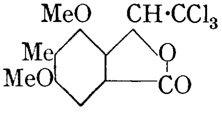
331. 1 : 3 : 5 : 8-*Tetrahydroxy-2-methylanthraquinone.*

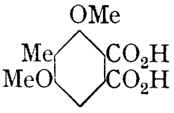
By E. H. Charlesworth and Robert Robinson.

In the course of work on the constitution of pigments extracted from the mycelia of various species of *Helminthosporium* (*Biochem. J.*, 1933, **27**, 499; 1934, **28**, 559; J., 1933, 488), Charles, Raistrick, Robinson, and Todd isolated and characterised a number of hydroxylated 6-methylquinizarins which are metabolic products of the moulds when grown in glucose solutions. The substance named in the title, being required for comparison, was synthesised.

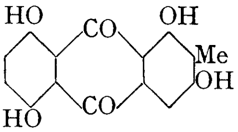
2 : 6-Dihydroxy-*p*-toluic acid was methylated and condensed with chloral in the presence of sulphuric acid with formation of 3 : 5-*dimethoxy*-4-*methyl*-α-*trichloromethylphthalide* (I).



(I.)



(II.)



(III.)

This substance was hydrolysed, the phthalidecarboxylic acid decarboxylated, and the 3 : 5-*dimethoxy*-4-*methylphthalide* oxidised to 3 : 5-*dimethoxy*-4-*methylphthalic acid* (II).

The anhydride of (II) was condensed with quinol dimethyl ether in the presence of aluminium chloride, and the crude product directly treated with hot sulphuric acid, affording 1 : 3 : 5 : 8-*tetrahydroxy*-2-*methylanthraquinone* (III).

Experimental.

4-*Carboxytoluene*-3-*sulphonyl Chloride.*—This substance was obtained in the course of attempts to improve the disulphonation of *p*-toluic acid, which involved difficulties. *p*-Toluoyl chloride (10 g., b. p. 225—227°) was added gradually with mechanical stirring to chlorosulphonic acid (60 c.c.) kept at about 10°. The mixture was maintained at 150° for 3 hours, the evolution of hydrogen chloride then ceasing. The product was poured on ice (500 g.), the separated solid washed, pressed on tile, and dried in a vacuum (yield, 14 g.), and a small portion twice crystallised from chloroform, giving small colourless plates, m. p. 110° (Found: S, 13·6; Cl, 15·3. $C_8H_7O_4ClS$ requires S, 13·6; Cl, 15·1%). The derivative is easily soluble in alcohol, ether, chloroform, and hot benzene and sparingly soluble in light petroleum.

3 : 5-*Dihydroxy*-p-*toluic Acid.*—Attempts to obtain this acid by following the method of Mitter and Gupta (*J. Indian Chem. Soc.*, 1928, **5**, 26; compare Weinreich, *Ber.*, 1887, **20**, 982) did not result in the production of a substance, m. p. 176°, as recorded by those authors. The only pure product isolated from the eventual alkali-fusion was *m*-hydroxybenzoic acid, m. p. 201°, identified by analysis and mixed melting point. It is not easy to see how this arises, as the *p*-toluic acid employed was free from benzoic acid. The most plausible explanation is oxidation of the methyl group and decarboxylation of the sulphoterephthalic acid produced.

Employing the method of Asahina and Asano (*Ber.*, 1933, **66**, 687), which was published while our work was in progress, we obtained an acid of m. p. 260° agreeing with the m. p. 262° of the Japanese chemists.

p-Toluic acid (50 g.) gave a crude potassium salt of the disulphonic acid (146 g.), which was fused with potassium hydroxide (650 g.) and a little water. We find that the yield is increased by a longer fusion than that prescribed by Asahina and Asano and recommend adding the potassium salt at 220° and fusing for 20 minutes at 250°, 15 minutes at 260°, and 15 minutes at 270°. The melt was dissolved in water, acidified with hydrochloric acid, and extracted thoroughly with ether. The ethereal extract was evaporated, and the residue treated with warm water (750 c.c.), which dissolved the phenolic acid, leaving a residue (about 6 g.) melting with decomposition at about 320°. The aqueous solution was saturated with salt and extracted with ether; evaporation of the solvent afforded a light cream-coloured product (26·5 g., m. p. 245—250°) which was used for the preparation of the methyl ether. A second purification by the same method gave fine needles, m. p. 260° with slight previous softening and darkening, having the properties recorded by Asahina and Asano. The composition $C_8H_8O_4,0{\cdot}5H_2O$ was confirmed by full analysis.

3 : 5-*Dimethoxy*-p-*toluic Acid*.—Methyl sulphate (90 c.c.) was added in 3 portions to a solution of 3 : 5-dihydroxy-*p*-toluic acid (25 g.) in aqueous sodium hydroxide (300 c.c. of 20%), in a flask filled with coal gas. After 30 minutes' shaking with cooling, sodium hydroxide (10 g. in 15 c.c. of water) was added, and the mixture refluxed for 1 hour. The cream-coloured crystalline material (25·2 g.) obtained on acidification crystallised from acetic acid (50 c.c.) in long needles (12·5 g.). A small sample, recrystallised from 50% acetic acid, formed clusters of colourless needles, m. p. 215° (Found : C, 61·5; H, 6·1. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%).

3 : 5-*Dimethoxy*-4-*methyl*-α-*trichloromethylphthalide* (I).—3 : 5-Dimethoxy-*p*-toluic acid (12·4 g.) was mixed in a stoppered flask with powdered chloral hydrate (15 g.), and sulphuric acid (57 c.c. and 3 c.c. of water) added. After 24 hours, the reaction mixture was poured on ice and the separated solid was washed with water and aqueous alcohol and crystallised from alcohol (150 c.c., charcoal), forming colourless plates (17·0 g., m. p. 128—130°). Recrystallisation afforded a pure specimen, m. p. 133—134° (Found : Cl, 32·4. $C_{12}H_{11}O_4Cl_3$ requires Cl, 32·7%). The substance is freely soluble in ether and benzene, less soluble in alcohol, and very sparingly soluble in light petroleum.

3 : 5-*Dimethoxy*-4-*methylphthalide*-α-*carboxylic Acid*.—The above trichloro-compound (14·3 g.) and aqueous sodium hydroxide (75 c.c. of 20%) were heated on the steam-bath and the yellowish solution formed after an hour was filtered from a few dark specks. On cooling, yellow plates of a sodium salt were deposited; sufficient water was added to dissolve this salt and the mixture was made strongly acid with hydrochloric acid. On keeping, the *carboxylic acid* separated as colourless needles (9·7 g.), m. p. 173—174°. A specimen was recrystallised from water, m. p. 174—175° (Found : C, 57·1; H, 5·0. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%). The acid is soluble in alcohol and hot water, but is sparingly soluble in ether and benzene.

3 : 5-*Dimethoxy*-4-*methylphthalide*.—Dimethoxymethylphthalidecarboxylic acid (9·7 g.), copper chromite (0·8 g.), and quinoline (28 c.c.) were heated (bath at 150—160°) until evolution of carbon dioxide ceased (*ca.* 12 minutes). The quinoline solution was decanted from the catalyst into dilute hydrochloric acid; the greenish precipitate crystallised from alcohol (125 c.c., charcoal) in long, narrow, pale yellow prisms (4·1 g., m. p. 157°); recrystallised, it formed colourless needles, m. p. 158° (Found : C, 63·3; H, 5·8. $C_{11}H_{12}O_4$ requires C, 63·4; H, 5·8%). The *phthalide* is easily soluble in alcohol, ether, or benzene; it is very sparingly soluble in hot water and almost insoluble in light petroleum.

An attempt was made to prepare this substance directly, by the condensation of 3 : 5-dimethoxy-*p*-toluic acid with formaldehyde in the presence of hydrochloric acid by the method of Perkin, Edwards, and Stoyle (J., 1925, **127**, 195), but the product crystallised from alcohol in needles, m. p. 131°, and contained chlorine.

3 : 5-*Dimethoxy*-4-*methylphthalic Acid* (II).—3 : 5-Dimethoxy-4-methylphthalide (4·3 g.) was dissolved in aqueous potassium hydroxide solution (100 c.c. of 5%), and potassium permanganate (6·1 g.) in water (200 c.c.) added at room temperature. After 24 hours the liquid was filtered and some remaining manganate was reduced by sulphur dioxide; it was then concentrated to a small volume and acidified with hydrochloric acid. The crude acid was purified by dissolution in hot water (100 c.c.) and filtration from unchanged phthalide. On cooling, the *acid* separated in elongated prisms (2·3 g.); recrystallised from water, m. p. 195—196° (decomp.) (Found : C, 55·4; H, 4·9. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%). This acid is readily soluble in hot water and it is sparingly soluble in ether or benzene.

The *anhydride* was prepared by carefully heating the acid (1·4 g.) at its melting point and crystallised from benzene (yield, 1·02 g.), m. p. 166°. It sublimed in long colourless needles (Found : C, 59·4; H, 4·5. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%).

1 : 3 : 5 : 8-*Tetrahydroxy*-2-*methylanthraquinone* (III).—Powdered aluminium chloride (2·2 g.) was added in 3 portions to a mixture of 3 : 5-dimethoxy-4-methylphthalic anhydride (1 g.) and quinol dimethyl ether (2 g.) in dry carbon disulphide (25 c.c.). The mixture was refluxed on the steam-bath for 24 hours, cooled, the carbon disulphide decanted, and the semi-solid mass decomposed with dilute hydrochloric acid and distilled in steam. The greenish-yellow viscous residue (1·1 g.) was dried and heated for 30 minutes with concentrated sulphuric acid (3 c.c.) at 150°. The reddish-blue solution was poured into water, and the deep brown amorphous material collected. It could not be purified by crystallisation in the first instance, but by sublimation at 240—250° in a high vacuum for 10 hours a bright red powder (0·21 g.), m. p. 265—267°, was obtained. This was twice crystallised from 50% acetic acid and obtained in thin, elongated, yellowish-red plates, m. p. 276—277° (Found : C, 62·9; H, 3·6. $C_{15}H_{10}O_6$ requires C, 62·9; H, 3·5%).

This product is not identical with the isomeric catenarin (m. p. 246°) (Raistrick, Robinson, and Todd, *Biochem. J.*, 1934, **28**, 559), as a mixture melted from 225° to 234°. The colour reactions of the synthetic product are very similar to those of catenarin. The following are the points of divergence noted. The colour in sulphuric acid is slightly bluer than that of catenarin. Alkaline solutions have identical colours, but those of catenarin are more rapidly oxidised in the air. The orange alcoholic solution of the synthetic compound exhibits a very feeble fluorescence, that of catenarin being much more pronounced. The synthetic compound is slightly the less soluble in aqueous alcohol.

The *tetra-acetyl* derivative was prepared by boiling (III) for a few minutes with acetic anhydride containing a trace of sulphuric acid. The yellow solution was poured into water; the precipitated acetyl derivative crystallised from acetic acid in small lemon-yellow plates, m. p. 223° (Found : C, 60·8; H, 4·1. $C_{23}H_{18}O_{10}$ requires C, 60·8; H, 4·0%).

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