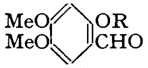
112. *The Chemistry of Fungi. Part I. The Synthesis of 6-Hydroxy-3 : 4-dimethoxyphthalic Acid.*

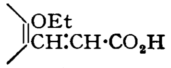
By J. B. D. Mackenzie and Alexander Robertson.

The phthalic acid (VI, R = Et) has been synthesised from the aldehyde (I, R = H) by way of (I, R = Et), (II), (III), (IV), and (V), and shown to be identical with a specimen obtained by the degradation of the methyl ester of *O*-dimethylcitromycetin by comparison of the respective anhydrides. Similarly, the isomeric acid (VIII, R = Et) has been prepared from the aldehyde (VII).

By alkaline fission of the methyl ester of *O*-dimethylcitromycetin, Hetherington and Raistrick (*Phil. Trans.*, **1931**, *B*, **220**, 209) obtained a phthalic acid derivative which they considered to be 6-hydroxy-3 : 4-dimethoxyphthalic acid (VI, R = H).* On account of the strong ferric reaction exhibited by this degradation product it seemed reasonably certain that the substance contained a hydroxyl group in the *o*-position to a carboxyl group, but, on the basis of the available evidence, the alternative structure (VIII, R = H) appeared to be equally feasible. In the course of studies on the structure of citromycetin and its derivatives it became clear that the orientation of this hydroxydimethoxyphthalic acid was an essential preliminary step, and accordingly the synthesis of the isomeric dimethoxyethoxyphthalic acids (VI, R = Et) and (VIII, R = Et) was undertaken.



(I.)



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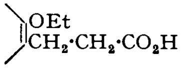

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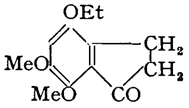

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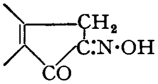

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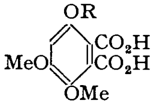

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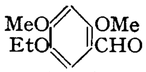
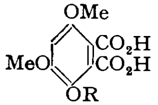


(VII.)



(VIII.)

Prepared from (I, R = H) by way of (I, R = Et) and (II), the β-*phenylpropionic acid* (III) was converted into the *indanone* (IV) in moderate yields by the action of aluminium chloride on the acid chloride from (III); cyclisation of (III) by means of phosphoric oxide in warm benzene gave only minute yields of (IV). The *oximino*-derivative (V) was prepared from (IV), and on oxidation with alkaline potassium permanganate gave rise to the phthalic acid (VI, R = Et), characterised by the formation of its anhydride. Comparison of the acid and its anhydride with the respective natural specimens prepared from citromycetin (*loc. cit.*) showed that they were identical, thus establishing that the hydroxydimethoxyphthalic acid from the methyl ester of *O*-dimethylcitromycetin has the orientation (VI, R = H). By the same series of reactions the isomeric 4 : 6-dimethoxy-3-ethoxyphthalic acid (VIII, R = Et) was prepared from the aldehyde (VII) and characterised by conversion into its *anhydride*.

EXPERIMENTAL.

4 : 5-*Dimethoxy*-2-*ethoxybenzaldehyde* (I, R = Et) (With L. M. TUNNICLIFFE).—2-Hydroxy-4 : 5-dimethoxybenzaldehyde, m. p. 107° (compare Head and Robertson, *J.*, 1930, 2434, who give m. p. 105°) (10 g.), was ethylated with ethyl iodide (5 ml.) and potassium carbonate (25 g.) in boiling acetone (300 ml.) in the course of 2 hours, and on isolation the *ethyl* ether separated from aqueous alcohol in colourless needles (10·5 g.), m. p. 105°, soluble in acetone, benzene, or chloroform (Found : C, 62·6; H, 6·9. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* formed crimson needles, m. p. 252°, from chloroform (Found : N, 14·5. $C_{17}H_{18}O_7N_4$ requires N, 14·4%).

This aldehyde (2 g.) in acetone (50 ml.) at 50° was oxidised by gradual addition of a solution of potassium permanganate (3·2 g.) in water (70 ml.) in the course of 45 minutes, and ½ hour later the cooled mixture was cleared with sulphur dioxide and filtered. The resulting 4 : 5-*dimethoxy*-2-*ethoxybenzoic acid*, which separated when the greater part of the acetone was evaporated, was freed from traces of unchanged aldehyde by means of aqueous sodium hydrogen carbonate, and crystallised from ethyl acetate, forming flat parallelograms (1·8 g.), m. p. 149° (Found : C, 58·2; H, 6·3. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%). Prepared with diazoethane, the *ethyl* ester of this acid separated from light petroleum (b. p. 60—80°) in rectangular prisms, m. p. 63° (Found : C, 61·4; H, 6·9. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%).

Attempts to prepare the corresponding phthalide by condensation of 4 : 5-dimethoxy-2-ethoxybenzoic acid (1 g.) or its ester with chloral (0·75 g.) in concentrated sulphuric acid (2 ml.) at room temperature for 3 days, with or without subsequent heating to 80° for ½ hour, were unsuccessful. The only product isolated was the unchanged benzoic acid.

β-4 : 5-*Dimethoxy*-2-*ethoxyphenylpropionic Acid* (III).—A mixture of 4 : 5-dimethoxy-2-ethoxybenzaldehyde (5 g.), malonic acid (10 g.), pyridine (25 ml.), and piperidine (0·5 g.) was heated on the steam-bath for 4 hours and then at 120° for 30 minutes. The cooled mixture was treated with dilute hydrochloric acid (500 ml.), and the 4 : 5-*dimethoxy*-2-*ethoxycinnamic acid* (II) thus precipitated was collected and purified by crystallisation from aqueous alcohol, benzene, or light petroleum (b. p. 60—80°), forming pale yellow prisms (6·0 g.), m. p. 171°, soluble in chloroform, methanol, or ethyl acetate (Found : C, 61·8; H, 6·5. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%).

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* Hetherington and Raistrick (*loc. cit.*) use, for 3 : 4 : 6-trihydroxyphthalic acid, the numbering 3 : 5 : 6-. On this system the compound (VI, R = H) would be 3-hydroxy-5 : 6-dimethoxyphthalic acid.—Editor.

The cinnamic acid (1 g.), dissolved in acetic acid (100 ml.), was hydrogenated with hydrogen and a palladium–charcoal catalyst, and on isolation the resulting *propionic acid* (III) separated from light petroleum (b. p. 60—80°) in colourless rhombic prisms (0·9 g.), m. p. 80°, soluble in alcohol or ethyl acetate (Found : C, 61·4; H, 7·4. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%).

6 : 7-*Dimethoxy*-4-*ethoxyindan*-1-*one* (With G. H. JONES).—The foregoing β-phenylpropionic acid (1 g.), dissolved in chloroform (50 ml.), was treated with phosphorus pentachloride (0·85 g.) and the mixture kept at room temperature for 2 hours. After removal of the solvent and phosphorus oxychloride under reduced pressure, more chloroform was added to the residue and the solution again evaporated. Freshly sublimed aluminium chloride (1 g.) was added to a solution of the residual acid chloride in benzene (75 ml.), and the mixture agitated for ½ hour, then maintained at 80° for 20 minutes, cooled, and poured on ice (500 g.). After addition of concentrated hydrochloric acid (20 ml.) to this mixture, the benzene layer was isolated, the aqueous liquor extracted with ether (6 × 100 ml.), and the combined benzene and ether solutions washed with aqueous sodium hydrogen carbonate, then with aqueous sodium hydroxide, and finally with water. Distillation of the residue left on evaporation of the dried extracts gave the *indanone*, b. p. 125°/0·005 mm., which formed colourless needles (0·3 g.), m. p. 117°, from light petroleum (b. p. 60—80°), soluble in alcohol, benzene, or ethyl acetate (Found : C, 65·8; H, 7·0. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in brick-red needles, m. p. 275° (decomp.) (Found : C, 54·5; H, 4·9; N, 13·4. $C_{19}H_{20}O_7N_4$ requires C, 54·8; H, 4·8; N, 13·5%).

3 : 4-*Dimethoxy*-6-*ethoxyphthalic Anhydride*.—A solution of the foregoing indanone (0·12 g.) and *iso*amyl nitrite (0·15 ml.) in methanol (0·5 ml.) was treated with concentrated hydrochloric acid (0·1 ml.) and then kept at 50° for ½ hour. The *oximino*-derivative, which separated from the cooled solution, was collected and recrystallised from methanol, forming pale yellow needles (0·08 g.), m. p. 221° (Found : N, 5·4. $C_{13}H_{15}O_5N$ requires N, 5·3%).

Cold saturated aqueous potassium permanganate was added dropwise to a solution of the foregoing oximino-compound (0·2 g.) in cold 5% aqueous potassium hydroxide (15 ml.) until the colour of the permanganate was no longer discharged. Sufficient sulphur dioxide was then slowly led into this mixture, kept at 0°, to clear the solution which was then acidified with hydrochloric acid, saturated with ammonium sulphate, and extracted with ether (30 ml. × 10). Evaporation of the combined dried extracts followed by crystallisation of the residue from ethyl acetate–light petroleum (b. p. 60—80°) gave 3 : 4-dimethoxy-6-ethoxyphthalic acid in colourless, slender prisms (0·1 g.), m. p. 195° (efferv.), freely soluble in ether, benzene, or ethyl acetate, and identical with a specimen prepared from citromycetin (*loc. cit.*) (Found : C, 53·4; H, 5·3. Calc. for $C_{12}H_{14}O_7$: C, 53·3; H, 5·2%). On being kept at 190°/14 mm. for 1 hour the acid decomposed, and the resulting anhydride formed a pale yellow sublimate. Recrystallised from ethyl acetate–light petroleum (b. p. 80—100°), this substance was obtained in colourless needles (0·05 g.), m. p. 196°, soluble in alcohol, ethyl acetate, or benzene, and was identical with a specimen prepared from a sample of the acid obtained from citromycetin (Found : C, 57·1; H, 4·8. Calc. for $C_{12}H_{12}O_6$: C, 57·1; H, 4·8%).

β-2 : 4-*Dimethoxy*-5-*ethoxyphenylpropionic Acid*.—Interaction of 2 : 4-dimethoxy-5-ethoxybenzaldehyde (Head and Robertson, *loc. cit.*) (7·5 g.), malonic acid (20 g.), pyridine (35 ml.), and piperidine (0·5 ml.) at about 95° for 4 hours and then at 120° (oil-bath) for ½ hour gave rise to 2 : 4-*dimethoxy*-5-*ethoxycinnamic acid* which separated from dilute alcohol in lemon needles (7 g.), m. p. 134°, freely soluble in alcohol or benzene (Found : C, 62·0; H, 6·5. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%). Hydrogenation of this acid (2·5 g.) with aid of a palladium–charcoal catalyst furnished the *propionic acid* which formed colourless elongated prisms (2 g.), m. p. 106°, from light petroleum (b. p. 60—80°), soluble in the common organic solvents except light petroleum (Found : C, 61·2; H, 7·2. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%).

4 : 6-*Dimethoxy*-7-*ethoxyindan*-1-*one*.—The foregoing β-phenylpropionic acid was converted into the acid chloride by the way used for the isomeride (III). A solution of the acid chloride (from 2·5 g. of acid) in benzene (100 ml.) was added dropwise to a mechanically-stirred mixture of benzene (100 ml.) and freshly sublimed aluminium chloride (2·1 g.) at 40°. The mixture was warmed to 70° in the course of 15 minutes, then kept there for the same period, and poured on ice (200 g.) and dilute 2N-hydrochloric acid (100 ml.). After isolation by the method employed for the isomeride (IV), the *indanone* was purified by distillation in a vacuum, b. p. 125—130°/0·005 mm., and then by crystallisation from light petroleum (b. p. 60—80°), forming colourless needles (1 g.), m. p. 105°, soluble in the common organic solvents except light petroleum (Found : C, 65·8; H, 6·6. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in brick-red needles, m. p. 264° (decomp.) (Found : N, 13·4. $C_{19}H_{20}O_7N_4$ requires N, 13·5%).

This indanone (1 g.) was nitrosated by the procedure adopted for (IV), and on isolation the *oximino*-derivative formed yellow needles (0·7 g.), m. p. 195—196° (decomp.), from ethyl acetate–light petroleum (b. p. 80—100°) (Found : N, 5·7. $C_{13}H_{15}O_5N$ requires N, 5·3%).

4 : 6-*Dimethoxy*-3-*ethoxyphthalic Anhydride*.—Saturated aqueous potassium permanganate was added dropwise to a solution of the foregoing oximino-compound (0·5 g.) in 5% aqueous potassium hydroxide (20 ml.) until a permanent pink colour remained, and the solution then cleared with sulphur dioxide and acidified. After isolation by means of ether, the phthalic acid was converted into the *anhydride* by being heated in a vacuum at 180°/0·05 mm. This derivative was obtained as a pale yellow sublimate, and on crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) formed colourless elongated parallelograms (0·1 g.), m. p. 149°, soluble in the usual organic solvents except light petroleum (Found : C, 57·4; H, 5·0. $C_{12}H_{12}O_6$ requires C, 57·1; H, 4·8%).

The authors are indebted to Messrs. Imperial Chemical Industries Limited for a research grant.

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