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SHORT COMMUNICATION

THE SYNTHESIS OF THE SPIRODIENONE-LACTONE, GEODOXIN

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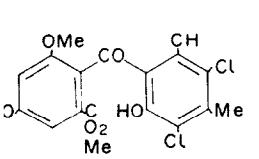
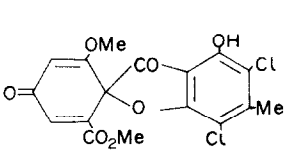
Abstract—2,6-Dichloro-*p*-orsellinyl chloride (VIII) and methyl 5-benzyloxy-2-hydroxy-3-methoxybenzoate (VI) were starting materials for the synthesis of the substituted ester (X) which was converted by oxidation with manganese dioxide to the spirodienone-lactone geodoxin (IV).

EARLIER studies[1] have established the molecular structure of geodoxin (IV), a metabolic product of *Aspergillus terreus* Thom. Moreover, there is evidence[3-5] which indicates that this unusual spirodienone-lactone is derived through a biosynthetic sequence starting from



(I)



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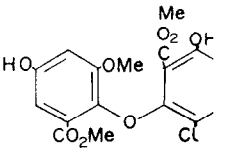

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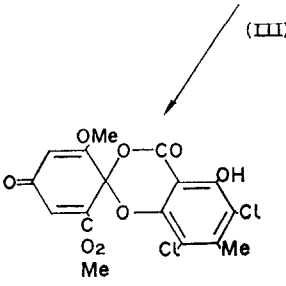
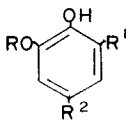
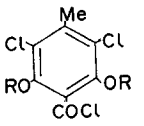


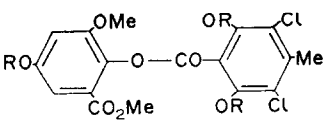
(IV)



(V) $R^1 = CO_2H$, $R^2 = H$ (VI) $R^1 = CO_2Me$, $R^2 = OCH_2Ph$



(VII) $R = CH_2Ph$ (VIII) $R = H$



(IX) $R = CH_2Ph$
(X) $R = H$

[1] C. H. HASSALL and T. C. MCMORRIS, *J. Chem. Soc.* 2831 (1959).
[2] C. H. HASSALL and J. R. LEWIS, *J. Chem. Soc.* 2312 (1961).
[3] R. F. CURTIS, P. C. HARRIES, C. H. HASSALL and J. D. LEVI, *Biochem. J.* **90**, 43 (1964).
[4] R. F. CURTIS, C. H. HASSALL and D. W. JONES, *Chem. and Ind.* 1283 (1959).
[5] C. H. HASSALL and A. I. SCOTT, in *Recent Developments in the Chemistry of Natural Phenolic Compounds* (edited by W. D. OLLIS), Pergamon Press, Oxford, p. 130 (1961).

the benzophenone, dihydrogeodin (I), and proceeding through the spirodienone, geodin (II), to geodin hydrate (III), the product of acid-catalysed hydrolysis. Geodoxin is formed from this diphenyl ether carboxylic acid by oxidation. Each of the intermediates has been identified as a fungal metabolite and each of these stages of the biosynthetic process has been simulated *in vitro*.[2,4,5] This preparation of geodoxin from geodin constitutes a partial synthesis.

We have investigated a more convenient procedure for the total synthesis of geodoxin. The methyl ester of 5-benzyloxy-2-hydroxy-3-methoxybenzoic acid (VI) was prepared by oxidation of *o*-vanillic acid (V) with ammonium persulphate[1] followed by methylation and benzylation. The suitably protected acid chloride (VII), which was prepared by standard methods, condensed with the phenol (VI) to give the ester (IX); this was deprotected by hydrogenation with palladium chloride–magnesium oxide. The product (X) was converted to DL-geodoxin (IV) in 20% yield by activated manganese dioxide,[6] in ether–acetone, but attempts to achieve a similar oxidation using silver oxide, lead dioxide, or potassium ferricyanide were unsuccessful. The synthetic material had properties which were identical with those of the natural geodoxin; the latter is not optically active.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus. IR spectra (P.E. 257, in KBr), UV spectra (Unicam SP800, in EtOH), NMR spectra (Varian HA 100, $CDCl_3$ with $SiMe_4$) and mass spectra (MS 9, 70 e.v.) were determined in the usual way. TLC utilized Kieselgel G developed with system 1 [$CHCl_3$–EtOAc (1:1, v/v)] or system 2 [$CHCl_3$–light petroleum (b.p. 60–80°) 1:1, v/v] Chromatograms were examined under light of 253·7 nm. Silica gel for chromatography was 200–300 mesh (Koch–Light and Co.). Organic solutions were dried ($MgSO_4$) and evaporated under reduced pressure.

Methyl 5-benzyloxy-2-hydroxy-3-methoxybenzoate (VI). Methyl 2,5-dihydroxy-3-methoxybenzoate[1] (6·8 g), anhydrous K_2CO_3 (4·6 g), benzyl chloride (45 ml), and methyl ethyl ketone (700 ml) were heated under reflux for 9 hr. Solvent was removed and the residual gum was treated with H_2O (100 ml), acidified and extracted with Et_2O (3 × 120 ml). Evaporation of the Et_2O gave a dark oil from which unreacted benzyl chloride was removed in a rotary evaporator at 60°. Chromatography of the residual gum (9·3 g) using silica gel (160 g) and elution with benzene, followed by benzene–EtOAc (98:2), gave an oil (8·0 g) which crystallized from benzene to give *methyl 5-benzyloxy-2-hydroxy-3-methoxybenzoate.*

As needles (4·97 g), m.p. 101–102°. [Found: C, 66·5; H, 5 5; *M* (mass spectrometry) 288. $C_{16}H_{16}O_5$ requires C, 66·6; H, 5·6%; *M*, 288]; λ_{max} 254, 342 nm (log ϵ 3·78, 3·40); ν_{max} 3200 (OH bonded), 1680 (conjugated CO), 1625 (OH bonded CO_2Me) cm^{-1}; τ 6 38 (3H, s, OCH_3), 6·10 (3H, s, CO_2CH_3), 5·03 (2H, s, $Ar.CH_2O$), 3·07–3·28 (2H, 1, 2Ar.H), 2·50–2 80 (5H, m, 5Ar.H), −0·62 [1H, 5 m, Ar.OH (exchanged with D_2O)].

2,6-*Dibenzyloxy-3,5-dichloro-4-methylbenzoic acid.* Methyl 3,5-dichloro-2,6-dihydroxy-4-methylbenzoate[1] (20 g), anhydrous K_2CO_3 (10 g), ethyl methyl ketone (1 l.), and freshly distilled benzyl chloride (150 ml) were heated under reflux for 10 hr. Working up and removal of excess benzyl chloride gave a pale yellow gum (26·3 g) which crystallized from MeOH to give *methyl 2,6-dibenzyloxy-3,5-dichloro-4-methylbenzoate* as colourless plates, (18·0 g) m.p. 92–93°. [Found: C, 63·8; H, 4·4; Cl, 16·6%; *M* (mass spectrometry for ^{35}Cl) 430. $C_{23}H_{20}O_4Cl_2$ requires C, 64·0; H, 4·7; Cl, 16 4%; *M*, 430]. This ester (18·0 g), in dioxan (450 ml), H_2O (500 ml), and KOH (50 g), was heated under reflux for 12 hr. H_2O (500 ml) was added and working up in the usual way gave a yellow oil (16·9 g) which crystallized from aq MeOH to give 2,6-*dibenzyloxy-3,5-dichloro-4-methylbenzoic acid* as colourless needles, m.p. 156–157°. (Found. C, 63·1; H, 3 95; Cl, 17·1; *M*, 416 $C_{22}H_{22}O_4Cl_2$ requires C, 63·3; 4·35; Cl, 17 0%; *M*, 416); λ_{max} 258, 265, 269, 287 nm (log ϵ 3·06, 2 99, 3·19); ν_{max} 3430 (OH bonded), 1700 (CO_2H) cm^{-1}; τ, 7·44 (3H, s, $Ar.CH_3$), 4·94 (4H, s, $-OCH_2$), 4 02 [1H, m (exchanged D_2O), CO_2H], 2·5–2·8 (1OH, m, 10 Ar.H).

(4′-*Benzyloxy-2′methoxycarbonyl-6′-methoxyphenyl*)2,6-*dibenzyloxy-3,5-dichloro-4-methyl benzoate (IX).* The foregoing acid (3·0 g), in Na-dried benzene (450 ml), was shaken with freshly distilled PCl_5 (6·0 g) for 12 hr. Solvent was removed to give a pale yellow resin which was extracted with boiling light petroleum (b.p. 100–120°, 3 × 40 ml). The extract was filtered while hot and then evaporated under reduced pressure to give a colourless solid (2·33 g)

[6] J. ATTENBURROW, A. F B. CAMERON, J. H. CHAPMAN, R. M EVANS, B. A. HEMS, A. B. A. JANSEN and T. WALKER, *J. Chem Soc.* 1094 (1952).

This crude mixture was not further purified, but was treated with the phenolic ester (VI), (1·82 g) in dry pyridine (23 ml) and kept overnight at room temp. Pyridine was removed to give a yellow gum (3·06 g) which contained six components on TLC (system 2). Chromatography using silica gel and elution with benzene–Et_2O (90:10) gave a minor component (60 mg) ,which was identified as the anhydride of the acid (IX). Further elution with benzene–Et_2O (80:20) gave a yellow gum (1·8 g) which crystallized from benzene–pentane to give the *benzoate* (15), colourless needles, m.p. 148°. [Found: C, 66·6; H, 4·7; Cl, 10·7; *M* (mass spectrometry) 686. $C_{38}H_{32}O_8Cl_2$ requires C, 66·4; H, 4·7; Cl, 10·3%; *M*, 686]; λ_{max} 257, 303 nm (log ϵ 3·40, 3·43); ν_{max} 1750 (.CO.O), 1720 (CO_2Me) cm^{-1}; τ, 7·42, (3H, s, Ar.CH_3), 6·72 (3H, s, OCH_3), 6·60 (3H, s, CO_2CH_3), 4·96 (2H, s, OCH_2 on phenol residue), 4·88 (4H, s, 2Ar.CH_2 on acid residue), 2·88–3·3 (2H, 2Ar.H), 2·50–2·80 (15H, m, 15Ar.H); R_f (system 3), 0·40. Elution with benzene–Et_2O (90:30) gave unchanged phenol ester (X), (636 mg).

Other attempts to prepare the acid chloride (VII) with excess oxalyl chloride and with $SOCl_2$ in benzene or dimethyl formamide gave, as the principal product, the anhydride of the corresponding acid, as needles from Et_2O, m.p. 130–133°. [Found: C, 64·7; H, 3·9; Cl, 17·4. $C_{44}H_{34}O_2Cl_4$ requires C, 64·8; H, 4·2; Cl, 17·4]; λ_{max} 258, 306 nm, (log ϵ 3·69, 3·61); τ, 7·50 (6H, s, Ar.CH_3), 5·60 (8H, s, 4Ar. CH_2O), 2·60–2·86 (20H, m, 20 Ar.H), R_f (system II), 0·75. This compound could be readily distinguished from the ester (IX) (quenched fluorescence in UV) by the intense green–blue fluorescence.

(*4′-Hydroxy-2′-methoxycarbonyl-6′-methoxyphenyl*)-2,6-*dihydroxy*-3,5-*dichloro*-4-*methyl benzoate* (X). The preceding benzyloxy derivative (687 mg), $PdCl_2$ (5%) on C (800 mg) and MgO (240 mg) in EtOAc (70 ml) were shaken with H_2 at room temp. and pressure for 30 min, when 1·1 M had been taken up. Working up gave a colourless solid (400 mg); crystallization (of 100 mg) gave the benzoate as colourless needles, (64 mg), m.p. 202–205°. [Found: C, 49·3; H, 3·2; Cl, 17·2. *M* (mass spectrometry) 416. $C_{17}H_{14}O_8Cl_2$ requires C, 49·0; H, 3·4; Cl, 17·0; *M*, 416]; λ_{max} 260, 323, 350 nm (log ϵ 4·30, 3·97, 3·72); ν_{max} 3500 (OH, unbonded) 3340 (OH, bonded), 1710 (CO), 1690 (OH bonded CO_2Me); τ, (C_5D_5N) 7·58, (3H, s, Ar.CH_3), 6·37 (3H, s, OCH_3), 6·34 (3H, s, Ar. CO_2CH_3), 2·68–3·00 (2H, 2Ar.H), 0·4–1·6 (3H, m, 3Ar.OH).

Geodoxin (IV). The preceding ester (200 mg), active MnO_2[6] (1·8 g) in EtO_2–acetone [1:1 (v/v), 40 ml] was shaken for 18 hr. After filtration and working up, chromatography using silica gel (23 g) and elution with benzene–EtOAc (95:5) gave geodoxin (36 mg), m.p. 202–205°, identical with natural material. [Found: C, 49·35; H, 2·85, *M* (mass spectrometry) 414. Calc. for $C_{17}H_{12}O_8Cl_2$: C, 49·2; H, 2·9, *M*, 414]. Further elution with benzene–EtOAc (90:10) gave unchanged ester (10) (20 mg).

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