15. *The Synthesis of Derivatives of* 5 : 6-*Dihydroxyindole. Part I.* 5 : 6-*Methylenedioxyindole and its* 2-*Methyl Derivative.*

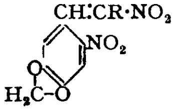
By H. Burton and (Miss) J. A. Duffield.

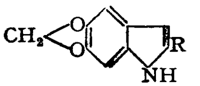
6 : *β-Dinitro*-3 : 4-*methvlenedioxystyrene* and its *β-methyl* derivative undergo reduction in an acidic medium, with loss of ammonia, yielding 5 : 6-*methylenedioxyindole* and its 2-*methyl* derivative, respectively. The indoles can be converted by suitable treatment with dry pyridine hydrochloride into the corresponding dihydroxy-derivatives, but the yields are not good.

Methods of preparation of indoles, apart from the Fischer synthesis, generally involve the ring closure of suitably substituted ortho-derivatives of benzene. We have investigated (cf. Nenitzescu, *Ber.*, 1925, **58**, *B*, 1063; van der Lee, *Rec. Trav. chim.*, 1925, **44**, 1089) the generality of the method whereby suitable 2(6) : β-dinitrostyrenes are reduced, since the corresponding diamino-derivatives are the postulated intermediates * in the Robinson mechanism (*J.*, 1924, **125**, 827) of the Fischer indole synthesis.

6 : β-*Dinitro*-3 : 4-*methylenedioxystyrene* (I; R = H) was obtained either by condensation of 6-nitropiperonal with nitromethane or by nitration of β-nitro-3 : 4-methylenedioxystyrene. 6 : β-*Dinitro*-3 : 4-*methylenedioxy*-β-*methylstyrene* (I; R = Me) was likewise formed either from 6-nitropiperonal and nitroethane or by nitration of β-*nitro*-3 : 4-*methylenedioxy*-β-*methylstyrene.*

(I.)





(II.)

When either of these dinitrostyrenes was reduced by iron and a catalytic amount of hydrochloric acid in an aqueous-alcoholic medium, there was a slow evolution of ammonia and the soluble product gave an immediate red coloration with Ehrlich's reagent in the cold, indicating, as expected, formation of the substituted indoles (II). Since this reduction occurred too slowly to be useful, the dinitrostyrenes were reduced in aqueous acetic acid, and the resulting 5 : 6-*methylenedioxy*- (II; R = H) and 5 : 6-*methylenedioxy*-2-*methyl-indole* (II; R = Me), respectively, were isolated in good yield.

Preliminary experiments on the demethylenation of these indoles by dry pyridine hydrochloride have been carried out. Originally, no attempts were made to isolate the dihydroxyindoles as such, since we had surmised that aqueous sodium hydroxide extracts of the reaction products would, in the presence of atmospheric oxygen, give rise to melanins. The significance of melanin formation from 5 : 6-dihydroxy-2-methylindole has been referred to by one of us (*Chem. and Ind.*, 1948, **313**) in connexion with the structure of tyrosinemelanin.

5 : 6-Dihydroxyindole, m. p. 140° (decomp.) (soft-glass tube †), and 5 : 6-dihydroxy-2-methylindole, m. p. *ca.* 180° (decomp.) (soft-glass tube †), have both been synthesised by the above procedures and also (cf. Robertson *et al.*, *Nature*, 1948, **161**, 525) starting from the appropriate 6 : β-dinitro-3 : 4-diacetoxystyrenes. We defer publication of these results as we are also investigating two other methods of synthesis of both compounds (see *Nature*, 1948, **161**, 725).

Experimental.

β-Nitrostyrenes.—Preliminary experiments by one of us and Dr. C. W. Shoppee in 1934 indicated that, for simple *p*-hydroxybenzaldehydes, condensation with nitromethane was best effected with either methylamine or aniline. For *p*-alkoxybenzaldehydes and related compounds, rapid condensation was effected with alcoholic potassium hydroxide (cf. Remfry, *J.*, 1911. **99**, 282).

Piperonal or 6-nitropiperonal (0·2 mol.) dissolved in alcohol (10 c.c. per 1 g. of aldehyde) was cooled to —5°, the nitroalkane (0·3 mol.) added, and the mixture treated with an ice-cold solution of potassium hydroxide (0·4 mol.) in water (2 c.c. per 1 g.) and alcohol (20 c.c. per 1 g.) which was added gradually with stirring. After 15—30 minutes, a test portion was acidified with hydrochloric acid and if a precipitate was obtained (*A*), the whole of the product was worked up. When an oil (or only a small amount of solid) separated, the reaction mixture (*B*) was kept below 0° for at least 18 hours and then acidified. The solid product was filtered off, and the filtrate extracted thrice with ether. The combined ethereal extracts were washed with aqueous sodium hydrogen sulphite (thrice) and then with water,

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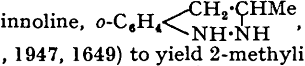
* We suggest that rearrangement of, *e.g.*, acetone phenylhydrazone might equally well give a tetrahydrocinnoline,



$o\text{-}C_6H_4{<}\begin{matrix}CH_2\cdot CHMe\\ NH\cdot NH\end{matrix}$

, which could then undergo loss of ammonia (cf. Atkinson and Simpson, *J.*, 1947, 1649) to yield 2-methylindole.

† We anticipate that both dihydroxyindoles will have higher m. p. in alkali-free glass tubes as both undergo ready atmospheric oxidation (to melanins) in the presence of alkali.

dried (Na_2SO_4), and evaporated. To the liquid or semi-solid residue was then added an equal weight of anhydrous sodium acetate and three times its weight of acetic anhydride, and the mixture was brought to the boil. The slight exothermic reaction was allowed to subside, and the product treated with water; the solid β-nitrostyrene was thus obtained.

β-Nitro-3 : 4-methylenedioxystyrene (*A*), yellow needles from acetic acid, m. p. 159°, was prepared in 40—50% yield.

6 : *β-Dinitro*-3 : 4-*methylenedioxystyrene* (*A*), yellow prisms from alcohol, m. p. 118° (Found: N, 12·0. $C_9H_6O_6N_2$ requires N, 11·8%), obtained from 6-nitropiperonal in 20% yield, was better obtained by adding cold nitric acid (*d* 1·5) (15 c.c.) to a suspension of 2′-nitro-3 : 4-methylenedioxystyrene (5 g.) in cold acetic acid (25 c.c.) so that the temperature did not rise above 0°. Dilution with water and crystallisation from alcohol gave the 6 : β-dinitro-derivative (yield 83—100%), m. p. and mixed m. p. 118°.

β-Nitro-3 : 4-*methylenedioxy-β-methylstyrene* (*A*, *B*), fine yellow needles from alcohol, m. p. 95° (Found: C, 58·3; H, 4·6; N, 6·8. $C_{10}H_9O_4N$ requires C, 58·0; H, 4·4; N, 6·8%), was prepared from piperonal in 33% yield.

6 : *β-Dinitro*-3 : 4-*methylenedioxy-β-methylstyrene* (*A*, *B*), yellow needles from alcohol, m. p. 155° (Found: C, 47·4; H, 3·2; N, 11·3. $C_{10}H_8O_6N_2$ requires C, 47·6; H, 3·2; N, 11·1%), was better prepared in 94% yield from β-nitro-3 : 4-methylenedioxy-β-methylstyrene (13 g.) in acetic acid (65 c.c.) with fuming nitric acid (39 c.c.), the mixture being kept at 0° for 3 hours before dilution with water. The product had m. p. and mixed m. p. 155° after crystallisation from alcohol.

5 : 6-*Methylenedioxyindole* (II; R = H).—6 : β-Dinitro-3 : 4-methylenedioxystyrene (4 g.) was dissolved in boiling 80% acetic acid (80 c.c.). To the hot (not boiling) solution, iron powder (20 g.) was added in portions to maintain a steady ebullition and until the reddish-brown colour which at first developed disappeared. The solution was then decanted into aqueous sodium hydrogen sulphite (100 g. in 500 c.c.) in a large separating funnel, and the mixture well shaken. The resulting mixture, containing much suspended solid, was extracted with ether until the extract gave a negative Ehrlich's reaction. The combined ethereal extracts were dried (Na_2SO_4) and evaporated. The crude *indole* (2·2 g.) crystallised from light petroleum (b. p. 40—60°) in colourless clusters of needles, m. p. 110° (Found: C, 67·9; H, 4·5; N, 8·6. $C_9H_7O_2N$ requires C, 67·1; H, 4·4; N, 8·7%), which gave an immediate blue-red colour with cold Ehrlich's reagent.

Reductions using alcoholic acetic acid or aqueous alcoholic acetic and hydrochloric acids were not so satisfactory.

5 : 6-*Methylenedioxy*-2-*methylindole* (II; R = Me).—Similar reduction of 6 : β-dinitro-3 : 4-methylenedioxy-β-methylstyrene gave the crude indole in almost quantitative yield. Recrystallisation from light petroleum gave colourless needles, m. p. 150° (Found: N, 8·0. $C_{10}H_9O_2N$ requires N, 8·0%). The *indole* gave an immediate bright red colour with cold Ehrlich's reagent, and showed a marked tendency to turn pink.

King's College of Household and Social Science, W.8.

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