61. *Synthesis of Compounds related to Mould Metabolic Products. Part I. 3 : 5-Dihydroxy-2-formylbenzoic Acid and 3 : 5-Dihydroxyphthalic Acid.*

By JOHN HOWARD BIRKINSHAW and ARTHUR BRACKEN.

Methyl 3 : 5-dihydroxybenzoate was converted by the Gattermann synthesis into *methyl* 3 : 5-*dihydroxy*-2-*formylbenzoate*, which on hydrolysis gave the free *acid*, and on mild potash fusion 3 : 5-dihydroxyphthalic acid.

THE mould *Penicillium stipitatum* Thom, when grown on a Czapek–Dox–glucose medium, produces a new acid, stipitatic acid, $C_8H_6O_5$ (Birkinshaw, Chambers, and Raistrick, *Biochem. J.*, 1942, **36**, in the press). This acid has certain properties which suggested that it might be a dihydroxyformylbenzoic acid, although other properties, notably its failure to yield aldehydo- or ketonic reactions, were not in accordance with this hypothesis. From the colour reaction with hypochlorite it appeared that stipitatic acid, if benzenoid in nature, would be a resorcinol derivative. The masking of the formyl group could only be ascribed to its being situated between a carboxyl and a hydroxyl group. Although it seemed unlikely that such a compound would not react with the usual aldehyde reagents, the synthesis of 3 : 5-*dihydroxy*-2-*formylbenzoic acid* was undertaken in order to exclude this possibility for the constitution of stipitatic acid. The synthetic product differed in m. p. and other properties from stipitatic acid.

Benzoic acid was converted into the disulphonate substantially by Brunner's method (*Monatsh.*, 1928, **50**, 216). Potash fusion of the dipotassium disulphonate (Barth and Senhofer, *Annalen*, 1871, **159**, 222, give inadequate details) afforded 3 : 5-dihydroxybenzoic acid in much better yield than that claimed by Graves and Adams (*J. Amer. Chem. Soc.*, 1923, **45**, 2439), who fused the acid barium salt of the disulpho-acid with potassium hydroxide. Moreover Brunner's method of sulphonation avoids the use of an autoclave.

Methyl 3 : 5-dihydroxybenzoate was subjected to a Gattermann reaction, following the method of Shah and Laiwalla (J., 1938, 1828), and *methyl* 3 : 5-*dihydroxy*-2-*formylbenzoate* was thus obtained. On cold alkaline hydrolysis it afforded 3 : 5-dihydroxy-2-formylbenzoic acid, although the possibility is not excluded that it also exists in the tautomeric hydroxyphthalide form. Both the methyl ester and the acid gave immediate precipitates of the corresponding *hydrazones* with 2 : 4-dinitrophenylhydrazine hydrochloride in 2N-hydrochloric acid.

Although, in accordance with the usual course of the Gattermann reaction, the formyl group should occupy a position *op* to the two hydroxyl groups, yet in view of the production of methyl 2 : 4-dihydroxy-3-formylbenzoate from the 2 : 4-dihydroxy-ester as shown by Shah and Laiwalla (*loc. cit.*) it was necessary to obtain definite evidence of the point of entry of the formyl group in the present case. This was done by conversion of the aldehydo- into a carboxyl group. Potash fusion of the synthetic ester under mild conditions (cf. Tiemann and Reimer, *Ber.*, 1877, **10**, 1570; Tiemann and Lewy, *ibid.*, p. 2210) gave a mixture of acids, from which 3 : 5-dihydroxyphthalic acid was readily separated as the lead salt. The acid after purification was identical with 3 : 5-dihydroxyphthalic acid obtained from *Penicillium brevi-compactum* Dierckx by Oxford and Raistrick (*Biochem. J.*, 1932, **26**, 1902). Further proof of its identity was obtained by conversion into 3 : 5-dimethoxyphthalic anhydride, which agreed in m. p. and mixed m. p. with the authentic product prepared by Fritsch's method (*Annalen*, 1897, **296**, 357) from 3 : 5-dimethoxybenzoic acid.

Although the synthesis of 3 : 5-dimethoxyphthalic acid and its anhydride were described by Fritsch, the present account appears to be the first recorded synthesis of 3 : 5-dihydroxyphthalic acid, which has hitherto been encountered only as a metabolic product of *P. brevi-compactum.*

EXPERIMENTAL.

Dipotassium Benzoic acid-3 : 5-*disulphonate*.—Benzoic acid (100 g.) was sulphonated with fuming sulphuric acid and chlorosulphonic acid at ordinary pressure according to the method of Brunner (*loc. cit.*). During the second and the third heating (in the presence of chlorosulphonic acid) the mixture was refluxed for 2 hours each time at a bath temperature of 245° (the highest temperature which could be obtained owing to the volatility of the chlorosulphonic acid); the head was then changed to downward air-condenser and chlorosulphonic acid was allowed to distil until the bath temperature reached 260°. As most of the excess of chlorosulphonic acid was thus removed, the amount of barium carbonate required for subsequent neutralisation was considerably reduced. The yield of air-dried crystalline dipotassium salt (of unknown water content) was 286 g.

3 : 5-*Dihydroxybenzoic Acid*.—The disulphonate (20 g.) was heated with 80 g. of potassium hydroxide and 15 ml. of water in a nickel crucible. The metal-bath temperature was raised as rapidly as frothing would permit to 360° with frequent stirring and maintained at that point for ¾ hour. The melt was pink in the early stages, later becoming colourless, then yellowish; it gradually acquired the colour and consistency of pea-soup. When the heating was finished, the melt was dissolved in water, and the solution acidified and extracted with ether. The crude extract was crystallised from water. The yield of anhydrous acid (dried at 105°) was 6·5 g., m. p. 234°. Thus the yield from 100 g. of benzoic acid is 93 g.

Methyl 3 : 5-*Dihydroxybenzoate*.—The dry acid (32·4 g.) was refluxed with methyl alcohol (200 ml.) containing concentrated sulphuric acid (5 ml.) for 16 hours. Then 150 ml. of the alcohol were distilled, and 100 ml. of water added to the residue. The solution became cloudy and after 16 hours at 0° had deposited a mass of crystals. These were collected and washed with water; yield 26·3 g., m. p. 165°. The filtrate was extracted with ether; the extract, after being washed with aqueous sodium bicarbonate, gave further crystals, which were recrystallised from aqueous methyl alcohol, giving a total yield of 32·7 g.

Methyl 3 : 5-*Dihydroxy*-2-*formylbenzoate*.—To methyl 3 : 5-dihydroxybenzoate (32·7 g.) and dry ether (300 ml.), cooled in a freezing mixture, anhydrous zinc cyanide (46 g.) was added; the mixture was stirred while a chilled solution of anhydrous aluminium chloride (52 g.) in dry ether (200 ml.) was introduced. Dry hydrogen chloride was passed in until the mixture was saturated (about 4 hrs.). After standing overnight, the ether was decanted, and the semi-solid washed with dry ether. A solution of the residue in 100 ml. of cold water, after being heated on the water-bath for 20 minutes and cooled, deposited colourless crystals (10 g.) and on recrystallisation from water *methyl* 3 : 5-*dihydroxy*-2-*formylbenzoate* separated in needles, m. p. 163·5°, not raised by sublimation. It gave a deep port-wine colour with ferric chloride in water or alcohol (Found: C, 54·9; H, 4·3; OMe, 14·8. $C_9H_8O_5$ requires C, 55·1; H, 4·1; OMe, 15·8%).

The 2 : 4-*dinitrophenylhydrazone* (0·2 g.), prepared from the ester (0·1 g.) in 3 ml. of alcohol and an excess of 2 : 4-dinitrophenylhydrazine hydrochloride in hydrochloric acid, crystallised from alcohol, in which it was only slightly soluble, in scarlet needles, m. p. 293° (decomp.) when heated from room temperature, 297° (decomp.) when introduced into the bath at 288° (Found: C, 47·7, 47·8; H, 3·0, 2·9; N, 14·7; OMe, 8·8. $C_{15}H_{12}O_8N_4$ requires C, 47·9; H, 3·2; N, 14·9; OMe, 8·3%).

3 : 5-*Dihydroxy*-2-*formylbenzoic Acid*.—A solution of the methyl ester (1 g.) in 15% aqueous sodium hydroxide (16 ml.) was acidified with 5N-hydrochloric acid after 3 days. The cream-coloured precipitate was washed and dissolved in saturated sodium hydrogen carbonate solution (10 ml.). Addition of an excess of 5N-hydrochloric acid precipitated 3 : 5-*dihydroxy*-2-*formylbenzoic acid* in needles (0·70 g.). Recrystallised twice from a little water (norit), in which it was very soluble at the b. p., it formed irregular colourless prisms, m. p. 233° to a black fluid. The acid gave a pale yellow colour in alkaline solution and, like the ester, a deep port-wine colour with aqueous ferric chloride [Found: C, 52·4, 52·3; H, 3·5, 3·6; equiv. by titration, 91·6. $C_8H_6O_5$ requires C, 52·8; H, 3·3%; equiv. (dibasic), 91·1].

The 2 : 4-*dinitrophenylhydrazone*, obtained from an aqueous solution of the acid and an excess of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, crystallised from alcohol in microscopic, elongated, hexagonal, crimson tablets, m. p. 301° (decomp.). It retained rather more than 1 mol. of water when dried in a vacuum at room temperature, but this was lost at 150° in a high vacuum (Found: loss at 150° in a high vacuum, 5·8. $C_{14}H_{10}O_8N_4,H_2O$ requires H_2O, 4·7%. Found for anhydrous material: C, 46·3; H, 2·9; N, 15·2. $C_{14}H_{10}O_8N_4$ requires C 46·4; H, 2·8; N, 15·5%).

3 : 5-*Dihydroxyphthalic Acid.*—A mixture of methyl 3 : 5-dihydroxy-2-formylbenzoate (1 g.), potassium hydroxide (10 g.), and water (2 ml.) in a bath at 170° was heated with constant stirring at 180° for 10 minutes and at 190° for 15 minutes; the test for aldehyde was then almost negative. The product was dissolved in water, acidified, and extracted with ether. The syrupy extract was dissolved in water (50 ml.), neutralised with sodium hydroxide (external indicator), and treated with excess of normal lead acetate solution. The precipitate was washed and treated with sulphuric acid. The filtrate from the lead sulphate was extracted with ether, which afforded a crystalline solid (0·46 g.). Recrystallisation from ethyl acetate–light petroleum gave elongated prisms (0·14 g.), m. p. 184—185°, remelting at 206—208°, not depressed by 3 : 5-dihydroxyphthalic acid, m. p. 188°, remelting at 208—210°, obtained by Oxford and Raistrick (*loc. cit.*) from *Penicillium brevi-compactum*; further, the red colours given by the two products with aqueous ferric chloride were identical. Further confirmation of identity was obtained by conversion of the synthetic acid into the dimethyl ether of the anhydride. The synthetic acid (0·1 g.) was methylated with an excess of diazomethane in ether (left overnight) and the ester groups were hydrolysed by boiling with 2N-sodium hydroxide for 2 hours. The extracted acid was heated with boiling acetic anhydride for 30 minutes. The acetic anhydride was then removed in a vacuum, and the product sublimed. It had m. p. 146—148°, not depressed by sublimed 3 : 5-dimethoxyphthalic anhydride prepared by Fritsch's method (*loc. cit.*).

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