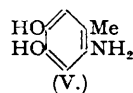
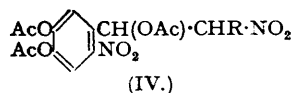
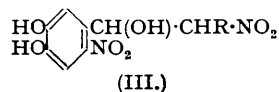
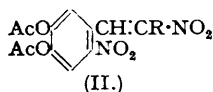
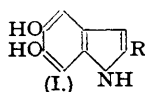


219. The Synthesis of Derivatives of 5:6-Dihydroxyindole.
Part II. 5:6-Dihydroxyindole and Related Compounds.

By H. BURTON, (MISS) J. A. DUFFIELD, and P. F. G. PRAILL.

2-Nitro-1-(2-nitro-4:5-dihydroxyphenyl)-ethyl and -propyl alcohols are acetylated by acetic anhydride-perchloric acid to the corresponding triacetates which are readily converted into the β :2-dinitro-4:5-diacetoxystyrenes. These are used as intermediates in the synthesis of 5:6-dihydroxyindoles. The Tyson method for the synthesis of indoles from suitable derivatives of 6-aminohomocatechol (2-amino-4:5-dihydroxytoluene) leads to dark amorphous products.

BURTON and DUFFIELD (*Nature*, 1948, **161**, 725; *J.*, 1949, 78) have indicated the methods they were investigating for the synthesis of 5:6-dihydroxyindoles of type (I). One of these procedures was also developed independently by Beer, Clarke, Khorana, and Robertson (*J.*, 1948, 2223), namely, reduction of the appropriately constituted β :2-dinitro-4:5-diacetoxystyrene (II) and subsequent hydrolysis of the resulting 5:6-diacetoxyindoles. Since much of our experimental work and most of our results were, in this synthesis, closely similar to, and in some cases identical with, those of Beer *et al.*, we have detailed only those procedures



which are new or which differ in a marked degree. We had found, for example, that the nitro-alcohols (III; R = H, Me) obtained by alkaline condensation of 6-nitroprotocatechuic aldehyde* with nitromethane and nitroethane were smoothly acetylated by acetic anhydride and a little perchloric acid, to give the triacetates (IV; R = H, Me) without any tendency for the formation of nitrostyrene. Elimination of acetic acid from (IV) to give the dinitrodiacetoxystyrenes (II; R = H, Me) occurred smoothly, as expected, when the triacetates were heated with acetic anhydride and sodium acetate. We found that this two-stage process was much more reliable than treatment of (III) with hot acetic anhydride and sodium acetate. In our hands the latter procedure often gave non-crystalline products, presumably because of incomplete reaction.

It was noted that the melting point of (IV; R = Me) altered on repeated crystallisation; this accords with the presence of two asymmetric centres in the molecule, a feature which was of no consequence from our point of view since either form must give (II; R = Me) on elimination of acetic acid.

The acetylation procedure with perchloric acid as catalyst was also applied successfully to the nitro-alcohols obtained from nitromethane and piperonaldehyde or vanillin; in all cases the limiting factor was the yield of the alcohol.

* This compound is mistakenly designated 2-nitroprotocatechuic aldehyde by Beer *et al.*

In agreement with Beer *et al.* (*loc. cit.*) and contrary to Harley-Mason (*J.*, 1948, 1244), we had no difficulty in preparing the 6-nitroprotocatechuic aldehyde required for the initial condensations by the method of Parijs (*Rec. Trav. chim.*, 1930, 49, 36), although our yields never exceeded 50% of the theoretical amount.* We had also used Harley-Mason's method but found that it possessed no advantage.

At the time of Harley-Mason's publication we had used freshly prepared, dry pyridine hydrochloride to remove the methylene group from 5 : 6-methylenedioxyindole and its 2-methyl derivative, but had found that the markedly exothermic process led to the production of much black material with only very small amounts of the required dihydroxyindole (see *Chem. and Ind.*, 1948, 313). We do not recommend this procedure.

Hydrolysis of 5 : 6-diacetoxyindole under relatively mild acidic conditions, although slow, gave a monoacetate, m. p. 150° (decomp.), which was readily distinguishable from 5 : 6-dihydroxyindole (I; R = H) and in alkaline solution underwent rapid conversion into melanin.

We have also investigated the Tyson method (*Org. Synth.*, 1943, 23, 42) for the synthesis of indoles by preparing suitable acyl derivatives of 6-aminohomocatechol (2-amino-4 : 5-dihydroxytoluene) (V). We have used, for example, the *OO*N-triacetyl derivative and also the *N*-formyl- and *N*-acetyl-*OO*-dibenzyl derivatives. In all the cases studied we obtained, not altogether unexpectedly, dark amorphous products.

EXPERIMENTAL.

Condensation of nitromethane or nitroethane with 6-nitroprotocatechuic aldehyde was carried out as described in Part I (*J.*, 1949, 78), except when it was found advantageous to keep the reaction mixture at 0° for longer than 18 hours. In such cases the reaction time is recorded.

Extraction of 5 : 6-dihydroxyindole was always effected with peroxide-free ether. Ether containing a trace of peroxide caused a rapid polymerisation, and gummy material was produced. Such material gave an immediate black colour with dilute sodium hydroxide, but showed a negative Ehrlich reaction. 5 : 6-Dihydroxy-2-methylindole showed a similar behaviour but the polymerised material gave a positive Ehrlich reaction.

2-Nitro-1-(2-nitro-4 : 5-diacetoxyphenyl)ethyl Acetate (IV; R = H).—The viscous syrup obtained from 6-nitroprotocatechuic aldehyde (2 g.) and nitromethane was dissolved in three times its weight of acetic anhydride, and two drops of 72% perchloric acid were added. After 30 minutes the reaction mixture, from which crystalline material often separated, was diluted with water (25 c.c.); after 1 hour the triacetate was collected, dried, and crystallised from benzene-light petroleum (b. p. 60—80° unless stated otherwise), colourless needles (3.2 g.), m. p. 128°, being obtained (Found: C, 45.7; H, 3.9; N, 7.8. $C_{14}H_{14}O_{10}N_2$ requires C, 45.4; H, 3.8; N, 7.6%).

β : 2-Dinitro-4 : 5-diacetoxystyrene (II; R = H).—A mixture of the above triacetate (2.5 g.), anhydrous sodium acetate (2.5 g.) and acetic anhydride (5 g.) was boiled for 1—2 minutes, allowed to cool, and then treated with water (25 c.c.). The resulting styrene (yield 96%) crystallised from aqueous alcohol in pale orange plates, m. p. 123—124°, unaltered by further recrystallisation (Found: C, 46.5; H, 3.4; N, 9.1. Calc. for $C_{12}H_{10}O_6N_2$: C, 46.5; H, 3.2; N, 9.05%). Beer *et al.* give m. p. 133—134°, but we have never been able to exceed the value of 123—124°.

2-Nitro-1-(2-nitro-4 : 5-diacetoxyphenyl)propyl Acetate (IV; R = Me).—The residue obtained from 6-nitroprotocatechuic aldehyde (4 g.) and nitroethane after 64 hours was treated with acetic anhydride and perchloric acid as described for the lower homologue. The triacetate separated from benzene-light petroleum in colourless needles (3.1 g.), m. p. 141—142° (Found: C, 47.3; H, 4.4; N, 6.8. $C_{15}H_{16}O_{10}N_2$ requires C, 46.9; H, 4.2; N, 7.3%), which showed some variation (see Introduction) in different experiments.

This was converted, in 96% yield, as described for its lower homologue, into *β : 2-dinitro-4 : 5-diacetoxy-β-methylstyrene* [2-nitro-1-(2-nitro-4 : 5-diacetoxyphenyl)prop-1-ene] (II; R = Me), colourless needles (from alcohol), m. p. 119° (Found: C, 48.1; H, 3.4; N, 9.0. Calc. for $C_{13}H_{12}O_6N_2$: C, 48.2; H, 3.7; N, 8.6%).

2-Nitro-1-(3 : 4-methylenedioxyphenyl)ethyl Acetate.—Triethylamine (1.7 g.) was added to piperonaldehyde (5 g.) and nitromethane (3 g.) in alcohol (20 c.c.) at room temperature, and the mixture kept for 18 hours at room temperature and subsequently at 0° for 2 days. The dark brown mixture was then diluted with an equal volume of ice-water and acidified at 0° with dilute acetic acid, whereupon a dark oil separated. The mixture was extracted 4 times with ether, and the combined ethereal extracts were washed thrice with aqueous sodium hydrogen sulphite and finally with water. On evaporation of the dried (Na_2SO_4) ethereal solution, a viscous gum was obtained which sometimes solidified to a waxy solid. This was dissolved in acetic anhydride (3 parts) and perchloric acid (72%) (3 drops), and after 18 hours at room temperature diluted with water. The crude product was dissolved in the minimum amount of boiling 96% alcohol; after cooling, the clear solution was decanted from tarry material which separated. When kept, the solution deposited a solid (2.5 g.), m. p. 92—96°; recrystallisation from benzene-light petroleum gave colourless prisms of the above acetate, m. p. 99° (Found: C, 52.1; H, 4.3; N, 5.4. $C_{11}H_{11}O_6N$ requires C, 52.2; H, 4.3; N, 5.5%).

Treatment of this with acetic anhydride and sodium acetate gave *β-nitro-3 : 4-methylenedioxy*styrene, m. p. and mixed m. p. 158—159°.

* It would appear that the yield recorded by Parijs, which, as pointed out by Beer *et al.*, is in excess of the theoretical amount, was that obtained from twice the weight of 6-nitropiperonylidene diacetate recorded.

1064 *The Synthesis of Derivatives of 5:6-Dihydroxyindole. Part II.*

2-Nitro-1-(4-acetoxy-3-methoxyphenyl)ethyl Acetate.—Vanillin (5.1 g.) in alcohol (20 c.c.) with nitromethane (3 g.) and triethylamine (1.7 g.) gave, by the above procedure, the crude *diacetate* (1.4 g.), which separated from benzene–light petroleum in colourless prisms, m. p. 122–123° (Found: C, 53.6; H, 5.3; N, 4.4. $C_{18}H_{16}O_5N$ requires C, 52.6; H, 5.1; N, 4.7%).

Treatment with acetic anhydride and sodium acetate gave β -nitro-4-acetoxy-3-methoxystyrene, orange needles (from alcohol), m. p. 162–163°.

5:6-Dihydroxyindole (I; R = H).—5:6-Methylenedioxyindole (5 g.) was intimately mixed with freshly prepared, dry pyridine hydrochloride (5 g.) in a boiling-tube and heated in a glycerol-bath until effervescence began. The internal temperature of the mixture was kept constant at about 165° by removal, when necessary, of the tube from the bath. After the reaction has subsided the product was treated with dilute hydrochloric acid (50 c.c.), and the mixture brought to the boil and immediately treated with an excess of crystalline sodium acetate. The mixture was then filtered to remove black solid, and the filtrate treated with charcoal. The filtrate was then extracted 3 times with ether, and the combined ethereal extracts were washed with a little water and dried (Na_2SO_4). The residue from the ethereal extract when kept in a vacuum desiccator over potassium hydroxide gave a little crystalline material which separated from benzene–light petroleum in colourless needles, m. p. 140° (decomp.) (Found: C, 64.2; H, 4.6; N, 9.1. Calc. for $C_8H_7O_2N$: C, 64.4; H, 4.7; N, 9.4%). A specimen, prepared from β :2-dinitro-4:5-diacetoxystyrene by reduction with iron powder and acetic acid to 5:6-diacetoxyindole [compact clusters of prisms (from benzene–light petroleum), m. p. 134–136° (Found: C, 62.0; H, 4.8; N, 5.9. Calc. for $C_{12}H_{11}O_4N$: C, 61.8; H, 4.7; N, 6.0%)] and subsequent hydrolysis, was identical (m. p. and mixed m. p.).

5:6-Dihydroxy-2-methylindole (I; R = Me).—The procedure detailed for (I; R = H) was applied to 5:6-methylenedioxy-2-methylindole, again using an equal weight of dry pyridine hydrochloride. The indole crystallised from benzene–light petroleum in colourless needles, m. p. 180° (decomp.) (Found: C, 66.1; H, 5.6. Calc. for $C_9H_9O_2N$: C, 66.3; H, 5.5%). Beer *et al.* state that this indole darkens at 180° and becomes black at 200° in a sealed m. p. tube.

When prepared from β :2-dinitro-4:5-diacetoxy- β -methylstyrene by way of 5:6-diacetoxy-2-methylindole, needles (from benzene–light petroleum), m. p. 134° (Found: C, 62.9; H, 5.4; N, 5.9. Calc. for $C_{12}H_{13}O_4N$: C, 63.2; H, 5.3; N, 5.7%), the dihydroxy-compound also had m. p. 180° (decomp.).

5(or 6)-Hydroxy-6(or 5)-acetoxyindole.—When a solution of 5:6-diacetoxyindole (0.5 g.) in 96% alcohol (12.5 c.c.) and phosphoric acid (5%; 6 c.c.) was boiled under reflux for 5 hours, the original straw-coloured solution became deep red. The cooled solution was mixed with 18% aqueous sodium acetate (12.5 c.c.) and extracted 4 times with ether. The ethereal solution was dried (Na_2SO_4) and then evaporated; the brown resinous residue was extracted with small portions of hot benzene, until the extracts no longer gave a positive reaction towards Ehrlich's reagent. The benzene solution was concentrated to *ca.* 10 c.c. and treated with charcoal if necessary, and the clear solution mixed with an equal volume of light petroleum (b. p. 60–80°). On keeping 0.26 g. of a mixture of 5:6-diacetoxyindole and the monoacetate separated

Owing to the lower solubility of the *monoacetate* in benzene, the mixture was readily separated by fractional crystallisation from this solvent. The monoacetate separated as colourless fluffy aggregates of needles (110 mg.), m. p. 150° (decomp.) (Found: C, 62.8; H, 4.9; N, 7.5. $C_{10}H_9O_3N$ requires C, 62.8; H, 4.7; N, 7.3%). 5:6-Diacetoxyindole (140 mg.) was recovered from the mother-liquors.

6-Aminohomocatechol Diacetate (2-Amino-4:5-diacetoxytoluene).—6-Nitrohomocatechol was acetylated by boiling it with acetic anhydride (3 parts) and fused sodium acetate (1 part) for 1 hour; the resulting diacetate crystallised from alcohol in very pale yellow needles, m. p. 103–105°. Hydrogenation of this diacetate (5 g.) in warm methanol (100 c.c.) in presence of Raney nickel (3 g.) gave 65–70% of the *aminodiacetoxytoluene* which separated from methanol in colourless needles, m. p. 173° (Found: C, 59.1; H, 5.9; N, 6.3. $C_{11}H_{13}O_3N$ requires C, 59.2; H, 5.8; N, 6.3%). The solubility of this compound in cold hydrochloric acid and its insolubility in cold dilute sodium hydroxide indicated that acetyl migration had not occurred.

Boiling with $1\frac{1}{2}$ times its weight of acetic anhydride for 2 minutes gave 2-acetamido-4:5-diacetoxytoluene, clusters of pale orange needles (from dilute acetic acid), m. p. 165° (Found: C, 58.6; H, 5.8; N, 5.4. $C_{13}H_{15}O_5N$ requires C, 58.9; H, 5.7; N, 5.3%).

6-Nitrohomocatechol Dibenzyl Ether (2-Nitro-4:5-dibenzylxytoluene).—A solution of 6-nitrohomocatechol (0.1 mol.) and benzyl chloride (0.2 mol.) in alcohol (100 c.c.) was heated to boiling and an air-free, 50% aqueous solution of potassium hydroxide (0.2 mol.) was slowly added. After refluxing until neutral, the solution was poured into water, and the *dibenzyl ether* crystallised from alcohol. Clusters of yellow needles (64%), m. p. 98–100° (Found: C, 71.5; H, 5.6. $C_{21}H_{19}O_4N$ requires C, 72.2; H, 5.5%), were obtained.

6-Aminohomocatechol Dibenzyl Ether.—This *amine* was obtained in quantitative yield by hydrogenation of 6-nitrohomocatechol dibenzyl ether (20 g.) in dioxan (100 c.c.) in presence of Raney nickel (24 g.) at room temperature. Recrystallisation from aqueous alcohol gave colourless needles, m. p. 81° (Found: C, 78.4; H, 6.6; N, 4.8. $C_{21}H_{21}O_2N$ requires C, 79.0; H, 6.6; N, 4.4%).

When the amine (1 g.) and formic acid (*d* 1.2) (2 c.c.) were heated on a steam-bath for 3 hours and then poured into water, an almost quantitative yield of 6-*formamidohomocatechol dibenzyl ether* was obtained, which crystallised from alcohol in light-brown needles, m. p. 135–136° (Found: C, 75.6; H, 6.0; N, 3.9. $C_{22}H_{21}O_3N$ requires C, 76.1; H, 6.1; N, 4.0%).

Acetylation was carried out by refluxing with acetic anhydride (1.5 parts) and acetic acid (1.5 parts) for 20 minutes. The *acetyl* derivative (yield 100%) separated from methanol or benzene–light petroleum in colourless needles which appear to contain half a molecule of water of crystallisation (Found: C, 74.9; H, 6.7. $C_{23}H_{23}O_3N \cdot 0.5H_2O$ requires C, 74.6; H, 6.5%).

When the above formyl derivative (4 g.) was added to a solution of potassium (0.75 g.) in *tert.*-butyl alcohol (12 c.c.) in an atmosphere of dry nitrogen and then heated in accordance with the procedure detailed by Tyson (*loc. cit.*), black amorphous material was formed. Similar results were obtained with 6-acetamidohomocatechol dibenzyl ether and with 2-acetamido-4:5-diacetoxytoluene. When the

thermal decomposition of the dibenzyloxy-compounds was carried out in a vacuum, a distillate was obtained but neither this, nor ethereal extracts of the residue after acidification, gave a reaction with Ehrlich's reagent.

We thank Low Temperature Carbonisation, Ltd., for a generous gift of homocatechol.

KING'S COLLEGE OF HOUSEHOLD AND SOCIAL SCIENCE
(UNIVERSITY OF LONDON), W.8.

[Received, January 30th, 1950.]
