II. A SYNTHESIS OF MORINDONE.

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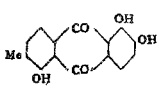
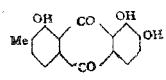
The mordant dyestuff, morindone, occurs in the root bark of *Morinda citrifolia* and *M. umbellata* mainly as the glucoside morindin. It was first isolated by Anderson (*Annalen*, 1849, **71**, 216) and was subsequently investigated by Thorpe and Greenall (*Journ. Chem. Soc.*, 1887, **51**, 52), Thorpe and Smith (*Ibid.*, 1888, **53**, 171) Perkin and Hummel (*Ibid.*, 1894, **65**, 851) and by Oesterle and Tisza (*Arch. Pharm.*, 1907, **245**, 534). As the result of these investigations it was established that morindone was a trihydroxy-6-methyl-anthraquinone, the position of the three hydroxy-groups remaining undetermined although from the general properties of the substance there appeared to be little doubt that two of the hydroxy-groups were in the 1 : 2–position.

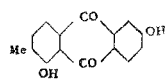
An analytical investigation led one of us to suggest (*Journ. Chem. Soc.*, 1918, **113**, 768) that morindone was either hydroxymethylanthrarufin (I) or hydroxymethylchrysazin (II), the former being preferred, since in its colour reactions, morindone more closely resembles hydroxyanthrarufin than hydroxychrysazin.



I



II



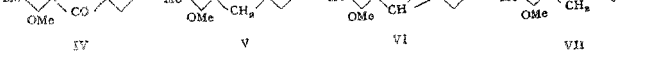
III

It is well known (*cf.* Liebermann, *Ber.*, 1876, **11**, 1617; *D.R.P.*, 195028, 196980) that 2-hydroxyanthraquinones on fusion with alkali, either alone or in the presence of oxidising agents, readily yield dihydroxyanthraquinones the second hydroxy-group entering the 1-position, a reaction which is analogous to the conversion of resorcinol into phloroglucinol by fusion with sodium hydroxide. Simonsen and Rau (*Journ. Chem. Soc.*, 1921, **118**, 1340) therefore synthesised 2 : 5-dihydroxy-6-methylanthraquinone (1 : 6-dihydroxy-2-methylanthraquinone, III) since on fusion with alkali this should yield the trihydroxy-methylanthraquinone (I). Unfortunately the yield of 2 : 5-dimethoxy-6-methylanthraquinone from 2 : 4'-dimethoxy-3-methylbenzophenone-6-carboxylic acid (IV) was so poor that systematic experiments on its oxidation were not possible.

Additional evidence of the correctness of the suggested formula for morindone was furnished by the synthesis of 1 : 2 : 8-trimethoxy-7-methylanthraquinone (*Journ. Chem. Soc.*, 1924, **125**, 721) which was found not to be identical with morindone trimethyl ether. In 1925 Adams and Jacobson (*Journ. Am. Chem. Soc.*, 1925, **47**, 283) devised an ingenious synthesis of 1 : 2 : 5-trihydroxy-6-methylanthraquinone (I) and showed this to be identical in all respects with morindone.

During the course of their experiments Simonsen and Rau obtained some evidence of the conversion of 2 : 5-dihydroxy-6-methylanthraquinone into morindone and it appeared to be not without interest to repeat and extend their experiments since it has been shown by Bistrzycki and his collaborators in a series of papers (*c. f. Helv. Chim. Acta*, 1923, **6**, 750) that an excellent yield of anthraquinone derivatives can usually be obtained if, instead of the benzophenone-carboxylic acid, the diphenylmethanecarboxylic acid is treated with sulphuric acid and the resulting anthrone subsequently oxidised to the corresponding anthraquinone.

The reduction of 2 : 4'-dimethoxy-3-methylbenzophenone-6-carboxylic acid (IV) to *2 : 4'-dimethoxy-3-methyldiphenylmethane-6-carboxylic acid* (V) offered some difficulty, but this acid was ultimately



obtained in an excellent yield by Scholl and Neovius' method (*Ber.*, 1911, **44**, 1075), although it is always accompanied by *2 : 4'-dimethoxy-3-methylphenylphthalide* (VI). When 2 : 4'-dimethoxy-3-methyldiphenylmethane-6-carboxylic acid is treated at the ordinary temperature with sulphuric acid it passes readily into *2 : 5-dimethoxy-6-methyl-9-anthrone* (VII), which on oxidation yields the dimethyl ether of 2 : 5-dihydroxy-6-methylanthraquinone (III). The dimethylation of the ether was most readily effected by somewhat prolonged digestion with aluminium chloride and the yield did not exceed 50 per cent. When the dihydroxyanthraquinone was fused with potassium hydroxide in presence of sodium arsenate at a temperature not exceeding 260°, the melt gradually changed from red to violet owing to formation of the trihydroxyanthraquinone. The oxidation was never complete, and if the temperature was allowed to rise above 260° profound decomposition took place and the melt became colourless. The mixture of hydroxyanthraquinones obtained on acidification of the melt was digested with barium hydroxide solution,

when the sparingly soluble barium salt of 1 : 2 : 5-trihydroxy-6-methylanthraquinone separated. The hydroxyanthraquinone from this barium salt was further purified by conversion into its acetyl derivative which, after repeated crystallisation from acetic acid, melted at 249° and was identical in all respects with the triacetyl derivative of morindone. On hydrolysis 1 : 2 : 5-trihydroxy-6-methylanthraquinone, m.p. 275°, was obtained and had all the properties of natural morindone.

EXPERIMENTAL.

2 : 4'-Dimethoxy-3-methyldiphenylmethane-6-carboxylic acid (V).

2 : 4'-Dimethoxy-3-methylbenzophenone-6-carboxylic acid (15 g.) was dissolved in sodium hydroxide solution (2 N; 475 cc.), an ammoniacal solution of copper sulphate (40 cc. from 2 N ammonia and 2 N copper sulphate) with zinc dust (25 g.) being added. The mixture was boiled under reflux for 140–150 hours, small additional quantities of sodium hydroxide solution and zinc dust being added every 12 hours. The hot reaction mixture was filtered, the residue washed with hot dilute ammonia and the filtrate acidified, when a pasty mass separated which rapidly solidified. The solid was dissolved in ether, the ethereal extract repeatedly washed with sodium bicarbonate solution, dried and evaporated. The viscid oil which remained slowly crystallised on keeping, more rapidly on inoculation, and was recrystallised from methyl alcohol, separating in glistening cubes m.p. 78–79°. *2 : 4'-Dimethoxy-3-methylphenylphthalide* was found to be readily soluble in the usual organic solvents; in cold alkalies it was insoluble but dissolved slowly on boiling (Found: C, 71·6; H, 5·7; $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·6 per cent.).

The sodium bicarbonate solution (see above) on acidification deposited *2 : 4'-dimethoxy-3-methyldiphenylmethane-6-carboxylic acid*. The acid, which was readily soluble in the ordinary organic solvents and very sparingly so in water, was best purified by crystallisation from methyl alcohol from which it separated in glistening leaflets, m.p. 103–104° (Found: C., 71·3; H, 6·2; M, 284·6; $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3 per cent.; M, 286).

2 : 5-Dimethoxy-6-methyl-9-anthrone (VII).

2 : 4'-Dimethoxy-3-methyldiphenylmethane-6-carboxylic acid (5 g.) was mixed with sulphuric acid (*d.* 1·84; 50 cc.) and the brown solution allowed to stand at room-temperature for ten minutes. The reaction mixture was poured on ice, the solid which separated collected,

triturated with dilute sodium carbonate solution to remove unchanged acid and recrystallised from acetic acid. The anthrone separated in faintly yellow needles, m.p. 111–112° (Yield 4 g. Found: C, 75·9; H, 6·2; $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0 per cent.).

2 : 5-Dimethoxy-6-methylanthraquinone.—The anthrone (1 mol.) having been dissolved in acetic acid, chromic acid (2 mols.) was gradually added, the oxidation being completed by digestion on the water bath. The anthraquinone was precipitated by water and recrystallised from either acetic acid or benzene, yellow needles, m.p. 192°[1] (Found: C, 72·9; H, 5·1; calc. C, 72·3; H, 5·0 per cent.).

2 : 5-Dihydroxy-6-methylanthraquinone.—The dimethyl ether (5 g.) was mixed with finely powdered aluminium chloride (10 g.), heated to 200° during one hour and maintained at this temperature for 30 minutes. A further quantity of aluminium chloride (5 g.) was added and the heating continued for another 15 minutes. The cooled reaction mixture was treated with ice and hydrochloric acid and the hydroxyanthraquinone collected. It was purified by solution in alkali and crystallisation from acetic acid, m.p. 280–281°.

1 : 2 : 5-Trihydroxy-6-methylanthraquinone.

2 : 5-Dihydroxy-6-methylanthraquinone (1 g.) was dissolved in potassium hydroxide solution (10 cc. of 50 per cent.) and the mixture heated in a nickel crucible with gradual addition of sodium arsenate (1 to 2 g.) at 220–230° (bath-temperature) for 1·5 hours. The red melt gradually became bluish violet owing to the conversion of the di- into trihydroxyanthraquinone. After dilution with water (100 cc.) the solution was boiled for 30 minutes and acidified. The mixture of hydroxyanthraquinones which separated was digested with an excess of barium hydroxide solution, when a sparingly soluble violet barium salt was precipitated. This was collected, decomposed with hydrochloric acid and the somewhat impure 1 : 2 : 5-trihydroxy-6-methylanthraquinone acetylated. The triacetyl derivative crystallised from acetic acid in needles, m.p. 249° uncorr. and this m.p. was unaltered on admixture with a specimen of triacetylmorindone. On hydrolysing the acetyl derivative, 1 : 2 : 5-trihydroxy-6-methylanthraquinone was obtained and crystallised from toluene in orange red needles m.p. 275° uncorr. It had all the properties of morindone and did not depress the m.p. of this substance (Found: C, 66·8; H, 3·8; calc. C, 66·6; H, 3·7 per cent.).

[1] The m.p. 182° given in the previous communication (*loc. cit.*, p. 1347) is a clerical error.