

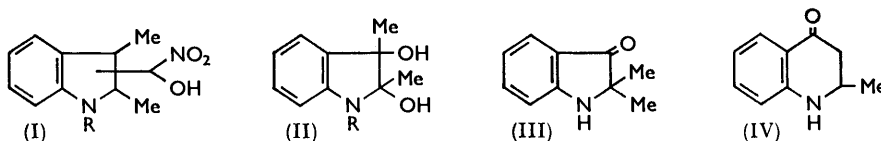
857. *The Nitration of 1-Acetyl-2,3-dimethylindole.*

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Further work on the nitration of 1-acetyl-2,3-dimethylindole has shown that the reaction occurs primarily at the 2,3-positions. The end-products are a glycol and *o*-acetamidoacetophenone. The structure of the former and the overall reaction sequence are discussed.

PREVIOUS work<sup>1</sup> on the nitration of 1-acetyl-2,3-dimethylindole showed that substitution products accounted for 40% of the starting material and that substitution occurred *meta* to the ring-nitrogen atom. Other products of the reaction were not investigated, but an indication of their nature has been given by Plant and his co-workers<sup>2</sup> who showed that reaction occurred at the 2,3-positions. They isolated a compound, m. p. 125° (decomp.), that was assigned the structure (I; R = Bz), and "from the preparation of a considerable quantity of 1-acetyl-2,3-dimethyl-6-nitroindole" a glycol (II; R = Ac) was obtained. Schofield and Ockenden<sup>3</sup> obtained identical material from the hydrolysis of its osmic ester. This result was unusual as *cis*-glycols are normally products of hydrolysis of osmic esters and Plant's glycol was obtained by oxidation with essentially a peracid. These considerations led us to re-examine the nitration of 1-acetyl-2,3-dimethylindole.

A compound, C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub>, m. p. 133—134°, was isolated in good yield from the mother-liquors that had yielded 1-acetyl-2,3-dimethyl-6-nitroindole. Oxidation of the former compound with periodate was very slow but after several days a high yield of *o*-acetamidoacetophenone was obtained. Treatment of the compound, C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub>, with dilute aqueous alkali provided, in almost theoretical yield a steam-volatile amphoteric ketone, C<sub>10</sub>H<sub>11</sub>NO, m. p. 89°. Solutions of the ketone showed an intense absorption band, λ<sub>max</sub> 396 mμ,<sup>4</sup> a green fluorescence in neutral aqueous solvents, and a blue fluorescence in chloroform.<sup>5</sup> It is therefore regarded as the indoxyl (III) (synthesized by an alternative route by Etienne<sup>6</sup>). It may be noted that these results are inconsistent with the expression (IV) for the ketone, suggested as an alternative structure for the isoquinamines<sup>7</sup> by Culvenor *et al.* The degradation products of the compound, C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub>, establish its structure as the glycol (II; R = Ac). Dr. Schofield kindly provided us with a specimen of his glycol and it was found to depress the melting point of the compound, C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub>, and to have a different infrared spectrum. It follows that the latter glycol has the *trans*-configuration and that this is the first example of *cis-trans*-isomerism in the dihydroindole series.



A further fraction obtained in working up the original nitration products provided dinitrogen tetroxide and *o*-acetamidoacetophenone. The *trans*-glycol (II; R = Ac) was recovered unchanged when treated with dinitrogen tetroxide; thus the glycol and the ketone represent alternative modes of degradation at the 2,3-position. It seemed likely that the nitro-alcohol (I; R = Ac) was an intermediate in the formation of these products; so the nitration of 1-benzoyl-2,3-dimethylindole<sup>2</sup> was repeated. Three products

<sup>1</sup> Atkinson, Simpson, and Taylor, *J.*, 1954, 165.

<sup>2</sup> Plant and Tomlinson, *J.*, 1933, 955; Plant and Whitaker, *J.*, 1940, 283.

<sup>3</sup> Schofield and Ockenden, *J.*, 1953, 612.

<sup>4</sup> Witkop and Ek, *J. Amer. Chem. Soc.*, 1951, **73**, 5664.

<sup>5</sup> Plant and Robinson, *Nature*, 1950, **165**, 36.

<sup>6</sup> Etienne, *Compt. rend.*, 1947, **225**, 124; *Bull. Soc. chim. France*, 1948, 651.

<sup>7</sup> Culvenor, Goldsworthy, Kirby, and Robinson, *J.*, 1950, 1490.

accounting for 70% of the starting material were isolated. Two of these were substitution products, analogous to those obtained from 1-acetyl-2,3-dimethylindole though they were isolated in only 20% yield. The main product,  $C_{17}H_{16}N_2O_4$ , was colourless but apparently differed from the compound described by Plant and Tomlinson,<sup>2</sup> for with alkali it gave dinitrogen tetroxide, *o*-acetamidoacetophenone, *o*-benzamidoacetophenone, and a compound,  $C_{17}H_{17}NO_3$ , m. p. 168°. The last compound with periodate gave a ketone,  $C_{17}H_{15}NO_3$ , that on mild alkaline hydrolysis provided *o*-benzamidoacetophenone. Thus the ketone is *N*-acetyl-*o*-benzamidoacetophenone and the expression (II; R = Bz) can be written for the compound of m. p. 168°. Identical material was obtained after performic oxidation of 1-benzoyl-2,3-dimethylindole and it is therefore probable that the glycol has the *trans*-configuration.

The products of mild alkaline degradation of the nitro-alcohol (I; R = Bz) were analogous to those isolated from 1-acetyl-2,3-dimethylindole. These results suggest that the nitro-alcohol is first formed by addition of nitric acid at the 2,3-position, this being followed by the loss of the nitro-group and the entry of a hydroxyl group *cis* and *trans* to that already present. As the *trans*-isomer is stable under the reaction conditions it will be the *cis*-isomer<sup>8</sup> that is oxidized to the *o*-acylaminoacetophenones. The lability of the nitro-alcohol is unexplained and numerous attempts to establish its structure failed.

#### EXPERIMENTAL

Microanalyses were by Dr. F. Pascher. Infrared spectra were determined on a Perkin-Elmer Infracord spectrophotometer.

*trans*-1-Acetyl-2,3-dihydroxy-2,3-dimethylindoline.—1-Acetyl-2,3-dimethylindole (6 g.) was suspended in glacial acetic acid (10 c.c.) and the stirred mixture treated dropwise at 20° with nitric acid ( $d$  1.42; 1.6 c.c.). After 1 hour's stirring at 20° the precipitate was collected and washed with acetic acid (2 × 2 c.c.), and the filtrate and washings were evaporated over potassium hydroxide at 20°/0.5 mm. The residue was treated with ethanol (10 c.c.), and the colourless precipitate collected (1.65 g., 23%); for *trans*-1-acetyl-2,3-dihydroxy-2,3-dimethylindoline separated as colourless hexagonal crystals, m. p. 133–134°, from benzene (Found: C, 65.2; H, 6.8; N, 6.1; O, 21.4.  $C_{12}H_{15}NO_3$  requires C, 65.2; H, 6.8; N, 6.3; O, 21.7%),  $\nu_{max}$ . 3650, 3450, 1645, 1220  $cm^{-1}$ .

*o*-Acetamidoacetophenone.—(a) The red alkaline extract "A" (see previous work<sup>1</sup>) (300 c.c.) was acidified with concentrated hydrochloric acid and extracted with ether (4 × 50 c.c.). The ethereal extracts were washed with 10% sodium carbonate solution (100 c.c.) and water (200 c.c.), dried ( $Na_2SO_4$ ), and evaporated, and the residue (11 g.) was distilled. Dinitrogen tetroxide was recovered from a trap at -80°; the distillate in the receiver (6.4 g., b. p. 142°/0.1 mm.) separated from light petroleum (b. p. 40–60°) as colourless needles, m. p. 74° alone or mixed with *o*-acetamidoacetophenone,  $\nu_{max}$ . 1685, 1649  $cm^{-1}$ .

(b) *trans*-1-Acetyl-2,3-dihydroxy-2,3-dimethylindoline (110 mg.) in warm ethanol (3 c.c.) was added to a solution of sodium periodate (500 mg.) in water (25 c.c.). The solution was treated with borate buffer (M/2; pH 7.85; 5 c.c.), left at 20–25° for 72 hr., concentrated on a rotatory evaporator at 20°/0.5 mm. to 10 c.c. and then extracted with ether (3 × 20 c.c.). The combined ethereal extracts were dried ( $Na_2SO_4$ ) and evaporated; the residue of *o*-acetamidoacetophenone (58 mg.; m. p. 70°), when recrystallized from light petroleum (b. p. 40–60°), had m. p. and mixed m. p. 74°.

2,2-Dimethylindoxyl.—The glycol (I; R = Ac) (0.5 g.) was treated with *n*-sodium hydroxide (40 c.c.) and steam-distilled until no more fluorescent drops passed over (3 hr.). The distillate (600 c.c.) was treated with sodium chloride (50 g.) and extracted with chloroform (3 × 100 c.c.). The extracts were dried ( $Na_2SO_4$ ) and evaporated. The residue (320 mg.) was collected with the aid of light petroleum (b. p. 60–80°; 3 c.c.). 2,2-Dimethylindoxyl separated from light petroleum (b. p. 40–60°) as yellow needles, m. p. 87–89° (0.31 g., 85%) (Found: C, 75.1; H, 6.85; N, 8.55. Calc. for  $C_{10}H_{11}NO$ : C, 74.6; H, 6.85; N, 8.7%),  $\lambda_{max}$  395  $\mu$

<sup>8</sup> Price and Knell, *J. Amer. Chem. Soc.*, 1942, **64**, 552; Criegee, Kraft, and Rank, *Annalen*, 1933, **507**, 159.

(log  $\epsilon$  3.61),<sup>4,7</sup>  $\nu_{\max}$ . 3140, 1675, 1616, 1401, 1375  $\text{cm}^{-1}$  [2,4-dinitrophenylhydrazones,<sup>6</sup> red needles (from ethanol), m. p. 238°].

1-Benzoyl-2,3-dimethylindole.—A solution from magnesium (25 g.) and methyl iodide (150 g.) in ether (250 c.c.) was treated with 2,3-dimethylindole (100 g.) in ether (350 c.c.). When evolution of methane ceased, ethyl benzoate (110 g.) in ether (140 c.c.) was added and the mixture stirred for a further 4 hr., then treated with iced water (1 l.). The ethereal layer was separated, dried ( $\text{CaCl}_2$ ), and evaporated. The residue of 1-benzoyl derivative, when recrystallized from ethanol, had m. p. 98° (115 g., 67%).

Nitration of 1-Benzoyl-2,3-dimethylindole.—1-Benzoyl-2,3-dimethylindole (19 g.) was suspended and stirred in glacial acetic acid (28 c.c.), and nitric acid (*d* 1.42; 4.7 c.c.) was added at 20°. After 3 hr. the mixture was filtered (filtrate A). The residue (11.4 g.) recrystallized from ethanol as prisms of 1-benzoyl-2,3-dimethyl-2(or 3)-hydroxy-3(or 2)-nitroindoline, m. p. 125–126° (decomp.) (Found: C, 65.8; H, 5.1; N, 8.2.  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$  requires C, 65.4; H, 5.1; N, 9.0%),  $\nu_{\max}$ . 3650, 1650, 1550  $\text{cm}^{-1}$  (aliphatic  $\text{NO}_2$ ). Overnight yellow needles separated from the filtrate A at 0°; these were collected (1.9 g.; m. p. 98–90°) and recrystallization from methanol gave yellow needles, m. p. 90°, or yellow rectangular prisms, m. p. 105°, of 1-benzoyl-2,3-dimethyl-6-nitroindole (Found: C, 69.3; H, 5.2; N, 9.55; O, 16.3.  $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3$  requires C, 69.4; H, 4.8; N, 9.5; O, 16.3%),  $\nu_{\max}$ . 1680, 1505  $\text{cm}^{-1}$ . The mother-liquors were diluted with water and the precipitated tar dried at room temperature/10 mm. over sodium hydroxide. The residue (5.6 g.) in 1:1 v/v benzene–light petroleum (b. p. 40–60°) (120 c.c.) was chromatographed on alumina (Brockmann grade II; 50 g.; 47 × 1.1 cm.). A yellow-green band was eluted with 10% v/v benzene–light petroleum that provided yellow prisms (1.0 g; m. p. 125–130°) on evaporation of the eluate. This 1-benzoyl-2,3-dimethyl-4-nitroindole separated from ethanol as yellow prisms, m. p. 129–130° (Found: C, 69.4; H, 4.8; N, 10.0%). The column was next washed with 1:99 methanol–benzene (500 c.c.), and the eluate evaporated to dryness. The residue (3 g.) was treated in methanol with 20% aqueous sodium hydroxide (0.2 c.c.), refluxed for 15 min., cooled, neutralized with hydrochloric acid, and evaporated. The mixed indoles were taken up in benzene (20 c.c.), washed with 5% sodium hydrogen carbonate solution, dried ( $\text{Na}_2\text{SO}_4$ ), treated with light petroleum (b. p. 40–60°; 20 c.c.), and applied to an alumina column (Brockmann grade II; 70 g.; 66 × 1.1 cm.). 2,3-Dimethyl-4-nitroindole (m. p. 178°; 0.5 g.) was eluted with 1:1 v/v benzene–light petroleum, and 2,3-dimethyl-6-nitroindole (m. p. 142°; 0.9 g.) with 0.5:99.5 methanol–benzene.

2,3-Dimethyl-4- and -6-nitroindole.—The 1-benzoylnitroindole (0.05 g.), methanol (3 c.c.), and 20% sodium hydroxide solution (0.2 c.c.) were refluxed together for 20 min. The mixture was evaporated, affording the nitroindoles (0.03 g.), whose m. p.s were undepressed on admixture with authentic specimens.

trans-1-Benzoyl-2,3-dihydroxy-2,3-dimethylindoline.—(a) 1-Benzoyl-2,3-dimethyl-2(3)-hydroxy-3(2)-nitroindoline (10 g.) was dissolved in 95% ethanol (600 c.c.), alumina (Brockmann grade I, 20 g.) was added, and the stirred mixture refluxed for 1 hr. The hot mixture was filtered, the alumina was washed with hot ethanol (2 × 20 c.c.), and the filtrate and washings were evaporated to 40 c.c. on a rotatory evaporator at 0°/2 mm. The crystals that separated (3.6 g.; m. p. 164–165°) were collected and the mother-liquors evaporated to dryness. The residue (6.4 g.) was titrated with isopropyl ether (20 c.c.), and the precipitate (A) (1.8 g.; m. p. 162–165°) collected. trans-1-Benzoyl-2,3-dihydroxy-2,3-dimethylindoline separated from ethanol as colourless prisms, m. p. 168° (5.2 g., 57%) (Found: C, 72.3; H, 5.8; N, 5.3.  $\text{C}_{17}\text{H}_{17}\text{NO}_3$  requires C, 72.1; H, 6.0; N, 4.9%),  $\nu_{\max}$ . 3500, 3400, 1645, 1215  $\text{cm}^{-1}$ . The filtrate from material (A) above was evaporated and the residue was dissolved in benzene (20 c.c.), treated with light petroleum (b. p. 60–80°; 20 c.c.), and run on to an alumina column (Brockmann grade II; 60 g.; 56 × 1.1 cm.). *o*-Benzamidoacetophenone (0.34 g.), m. p. 98° (Found: C, 75.1; H, 5.3; N, 5.9. Calc. for  $\text{C}_{15}\text{H}_{13}\text{NO}_2$ : C, 75.3; H, 5.4; N, 5.9%), was eluted with 10% v/v benzene–light petroleum (b. p. 60–80°), and *o*-acetamidoacetophenone (0.3 g., m. p. 74°) with 25% v/v benzene–light petroleum.

(b) 1-Benzoyl-2,3-dimethylindole (5 g.) was suspended in acetic acid (25 c.c.), and a 30% solution (2.5 c.c.) of hydrogen peroxide in acetic acid (25 c.c.) was added. The stirred suspension was treated with concentrated sulphuric acid (0.25 c.c.), heated to 40°, and left at room temperature overnight. The solution was diluted with water (200 c.c.) and extracted with benzene, and the benzene solution was washed with dilute sodium carbonate solution until acid-free, concentrated, and run on to an alumina column (Brockmann grade IV; 40 g.; 25 × 2

cm.). The column was developed with benzene (500 c.c.), the eluates being discarded. Ethanol then eluted a fraction which on evaporation provided colourless crystals (0.7 g.; m. p. 161—165°) giving, on recrystallization from ethanol, the above glycol, m. p. 168°.

*o*-(*N*-Acetyl-*N*-benzamido)acetophenone.—The glycol of m. p. 168° (0.14 g.), in hot ethanol (15 c.c.), was poured into a solution of sodium periodate (0.5 g.) in water (50 c.c.), treated with borate buffer (0.5M; pH 7.8; 5 c.c.) and left at room temperature for 80 hr., then concentrated to 20 c.c. and extracted with ether (3 × 50 c.c.). The dried (Na<sub>2</sub>SO<sub>4</sub>) extract was evaporated and the residue (0.5 g.) digested with benzene. The precipitate (0.05 g.; m. p. 165°) was collected and the mother-liquors were evaporated. *o*-(*N*-Acetyl-*N*-benzamido)acetophenone separated from isopropyl ether as (very characteristic) columnar hexagons, m. p. 125° (0.1 g.) (Found: C, 73.0; H, 5.6; N, 5.4; O, 15.9. C<sub>17</sub>H<sub>15</sub>NO<sub>3</sub> requires C, 72.6; H, 5.3; N, 5.0; O, 17.1%),  $\nu_{\max}$  1712, 1695, 1680 cm.<sup>-1</sup>.

*Stability of Glycols to Dinitrogen Tetroxide.*—The glycol (0.5 g.) was treated in hot ethanol (25 c.c.) with alumina (1 g.). The stirred solution was refluxed whilst dinitrogen tetroxide was passed in for 30 min. The hot solution was filtered, the alumina was washed with hot ethanol (2 × 10 c.c.), and the combined filtrates and washings were evaporated to dryness. The glycol (II; R = Ac) was obtained with 80% recovery and the glycol (II; R = Bz) with 92% recovery.

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