration of the aqueous residue gave a dark-brown solid, soluble in alcohol and sodium hydroxide solution, which gave a red colour with Ehrlich's reagent. A trace only of phenolic material was removed from the above ethereal extract by sodium hydroxide.

(iii) A mixture of 6-benzyloxyindole (1 g.), acetic acid (20 c.c.), and a 54% solution of hydrogen bromide in acetic acid (10 c.c.) was heated on the steam-bath for 15 minutes and, after dilution with air-free water, was distilled until free from benzyl bromide; all the operations were carried out in an atmosphere of nitrogen. The hot solution was filtered from a little tar, and the residual hydrobromic acid removed with solid sodium acetate, whereupon an orange-brown solid (*B*) (Found: N, 7·6%) was precipitated. Neutralisation of the filtrate with sodium bicarbonate gave a small amount of a similar precipitate (Found: N, 8·9%). Solid (*B*) was only slightly soluble in hot acetic acid; it dissolved in aqueous sodium hydroxide to a brick-red solution which gradually turned brown, and with Ehrlich's reagent in the hot gave a reddish-violet colour which subsequently became green.

Attempts to prepare 5-Hydroxyindole.—(i) A mixture of 5-benzyloxyindole (1 g.), acetic acid (20 c.c.), and hydriodic acid (*d* 1·7; 20 c.c.) was heated on the steam-bath for 15 minutes and then steam-distilled until free from benzyl iodide. Filtration of the residue removed an amorphous black solid (Found: N, 4·7%), which dissolved in aqueous sodium hydroxide to a brown solution; neutralisation (sodium bicarbonate) of the filtrate gave a grey precipitate (Found: N, 4·9%), also soluble in aqueous sodium hydroxide to a dark green solution.

(ii) The experiment was carried out as under (iii) (above). Removal of the excess of hydrobromic acid with solid sodium acetate precipitated a small amount of a dark brown solid (Found: N, 5·5%), and subsequent neutralisation (sodium bicarbonate) also gave a brown solid (Found: N, 9·0%) as the major product. Both solids dissolved in aqueous sodium hydroxide, yielding brown solutions.

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THE UNIVERSITY, LEEDS.

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