Studies in Mycological Chemistry. Part III. Some Hydroxy- and Methoxy-benzenepolycarboxylic Acids.*

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Syntheses of 3-hydroxybenzene-1 : 2 : 5-tricarboxylic acid and of 3-methoxy- and 3-hydroxy-benzene-1 : 2 : 4 : 5-tetracarboxylic acid are described. The evidence for their orientation is discussed and details of their chromatographic behaviour (on paper) are given.

The three acids mentioned above, together with 3-methoxybenzene-1 : 2 : 5-tricarboxylic acid, were required as reference compounds in connection with the identification of certain acids obtained by the oxidative degradation of purpurogenone, a metabolic product of *Penicillium purpurogenum* Stoll (see following paper).

Of these four acids, only one (the last mentioned) had previously been synthesised (Posternak, *Helv. Chim. Acta*, 1940, **23**, 1046; see also Groves, *J.*, 1954, 1817). Posternak obtained this acid by a two-stage oxidation of the substituted acetophenone prepared from 3 : 5-dimethylanisole and acetyl chloride (Friedel–Crafts reaction) (von Auwers and Borsche, *Ber.*, 1915, **48**, 1698). The somewhat unexpected orientation of this ketone had been established by the latter workers. The orientation of the Posternak acid is now confirmed for it has been shown that demethylation yields a hydroxybenzenetricarboxylic acid which gives an intense reddish-violet ferric reaction—proving the existence of one carboxyl group in an *ortho*-position to the hydroxy-group. The demethylation was achieved either by alkali fusion or by use of hydriodic acid.

A claim to have prepared 3-methoxybenzene-1 : 2 : 4 : 5-tetracarboxylic acid (m. p. 250—251°) was made by Nikuni (*J. Agric. Chem. Soc. Japan*, 1941, **17**, 779; *Chem. Abs.*, 1942, **36**, 4814) who obtained the acid by oxidative degradation of methylated α-sorigenin. (α-Sorigenin is the aglycone of α-sorinin which is found in the bark of *Rhamnus japonica.*) A full account of this work is not available to us but it appears that the orientation of this acid was not rigorously proved. 3-Methoxybenzene-1 : 2 : 4 : 5-tetracarboxylic acid (m. p. 249—251°) has now been synthesised by a route which leaves no doubt as to its orientation, and the similarity of its physical properties to those of Nikuni's acid indicates that the latter was correctly orientated. The acid was synthesised from 2 : 6-bishydroxymethyl-3 : 5-dimethylphenol, the orientation of which has been convincingly proved by Finn, Lewis, and Megson (*J. Soc. Chem. Ind.*, 1950, **69**, 129). Finn *et al.* (*loc. cit.*) describe the methylation and oxidation of this compound to 2-methoxy-4 : 6-dimethylbenzene-1 : 3-dicarboxylic acid but, in our hands, their method proved unsatisfactory. An improved procedure is described below. Finally, the dicarboxylic acid was oxidised, by alkaline potassium permanganate solution, to the desired tetracarboxylic acid. An attempt to synthesise the latter acid by chromic acid oxidation of durenyl acetate by the Fischer–Gross method (*J. prakt. Chem.*, 1911, **84**, 369, 372) was unsuccessful. Demethylation of the acid (by means of hydriodic acid) led to 3-hydroxybenzene-1 : 2 : 4 : 5-tetracarboxylic acid, together with other hydroxybenzenepolycarboxylic acids which had been produced by partial decarboxylation.

The two hydroxybenzenepolycarboxylic acids, mentioned above, are readily soluble in water but sparingly soluble in dilute 2—4N-hydrochloric acid and this property has been exploited for their isolation. Partial decarboxylation occurs somewhat readily when their aqueous solutions are boiled and undoubtedly accounts for the high equivalent weights (recorded below) which were determined by Pregl's method (Pregl and Grant, "Quantitative Organic Microanalysis," 5th English Ed., Churchill, London, 1951, p. 165).

The four benzenepolycarboxylic acids, considered here, may be run on paper chromatograms. A knowledge of their R_F values and of the colours of the "spots" formed when

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the chromatograms are sprayed with ferric chloride solution is a valuable aid in their identification (see following paper).

EXPERIMENTAL.

Chromatographic Procedure.—The method used was essentially that of Bate-Smith and Westall (*Biochim. Biophys. Acta*, 1950, **4**, 427). A previously determined suitable quantity of the acid, dissolved in acetone or ether, was spotted on a strip of Whatman's No. 1 paper. The (descending) solvent was either the upper layer formed by equilibrating *n*-butanol (40 c.c.), glacial acetic acid (10 c.c.), and water (50 c.c.) or the lower layer formed from *m*-cresol (50 c.c.), glacial acetic acid (2 c.c.), and water (48 c.c.). R_F values obtained with the former solvent are represented as R_F(b) and those with the latter solvent as R_F(c). The chromatograms were allowed to run for 16—26 hr. at 16—18°, were " dried off " in a current of air (followed by, in the case of the *m*-cresol solvent mixture, heating them in an oven at 100°), and were then sprayed with 1% (for the hydroxy-acids) or 2% (for the methoxy-acids) neutral, aqueous ferric chloride. The former acids yield spots of a red shade while the latter acids yield yellow-brown stains.

3-*Methoxybenzene*-1 : 2 : 5-*tricarboxylic Acid.*—This acid was prepared by Posternak's method (*loc. cit.*). It had R_F(b) 0·76.

3-*Hydroxybenzene*-1 : 2 : 5-*tricarboxylic Acid.*—(i) The foregoing acid (0·72 g.), acetic acid (15 c.c.), and hydriodic acid (*d* 1·7; 15 c.c.) were heated under reflux for 5 hr. Water (10 c.c.) was added and the volume of the mixed solvents was reduced, by gentle heating *in vacuo*, to *ca.* 2 c.c. in order to induce separation of the organic acid. To the cooled mixture, 2N-hydrochloric acid (3 c.c.) was added. The hydroxy-acid was filtered off, washed with 2N-hydrochloric acid (3 c.c.), and dried (0·45 g., m. p. 219—221°). Recrystallisation from hot 4N-hydrochloric acid yielded 3-*hydroxybenzene*-1 : 2 : 5-*tricarboxylic acid* (0·36 g.) in microscopic prisms, m. p. 217—218° (effervescence) (Found : C, 47·7; H, 2·7%; equiv., 76·4. $C_9H_6O_7$ requires C, 47·8; H, 2·7%; equiv., 75·4). It had R_F(b) 0·61, R_F(c) 0·02. [Hydrobromic acid (*d* 1·49) alone, or mixed with glacial acetic acid was inefficient as a demethylating agent.] This hydroxy-acid is readily soluble in water or ethanol. Its aqueous solution gives an intense reddish-violet ferric reaction.

(ii) The same acid (but of inferior quality and in smaller yield) was prepared thus. The methoxy-acid (0·15 g.), potassium hydroxide (1 g.; pellets), and water (2 drops) were held at fusion point for 1 min. The cooled mass was dissolved in water and filtered through glass-wool. Acidification of the solution and ether-extraction yielded the hydroxy-acid (50 mg.) which was recrystallised by allowing its solution in ether–benzene to evaporate slowly. The yield was 18 mg. and the m. p. 213—215° (effervescence).

2 : 6-*Bishydroxymethyl*-3 : 5-*dimethylanisole.*—2 : 6-Bishydroxymethyl-3 : 5-dimethylphenol was prepared (yield, 41% of recrystallised material, m. p. 146°) by the method of Finn *et al.* (*loc. cit.*) who give m. p. 147—148°. This material (7·7 g.), anhydrous potassium carbonate (8·2 g.), methyl sulphate (4·9 c.c.), and dry acetone (120 c.c.) were heated under reflux for 17 hr. and the hot solution was filtered. The residue was extracted with boiling acetone (2 × 70 c.c.), and the potassium salts were discarded. The combined acetone solutions, when cooled, yielded 2 : 6-bishydroxymethyl-3 : 5-dimethylanisole (3·0 g.); a further 2·7 g. of material were obtained by concentrating the mother-liquor to 30 c.c. Recrystallisation of the combined crops from water gave 4·2 g. of material, m. p. 168°. Finn *et al.* give m. p. 166°.

2-*Methoxy*-4 : 6-*dimethylbenzene*-1 : 3-*dicarboxylic Acid.*—To a suspension of the foregoing material (3·92 g.) in 2N-sodium hydroxide (20 c.c.) was added a solution of potassium permanganate (6·63 g.) in water (100 c.c.) and the mixture was left, with occasional shaking, at room temperature for 3 hr. The mixture was then saturated with sulphur dioxide and, after the addition of concentrated hydrochloric acid (12 c.c.), was kept at −2° for 12 hr. The crude acid was collected and triturated with a saturated solution of sodium hydrogen carbonate (50 c.c.). The mixture was filtered (to remove *ca.* 0·2 g. of insoluble material), and, to the filtrate was added concentrated hydrochloric acid (10 c.c.) in order to precipitate the dicarboxylic acid (2·0 g.), m. p. 232—234° (effervescence). Finn *et al.* give m. p. 236°.

3-*Methoxybenzene*-1 : 2 : 4 : 5-*tetracarboxylic Acid.*—To a warm (50°) solution of the foregoing dicarboxylic acid (0·34 g.) in 2N-sodium carbonate (3 c.c.) was added a warm solution of potassium permanganate (0·96 g.) in water (10 c.c.), and the combined solutions were heated on the steam-bath for 3 hr. The small excess of permanganate was destroyed by the addition of a few drops of methanol. The mixture was filtered whilst hot and the manganese dioxide was thoroughly extracted and washed with boiling water. The combined filtrates and washings were evaporated to 6 c.c. and acidified (concentrated hydrochloric acid) to *ca.* pH 1. The solution, after 16 hr. at −2°, had deposited a mass of small, silky needles (0·19 g.) of an acid potassium salt. To a solution of this salt in water (1·5 c.c.) was added concentrated hydrochloric acid (10 drops), and the solution was left at −2° for 3 days. 3-*Methoxybenzene*-1 : 2 : 4 : 5-*tetracarboxylic acid* (80 mg.) separated as prisms, m. p. 249—251° (decomp.) after becoming yellow at *ca.* 200° (Found: C, 46·3; H, 2·85; OMe, 10·9%; equiv., 70·9. $C_{10}H_5O_8{\cdot}OMe$ requires C, 46·5; H, 2·85; OMe, 10·9%; equiv., 71·0). It had R_F(b) 0·61. This acid is easily soluble in water. Addition of ferric chloride to its aqueous solution produces a yellow colour which is followed, almost immediately, by the formation of a buff-coloured, flocculent precipitate.

In the above method it was difficult to judge the amount of hydrochloric acid which was required for the precipitation of the acid potassium salt from the solution of the acid in excess of alkali. An alternative method for isolating the acid (in superior yield but of slightly inferior quality) was as follows. The dicarboxylic acid (1·94 g.) was oxidised as described above and the filtrate and washings (from the manganese dioxide precipitate) were concentrated to 30 c.c. To the warm solution was added a large excess of concentrated hydrochloric acid (19 c.c. in all). The precipitation of the tetracarboxylic acid (1·62 g., m. p. 244—246°) was complete after 1 hr. at −2°. (Recrystallisation from boiling 3N-hydrochloric acid did not improve the quality of the product. Decarboxylation probably occurred.)

3-*Hydroxybenzene*-1 : 2 : 4 : 5-*tetracarboxylic Acid.*—The methoxy-acid (0·6 g.), acetic acid (10 c.c.), and hydriodic acid (*d* 1·7; 10 c.c.) were heated under reflux for 5 hr. (Dissolution was complete after 15 min.) To the cooled solution was added water (7 c.c.), and the volume of the solvents was reduced, by gentle heating *in vacuo*, to *ca.* 1·5 c.c. After the addition of 2N-hydrochloric acid (2·5 c.c.), the crude hydroxy-acid was filtered off and washed with 2N-hydrochloric acid (3 c.c.). An attempt to recrystallise this crude acid (0·3 g.) from boiling N-hydrochloric acid led to the separation of a product (30 mg.) which was shown by analysis (for carbon and hydrogen) and by chromatography to be a mixture of hydroxy-acids formed by partial decarboxylation of the desired hydroxybenzenetetracarboxylic acid. The mother-liquor was evaporated *in vacuo* to dryness and the residue (which was shown by chromatography to contain only traces of hydroxy-acids produced by partial decarboxylation) was recrystallised from twenty times its weight of hot 4N-hydrochloric acid, the solution having been heated to a minimum extent before filtration to remove the less soluble, partially decarboxylated products. 3-*Hydroxybenzene*-1 : 2 : 4 : 5-*tetracarboxylic acid* (yield *ca.* 10%) separated as small prisms (Found: C, 44·6; H, 2·15%; equiv., 69·5. $C_{10}H_6O_9$ requires C, 44·4; H, 2·25%; equiv., 67·5) which, when heated, became yellow at 172°; the main portion sublimed at 239° to give a deep-yellow, crystalline sublimate; the small residue finally melted at 310°. This acid had R_F(b) 0·29 and is readily soluble in water. Its aqueous solution gives a dark reddish-violet ferric reaction.

Oxidation of Durenyl Acetate.—*Durenyl acetate*, prepared from durenol and acetic anhydride (containing a trace of concentrated sulphuric acid), was recrystallised from warm aqueous acetic acid, to give plates, m. p. 78—79° (Found: C, 74·8; H, 8·2. $C_{12}H_{16}O_2$ requires C, 74·9; H, 8·4%). This material (0·6 g.) was readily oxidised in warm (60°) acetic acid–acetic anhydride by chromic anhydride (2·5 g.) but an attempt to isolate the hydroxybenzenetetracarboxylic acid led to only a trace of colourless crystalline material which gave a violet ferric reaction.

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