62. *Halogen Derivatives of the Methyl Ethers of Orcinol,* p-*Orsellinic Acid and Phloroglucinolcarboxylic Acid.*

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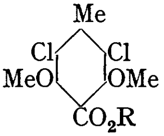
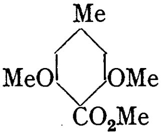
Conditions for the chlorination of methyl *p*-orsellinate dimethyl ether to its 2 : 6-*dichloro*-derivative are described. From the latter are prepared 2 : 6-*dichloro*-3 : 5-*dimethoxy*- and 2 : 6-*dichloro*-3-*hydroxy*-5-*methoxy*-p-*toluic acids*, 2 : 6-*dichloro*-3 : 5-

dimethoxyterephthalic acid, 2 : 6-*dichloro*-5-*methoxy*-m-*cresol,* and 2 : 6-*dichloro-orcinol dimethyl ether.* 2-*Bromo*-3 : 5-*dimethoxybenzoic acid* and *methyl* 3-*chloro*-2 : 4 : 6-*trimethoxybenzoate* also are described.

IN the course of work upon the constitution of the chlorine-containing mould metabolic products geodin and erdin (Raistrick and Smith, *Biochem. J.*, 1936, **30**, 1315; Clutterbuck, Koerber, and Raistrick, *ibid.*, 1937, **31**, 1089) it became necessary to synthesise 2 : 6-*dichloro*-3 : 5-*dimethoxy*-p-*toluic acid* (I; R = H) for comparison with an acid obtained by degradation of the above mould products. The chlorination of methyl *p*-orsellinate dimethyl ether (II) proceeded smoothly in carbon tetrachloride solution at room temperature in presence of excess of chlorine and a little aluminium–mercury couple as catalyst, to yield a dichloro-derivative, the structure of which was proved to be (I; R = Me) by hydrolysis to the acid, followed by oxidation of the methyl side chain by boiling alkaline potassium permanganate, a dibasic acid $C_{10}H_8O_6Cl_2$ being obtained. Since no chlorine is eliminated in the oxidation, it follows that both atoms are attached to the nucleus; hence the only possible structures for the original chloro-ester and the acid obtained by oxidation are (I; R = Me) and (III) respectively.


(I.)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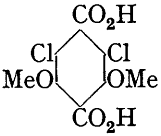
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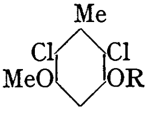
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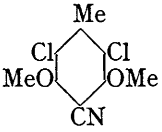
(V.)

Alkaline hydrolysis of (I; R = Me) yields what is apparently a monobasic *acid,* $C_{20}H_{20}O_8Cl_4$, which on crystallisation from water is converted wholly into the simple acid $C_{10}H_{10}O_4Cl_2$ (I; R = H). The structure of the bimolecular acid is under investigation.

Decarboxylation of (I; R = H) by 80% (by weight) sulphuric acid at 125—130° yielded 2 : 6-*dichloro*-5-*methoxy*-m-*cresol* (IV; R = H), which on methylation yielded 2 : 6-*dichloro*-3 : 5-*dimethoxytoluene* (IV; R = Me). This compound (m. p. 133—134°) was proved by a mixed melting point determination to be identical with a specimen kindly supplied by Professor T. J. Nolan, University College, Dublin, who prepared the compound by the direct chlorination of orcinol dimethyl ether (unpublished work, private communication), a method which of course cannot fix with certainty the orientation of both chlorine atoms. The dichloro-ester (I; R = Me), when similarly treated with sulphuric acid, gave also 2 : 6-*dichloro*-3-*hydroxy*-5-*methoxy*-p-*toluic acid* in fair yield.

In an attempt to synthesise dihydroerdin trimethyl ether the nitrile corresponding to (I; R = H), *viz.*, 2 : 6-*dichloro*-3 : 5-*dimethoxy*-p-*toluonitrile* (V), was prepared, but all attempts to link it with the orcinol nucleus by the Hoesch reaction with zinc chloride as catalyst, or with orcinol dimethyl ether with aluminium chloride as catalyst, failed. The latter catalyst apparently led only to complete demethylation of the nitrile. Similarly, all attempts to introduce a nitro-group, without alteration of the rest of the molecule, into the free position in (IV; R = Me) failed, as did attempts to link this compound with phthalic and 3 : 5-dimethoxyphthalic anhydrides by means of the Friedel–Crafts reaction (aluminium chloride as catalyst). It is clear, therefore, that the two methoxy-groups in (IV; R = Me) greatly influence the reactivity of the position between them, whether free or substituted [cf. Turner (J., 1915, **107**, 1459) on the non-reactivity of 2 : 6-diethoxybenzonitrile towards Grignard reagents].

In connection with other constitutional work on a third chlorine-containing mould metabolic product, griseofulvin, $C_{17}H_{17}O_6Cl$, isolated from the mycelium of *Penicillium griseo-fulvum*, it became necessary to synthesise *methyl* 3-*chloro*-2 : 4 : 6-*trimethoxybenzoate* for comparison with a substance obtained by oxidation of the metabolic product and subsequent methylation of one of the degradation products. The required chloro-ester was readily obtained in fair yield merely by treating the fully methylated phloroglucinol-carboxylic acid with the correct amount of chlorine in carbon tetrachloride solution, no catalyst being necessary.

2-Bromo-3 : 5-dimethoxybenzoic acid has been obtained in small yield by the alkaline permanganate oxidation of 2-bromo-orcinol dimethyl ether.

EXPERIMENTAL.

Methyl 2 : 6-*Dichloro*-3 : 5-*dimethoxy*-p-*toluate* (I; R = Me).—To methyl *p*-orsellinate dimethyl ether (II) (20 g., m. p. 84—86°; Herzig, Wenzel, and Kurzweil, *Monatsh.*, 1903, **24**, 896, give 80—84°) and the catalyst (1 sq. inch of aluminium foil dipped in half-saturated mercuric chloride solution for 1 minute, then washed, and dried with filter-paper) was added carbon tetrachloride saturated with dry chlorine (200 c.c.), followed by a further quantity (300 c.c.) and then more pieces of the catalyst when the vigorous reaction had moderated. After 12 hours, the liquid was filtered and the solvent and the excess of chlorine were removed by distillation on the water-bath and finally by evaporation in a current of dry air. Yield, 28 g. after drying in a vacuum. The product crystallised from light petroleum (b. p. 60—80°) (20 c.c.) in colourless prisms (18·3 g.), m. p. 81—83°. A further quantity (2 g.) was obtained by evaporation of the mother-liquor to small volume. The m. p. was raised to 86—88° by repeated crystallisation from aqueous alcohol, from which the *dichloro*-ester separated in colourless, blunt-ended needles, readily soluble in alcohol, moderately soluble in light petroleum, and practically insoluble in water (Found: C, 47·5; H, 4·5; Cl, 25·65; OMe, 33·3. $C_{11}H_{12}O_4Cl_2$ requires C, 47·3; H, 4·4; Cl, 25·4; 3OMe, 33·3%).

2 : 6-*Dichloro*-3 : 5-*dimethoxy*-p-*toluic Acid* (I; R = H).—A solution of the above ester (5 g.) in alcohol (30 c.c.) and 0·5N-sodium hydroxide (60 c.c.) was refluxed for 1½ hours. After most of the alcohol had been removed by distillation in a vacuum, the liquid was acidified with dilute sulphuric acid; the oil obtained solidified to a crystalline mass (5 g.). Recrystallised from ethyl acetate–light petroleum, this formed short needles, m. p. 200—230° (decomp.), insoluble in cold water and in benzene but moderately soluble in ethyl acetate. Although fairly readily soluble in hot dioxan, it separated as a jelly on cooling [Found for air-dried material: C, 45·2; H, 4·1; OMe, 23·3; *M* (in camphor), 542. $(C_{10}H_{10}O_4Cl_2)_2$ requires C, 45·3; H, 3·8; OMe, 23·4%; *M*, 530]. The *substance* thus appeared to be a polymeride of the expected acid $C_{10}H_{10}O_4Cl_2$ (*M*, 265), but its equiv. (by titration) was low for a monobasic acid $C_{20}H_{20}O_8Cl_4$ (Found: 444, 453. Calc.: 530). After the substance had been dried at 100° in a high vacuum, the m. p. was 235—237° (slight shrinking at 200°) and the equiv. was considerably greater than before [Found: loss in wt., 4·7, 4·0%; equiv., 546, 538; *M* (in camphor), 526].

Crystallisation of the above compound or of the crude hydrolysis product from a large volume of boiling water gave, almost quantitatively, fine long needles of the simple *acid* (I; R = H). Crystallisation was greatly facilitated by addition of a trace of dilute hydrochloric acid to the cooled liquid. The substance had m. p. 118—119°, raised to 121—122° by further crystallisations. It was readily soluble in benzene and very readily soluble in ethyl acetate (Found for a specimen sublimed in a high vacuum at 80—90°: C, 45·3; H, 3·9; Cl, 26·9; OMe, 24·2; equiv., 270. $C_{10}H_{10}O_4Cl_2$ requires C, 45·3; H, 3·8; Cl, 26·8; 2OMe, 23·4%; equiv., 265).

2 : 6-*Dichloro*-3 : 5-*dimethoxyterephthalic Acid* (III).—A solution of the dichlorodimethoxytoluic acid (I) (0·19 g.), m. p. 121—122°, in 0·1N-sodium hydroxide (20 c.c.) was boiled under reflux with dropwise addition of 5% aqueous potassium permanganate (4 c.c.). After further refluxing for 20 minutes, the mixture was cooled, decolorised with sulphur dioxide, and extracted with ether. The *acid* obtained (0·17 g.) formed very small prisms, m. p. 235—237° (without apparent decomp.), from ethyl acetate–light petroleum. When it was heated with resorcinol, no fluorescein was formed (Found: Cl, 24·1; OMe, 20·3, 20·5; equiv., 145. $C_{10}H_8O_6Cl_2$ requires Cl, 24·05; 2OMe, 21·0%; equiv., 147·5).

2 : 6-*Dichloro-orcinol Dimethyl Ether* (IV; R = Me).—The crude dichlorodimethoxytoluic acid (7 g.) was heated with a mixture of water (50 c.c.) and concentrated sulphuric acid (110 c.c.) at 125—130° for 15 minutes with occasional shaking; after ½ hour, an equal volume of water was added. The precipitated solid (after cooling) was collected and added to an ethereal extract of the acid filtrate from the reaction mixture, and the whole washed with sodium hydrogen carbonate solution, dried and evaporated. The crude decarboxylation product had m. p. 95—105°, raised by repeated crystallisation from hot water to 129—130°. The substance formed colourless needles, was soluble in dilute sodium hydroxide solution, slightly volatile in steam, and was undoubtedly 2 : 6-*dichloro*-5-*methoxy*-m-*cresol* (IV; R = H) (Found: OMe, 15·0. $C_8H_8O_2Cl_2$ requires OMe, 14·95%). It gave no coloration with ferric chloride.

The bulk of the crude decarboxylation product was treated with excess of ethereal diazomethane without preliminary purification. After 12 hours, the solvent was removed, and the residue (3·9 g.) crystallised from light petroleum, yielding colourless needles, m. p. 133—134°, of 2 : 6-*dichloro-orcinol dimethyl ether*, readily soluble in alcohol, but only very sparingly in water or dilute sodium hydroxide solution (Found for a specimen sublimed in a high vacuum at 60—70° : C, 48·9; H, 4·6; Cl, 31·9; OMe, 28·2. $C_9H_{10}O_2Cl_2$ requires C, 48·9; H, 4·6; Cl, 32·1; 2OMe, 28·1%).

2 : 6-*Dichloro*-3-*hydroxy*-5-*methoxy*-p-*toluic Acid*.—The dichloro-ester (I; R = Me) (5 g.) was gradually heated to 125° with a mixture of concentrated sulphuric acid (60 c.c.) and water (30 c.c.), immediately cooled, and diluted with an equal volume of water; it was again cooled and extracted with ether. The partially demethylated *acid*, removed from the extract with sodium bicarbonate solution and repeatedly crystallised from aqueous alcohol, formed short needles, m. p. 202—203°, giving an intense violet colour with aqueous-alcoholic ferric chloride (Found : C, 43·2; H, 3·3; Cl, 27·9; OMe, 11·7. $C_9H_8O_4Cl_2$ requires C, 43·0; H, 3·2; Cl, 28·25; OMe, 12·35%). It yielded the original dichloro-ester when methylated with diazomethane.

The *methyl* ester, obtained by the hydrogen chloride method and crystallised several times from aqueous alcohol, formed long, colourless needles, m. p. 97°, which did not give any colour with ferric chloride (Found : C, 45·4; H, 3·7; Cl, 26·5; OMe, 22·7. $C_{10}H_{10}O_4Cl_2$ requires C, 45·3; H, 3·8; Cl, 26·8; 2OMe, 23·4%).

Attempts to nitrate the dichloro-ether (IV; R = Me) mostly resulted in oxidation without introduction of a nitro-group; *e.g.*, 50% nitric acid at 100° gave a nitrogen-free substance, m. p. 203—207°, and nitration in hot glacial acetic acid solution gave colourless needles, m. p. 120—122°, also free from nitrogen and not identical with the starting material; possibly 2 : 4-dichlororesorcinol dimethyl ether (m. p. 118°). With concentrated nitric acid in acetic anhydride at 0°, a yellow substance containing nitrogen was obtained, but was undoubtedly a nitrophenol (soluble in sodium hydroxide solution), one methoxy-group having been demethylated (Found : OMe, 14·5%).

2 : 6-*Dichloro*-3 : 5-*dimethoxy*-p-*toluonitrile* (V) (With Dr. D. A. Woolley of Wisconsin University).—The corresponding acid (I; R = H) (3 g.) was triturated with phosphorus pentachloride (3 g.), and the resulting brown liquid kept for 15 minutes (thionyl chloride could also be used for the preparation of the acid chloride) and then poured into aqueous ammonia (*d* 0·880; 100 c.c.). The precipitated *amide* was collected, washed, and crystallised from aqueous alcohol, forming needles (2·45 g.), m. p. 167° (Found : N, 5·2. $C_{10}H_{11}O_3NCl_2$ requires N, 5·3%). Attempts to prepare this amide by heating the ester (I; R = Me) with alcoholic ammonia in a sealed tube at 100° were unsuccessful.

The amide (2·4 g.) was intimately mixed with phosphoric oxide (15 g.) and heated at 180° for 15 minutes. The mass, after cooling, was broken up and added to water (100 c.c.); the product was collected, washed, and crystallised from aqueous alcohol, forming long needles of 2 : 6-*dichloro*-3 : 5-*dimethoxy*-p-*toluonitrile*, m. p. 124° (Found for a specimen sublimed in a high vacuum : C, 49·0; H, 3·7; N, 5·2. $C_{10}H_9O_2NCl_2$ requires C, 48·8; H, 3·7; N, 5·7%).

Methyl 3-*Chloro*-2 : 4 : 6-*trimethoxybenzoate*.—Crude phloroglucinolcarboxylic acid (Skraup, *Monatsh.*, 1889, **10**, 724) was thrice methylated with excess of ethereal diazomethane; the product, after crystallisation from methyl alcohol, was insoluble in sodium hydroxide solution; m. p. 65—67°. This methyl 2 : 4 : 6-trimethoxybenzoate (1·79 g.; 0·0079 g.-mol.), dissolved in carbon tetrachloride (25 c.c.), was treated with a solution of chlorine (0·562 g.; 0·0158 g.-atom) in carbon tetrachloride (7·2 c.c.); there was an immediate reaction, with production of heat and evolution of hydrogen chloride. After a few hours, the solvent was removed by a stream of dry air and the somewhat pasty product was dried in a vacuum over concentrated sulphuric acid, pressed on porous plate, and recrystallised from light petroleum. It formed clusters of elongated hexagonal plates, m. p. 126—128°, readily soluble in most of the usual organic solvents (Found : C, 51·1, 51·05; H, 5·1, 5·2; Cl, 13·2, 13·25; OMe, 47·2, 47·8. $C_{11}H_{13}O_5Cl$ requires C, 50·7; H, 5·0; Cl, 13·6; 4OMe, 47·6%).

2-*Bromo*-3 : 5-*dimethoxybenzoic Acid*.—2-Bromo-3 : 5-dimethoxytoluene (0·13 g.) [Asahina and Fuzikawa, *Ber.*, 1934, **67**, 168; obtained by us by heating 2-bromo-*p*-orsellinic acid dimethyl ether at 200° (cf. Fuzikawa, *Ber.*, 1935, **68**, 75)] was refluxed with 0·1N-sodium hydroxide (15 c.c.), and 5% potassium permanganate solution slowly added until oxidation appeared to be complete (6 c.c. during 3½ hours). The mixture was decolorised with sulphur dioxide and acidified, and the colourless, crystalline precipitate collected (0·05 g.). It formed square prisms, m. p. 208—210°, from aqueous alcohol (Found : C, 41·7; H, 3·6; OMe, 22·6; equiv., 263. $C_9H_9O_4Br$ requires C, 41·4; H, 3·5; 2OMe, 23·8%; equiv., 261). The yield was not appreciably increased by using sodium carbonate solution in place of the hydroxide. The *methyl* ester, readily obtained by means of ethereal diazomethane, formed parallelepipeds, m. p. 59·5—60·5°, from aqueous alcohol, readily soluble in cold light petroleum (Found : C, 43·8; H, 4·2; Br, 30·6. $C_{10}H_{11}O_4Br$ requires C, 43·6; H, 4·0; Br, 29·1%).

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