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A SYNTHESIS OF 3,5-DIMETHOXY-4-CARBOMETHOXYPHTHALIC ACID

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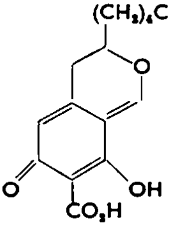
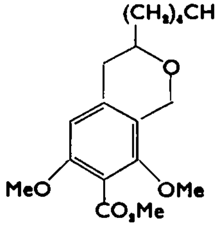
Abstract—The title acid (III, R = Me) has been prepared by permanganate oxidation of the polyester (IV, R = R′ = Me). In this simple synthesis, the carboxyl group, generated by degradation of the side-chain of the polyester, is probably responsible for the selective hydrolysis of the ester group *ortho* to it.

The evidence[1] supporting the structure (I) for the mould metabolite, pulvilloric acid, includes degradation of the ester (II), derived from the metabolite by reduction and methylation, to the phthalic acid (III; R = Me).



I



II

The structure of this acid (III; R = Me) was apparent from earlier evidence for the substitution pattern in the nucleus of pulvilloric acid, from colour tests and spectral data, and from its conversion into a cyclic anhydride. Its identity was confirmed by the synthesis described herein.

The polyester (IV; R = Me, R′ = H), which is readily available[2] from self-condensation of the dimethyl ester of acetone dicarboxylic acid, contains the same pattern of carbon and oxygen substitution as the nucleus of the desired acid (III; R = Me). Methylation of this polyester with methyl iodide and potassium carbonate gives the dimethyl ether (IV; R = R′ = Me).[3] When this material was subjected to permanganate oxidation in aqueous pyridine, the sole product isolated was the phthalic acid (III; R = Me). It was identical to the acid obtained by permanganate oxidation of the ester (II), and was converted into the anhydride (VII; R = Me) upon dehydration with acetic anhydride. Thus, under the conditions of the oxidation of the polyester (IV; R = R′ = Me), the ester group in the *ortho* position to the original side-chain is hydrolysed, while the other ester group survives unchanged.

The most probable course of this reaction involves oxidation of the polyester (IV; R = R′ = Me) to the acid (V; R = Me), followed by hydrolysis of the ester group *ortho* to the carboxyl function. There are many examples of intramolecular

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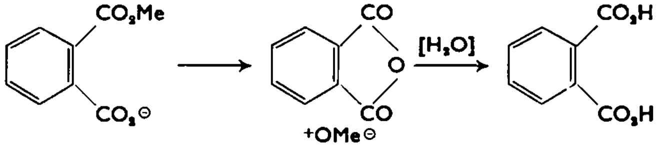
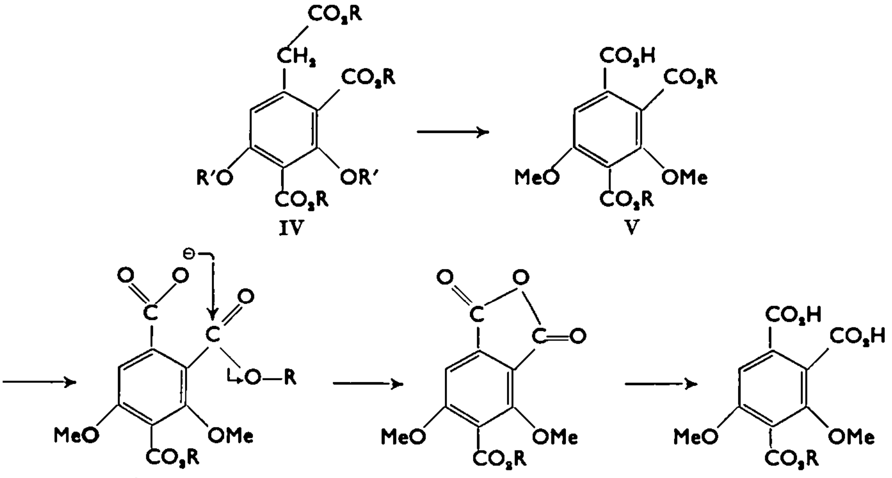
[1] J. F. W. McOmie, A. B. Turner, M. S. Tute and B. K. Bullimore, *Chem. & Ind.* 1689 (1963); *J. Chem. Soc.* in press.

[2] W. Theilacker and W. Schmid, *Liebigs Ann.* **570**, 15 (1950).

participation of carboxylate ions in displacements at ester carbon atoms,[3] and, in particular, in the hydrolysis of methyl hydrogen phthalate, which involves phthalic anhydride as an intermediate:[4]



A similar process could account for the selective hydrolysis of one ester group in the present case, as sufficient base is liberated during the oxidation to allow formation of the carboxylate anion (VI):

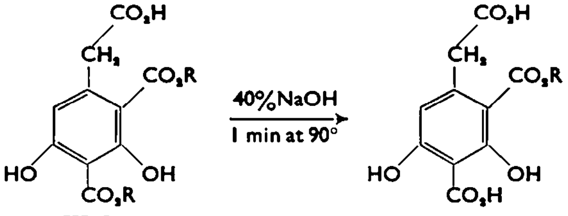


IV V VI VII III

As it is also conceivable that the ester group is hydrolysed at an earlier stage in the reaction, e.g. by participation of a benzylic hydroxyl group (with the formation of an intermediate lactone), a study of the mechanism is being undertaken.

Permanganate oxidation of the corresponding polyethyl ester (IV; R = Et, R' = Me) follows a similar course, giving the phthalic acid (III; R = Et) in good yield.

In a similar situation, no nucleophilic participation of the carboxylate ion is apparent when it is removed from the aromatic nucleus by one methylene group. Thus, Theilacker and Schmid[2] report the selective hydrolysis of the other ester group of the diester (VIII).



VIII

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[3] B. Capon, *Quart. Revs.* 45 (1964).

[4] M. L. Bender, F. Chloupek and M. C. Neveu, *J. Amer. Chem. Soc.* **80**, 5384 (1958); See also A. Ågren, V. Hedsten and B. Jonsson, *Acta Chem. Scand.* **15**, 1532 (1961).

EXPERIMENTAL

3,5-*Dimethoxy-4-carbomethoxyphthalic acid* (III; R = Me). Potassium permanganate (1·5 g) was added during 1 hr to a solution of methyl 2,4-dicarbomethoxy-3,5-dimethoxyphenyl acetate[3] (0·75 g) in pyridine (2 ml) and water (6 ml) at 55–60°. After a further 4 hr at this temp, excess permanganate was removed with SO_2 and the precipitated MnO_2 was removed by filtration. Most of the pyridine was distilled off *in vacuo* and the solution was acidified with H_2SO_4. On cooling to 0°, needles of *the acid* (III; R = Me; 0·12 g; m.p. 164–167°) were deposited. These were recrystallized from aqueous MeOH to m.p. 172–173°. (Found: C, 50·6; H, 4·1. $C_{12}H_{12}O_8$ requires: C, 50·7; H, 4·2%.) It was undepressed upon admixture with the degradation product (m.p. 174–175°) of II. The IR spectra of the two products were identical.

3,5-*Dimethoxy-4-carbomethoxyphthalic anhydride* (VII; R = Me). The above acid (11 mg) was refluxed with acetic anhydride (3 ml) for 45 min. The residue left after evaporation of the liquid was sublimed at 140–150°/15 mm, giving *the anhydride* (VII; R = Me; 8 mg; m.p. 164–165°) unchanged after resublimation. (Found: C, 54·3; H, 4·0. $C_{12}H_{10}O_7$ requires: C, 54·1; H, 3·8%.)

3,5-*Dimethoxy-4-carbomethoxyphthalic acid* (III; R = Et). Permanganate oxidation of ethyl 2,4-dicarbethoxy-3,5-dimethoxyphenyl acetate,[3] in the same manner as described above for the methyl ester, gave *the acid* (III; R = Et; 0·4 g; m.p. 150–155°). Recrystallization from water gave needles, m.p. 160–163°. (Found: C, 52·3; H, 4·7; OMe, 32·9. $C_{13}H_{14}O_8$ requires: C, 52·4; H, 4·7; OMe, 31·2%), $\lambda_{\max\ \mathrm{EtOH}}$ 251 and 301 mμ (log ε 3·25 and 2·65).