Synthesis of (±)-Di-*O*-methylcurvularin

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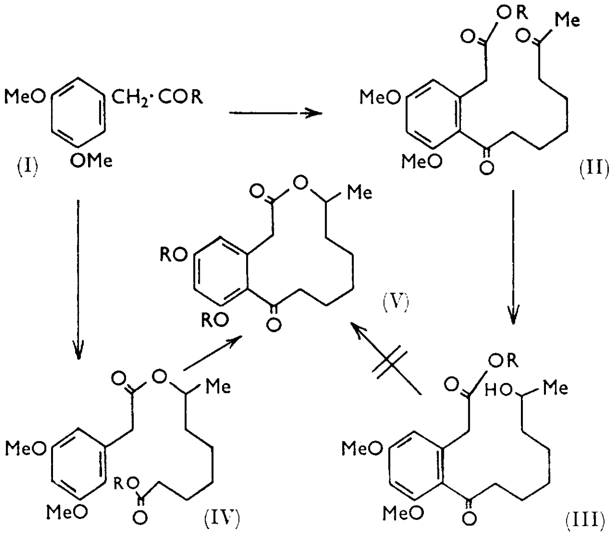
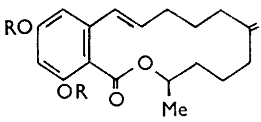
A synthesis of (±)-di-*O*-methylcurvularin (V; R = Me) from 3,5-dimethoxyphenylacetic acid and 7-oxo-octanoic acid is described.

CURVULARIN, a metabolite of various *Curvularia* species, has been assigned the structure (V; R = H) on the basis of extensive spectroscopic and degradative studies.[1,2] We now report the synthesis of a racemate corresponding to structure (V; R = Me), spectroscopically and chromatographically identical with di-*O*-methylcurvularin prepared from the natural material.

In an earlier Paper[3] we described a synthesis of the naphthalene rearrangement product of di-*O*-methylcurvularin and in the course of this work we prepared the hydroxy-ester (III; R = Me). Initially our aim was to hydrolyse this compound to the hydroxy-acid (III; R = H), which on cyclisation was expected to give the required lactone. It proved difficult to obtain good yields of the acid by hydrolysis and it was most conveniently obtained by hydrogenolysis of the benzyl ester (III; R = Ph·CH$_2$). However, all attempts to cyclise the hydroxy-acid with trifluoroacetic anhydride or dicyclohexylcarbodi-imide under a variety of conditions were unsuccessful and this approach was abandoned.

An alternative route, involving the formation of the ester (potential lactone) linkage prior to an intramolecular acylation, was investigated. (Several examples of the synthesis of medium-ring ketones by intramolecular Friedel–Crafts reactions have been reported.[4]) Benzyl 7-hydroxyoctanoate, prepared by benzylation and sodium borohydride reduction of 7-oxo-octanoic acid,[5] reacted smoothly at room temperature with 3,5-dimethoxyphenylacetyl chloride (I; R = Cl) to yield the derivative (IV; R = Ph·CH$_2$) with the desired potential lactone linkage. Hydrogenolysis afforded the acid (IV; R = H) which, when set aside at room temperature in a mixture of trifluoroacetic acid and anhydride,[6] gave, after chromatography, crystalline (±)-di-*O*-methylcurvularin (15%). The solution i.r., u.v., ^{1}H n.m.r. spectra, and thin-layer chromatographic (t.l.c.) behaviour of this material were identical in every respect with those of (—)-di-*O*-methylcurvularin prepared from the natural product. The structure of curvularin (V; R = H) is thus confirmed.





(VI)

A synthesis of the related macrolide, zearalenone (VI), has been reported;[7] the key stage involved the cyclisation, with trifluoroacetic anhydride in benzene, of

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[1] A. J. Birch, O. C. Musgrave, R. W. Rickards, and H. Smith, *J. Chem. Soc.*, 1959, 3146.

[2] O. C. Musgrave, *J. Chem. Soc.*, 1957, 1104; 1956, 4301.

[3] B. W. Bycroft, J. C. Roberts, and P. M. Baker, *J. Chem. Soc.*, 1964, 2289.

[4] R. Huisgen and U. Reitz, *Tetrahedron*, 1958, **2**, 271, and references therein.

[5] C. R. Hauser, F. W. Swamer, and B. I. Ringler, *J. Amer. Chem. Soc.*, 1948, **70**, 4023.

[6] Cf. E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, 1951, 718.

[7] D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Chem. Comm.*, 1967, 225.

a hydroxy-acid similar to the intermediate (III; R = H).

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. Spectra were measured with Unicam spectrophotometers (SP 800 for u.v., SP 200 for i.r.; solvent ethanol for u.v.). The ^{1}H n.m.r. spectra were recorded on a Perkin-Elmer R 10 spectrometer (60 Mc./sec.), with tetramethylsilane as internal reference.

3,5-*Dimethoxyphenylacetic Acid* (I; R = OH).—(*a*) Basic hydrolysis of methyl 3,5-dimethoxyphenylacetate [3] gave the required acid (90%) as pale yellow needles, m. p. 100—102° (lit.,[8] m. p. 100—102°).

(*b*) 3,5-Dihydroxyphenylacetic acid was prepared from dimethyl acetonedicarboxylate by the method of Theilacker and Schmid.[9] Methylation of the crude acid with dimethyl sulphate in acetone over anhydrous potassium carbonate yielded methyl 3,5-dimethoxyphenylacetate (45% overall), basic hydrolysis of which gave an acid identical in every respect with the product of (*a*).

Benzyl 3,5-*Dimethoxyphenylacetate* (I; R = $O{\cdot}CH_2{\cdot}Ph$).—The acid (I; R = OH) (1·16 g.) was dissolved in dry benzene (3 ml.) and oxalyl chloride (1·7 ml.) was added. After the initial reaction had subsided the mixture was heated on a steam-bath for 2 hr. Removal of the solvent and the excess of oxalyl chloride *in vacuo* left a residue which was dissolved in a mixture of benzyl alcohol (0·6 ml.) and dry pyridine (2 ml.). The solution was kept at room temperature for 2 hr. and then poured into water (20 ml.). The product was collected in ether and the ethereal solution was washed with N-hydrochloric acid and water. Removal of the ether and distillation of the residue gave the *ester* as a pale yellow oil (1·3 g., 76%), b. p. 194—198°/0·5 mm. (Found: C, 71·4; H, 6·6. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

Benzyl 3,5-*Dimethoxy*-2-(7-*oxo-octanoyl*)*phenyl Acetate* (II; R = $Ph{\cdot}CH_2$).—A solution of the ester (I; R = $O{\cdot}CH_2{\cdot}Ph$) (1·27 g.) and 7-oxo-octanoic acid (0·77 g.) in trifluoroacetic anhydride (10 ml.) was stirred at room temperature for 24 hr. and then poured into an excess of sodium hydrogen carbonate solution. The product was isolated with ether and the dried ethereal solution was filtered through a short column of alumina (Spence, H). Removal of the solvent left the *ester* as a pale yellow oil which could not be crystallised (Found: C, 70·1; H, 6·86. $C_{25}H_{30}O_6$ requires C, 70·4; H, 7·04%), $\nu_{max.}$ (liquid film) 1728 (ester), 1700 (dialkyl ketone), and 1679 (alkyl aryl ketone) cm.$^{-1}$.

3,5-*Dimethoxy*-2-(7-*oxo-octanoyl*)*phenylacetic Acid* (II; R = H).—The ester (II; R = $CH_2{\cdot}Ph$) (1·5 g.) in dry tetrahydrofuran (15 ml.) was catalytically hydrogenated with palladised charcoal (1 mol. uptake after 6 hr.). The catalyst was filtered off and the solution was extracted exhaustively with saturated sodium hydrogen carbonate solution. The aqueous phase was acidified with 2N-hydrochloric acid and extracted several times with ether. The combined ethereal solutions were washed with water, dried ($MgSO_4$), and evaporated. The residue gave the keto-acid as prisms (1·01 g., 85%), m. p. 81—83° (from aqueous methanol) (Found: C, 64·0; H, 6·7. $C_{18}H_{24}O_6$ requires C, 64·3; H, 7·1%), $\nu_{max.}$ (KBr) 1700b acid and dialkyl ketone) and 1684 (alkyl aryl ketone) cm.$^{-1}$.

3,5-*Dimethoxy*-2-(7-*hydroxy*)*octanoylphenylacetic Acid* (III; R = H).—Reduction of the acid (II; R = H) with sodium borohydride in sodium hydrogen carbonate solution gave virtually quantitative yields of the *hydroxy-acid* as prisms, m. p. 90—93° (Found: C, 64·0; H, 7·5. $C_{18}H_{26}O_6$ requires C, 63·9; H, 7·6%), $\nu_{max.}$ (KBr) 3436 (aliphatic OH) and 1696b (acid and aryl alkyl ketone) cm.$^{-1}$.

Attempted Cyclisation of 3,5-*Dimethoxy*-2-(7-*hydroxy*)*octanoylphenylacetic Acid*.—(*a*) A solution of the acid (50 mg.) in trifluoroacetic anhydride (1·0 ml.) was kept at room temperature for 4 hr. and then poured into an excess of sodium hydrogen carbonate solution. The product was isolated with ether and the dried ethereal solution was evaporated to small volume. No di-*O*-methylcurvularin was found (t.l.c.).

Further experiments with the same amounts of reactants but with trifluoroacetic acid or ether as solvent did not yield the desired product.

(*b*) The acid (50 mg.) was dissolved in dry ether (10 ml.), dicyclohexylcarbodi-imide [10] (30 mg.) was added, and the mixture was left at room temperature for 4 hr. Again none of the required product was formed (t.l.c.).

Benzyl 7-*Oxo-octanoate*.—Benzylation of 7-oxo-octanoic acid [5] by the method outlined before gave the keto-ester (74%) as an oil, b. p. 174—178°/4·5 mm., $\nu_{max.}$ (liquid film) 1733 (ester) and 1710sh (dialkyl ketone) cm.$^{-1}$. The *semicarbazone* formed needles, m. p. 80—82° (from aqueous ethanol) (Found: C, 63·4; H, 7·6; N, 13·3. $C_{16}H_{23}N_3O_3$ requires C, 63·0; H, 7·5; N, 13·8%).

Benzyl 7-*Hydroxyoctanoate*.—Reduction of the 7-oxo-compound with sodium borohydride in ethanol gave a virtually quantitative yield of the *hydroxy–ester*, b. p. 145—149°/3 mm. (Found: C, 71·7; H, 8·8. $C_{15}H_{22}O_3$ requires C, 72·0; H, 8·8%), $\nu_{max.}$ (liquid film) 3435 (OH) and 1732 (ester) cm.$^{-1}$.

Benzyl 7-(3,5-*Dimethoxyphenylacetoxy*)*octanoate* (IV; R = $CH_2{\cdot}Ph$).—Oxalyl chloride (5·5 ml.) was added to a suspension of 3,5-dimethoxyphenylacetic acid (4·0 g.) in dry benzene (5 ml.). After the initial reaction had subsided the mixture was heated under reflux for 2 hr., cooled, and the solvent and the excess of oxalyl chloride were removed *in vacuo*. The residue was dissolved in dry pyridine (10 ml.) and benzyl 7-hydroxyoctanoate (4·74 g.) was added. The solution was left at room temperature for 4 hr. and poured into water; the product was collected in ether. The combined ethereal extracts were washed with N-hydrochloric acid and water, and dried ($MgSO_4$). Removal of the ether and distillation of the residue gave the *condensation product* as a yellow oil (4·8 g., 55%), b. p. (oil-bath temp.) 240°/0·9 mm. (Found: C, 70·0; H, 7·35. $C_{25}H_{32}O_6$ requires C, 70·0; H, 7·47%), $\nu_{max.}$ (liquid film) 1729 cm.$^{-1}$, τ (CCl_4) 8·84 (3H, doublet, J = 6 c./sec.), 6·57 (2H, singlet), 6·26 (6H, singlet), 4·92 (2H, singlet), 3·6—3·7 (3H, multiplet), and 2·65 (5H, singlet).

7-(3,5-*Dimethoxyphenylacetoxy*)*octanoic Acid* (IV; R = H).—Catalytic hydrogenation of the benzyl ester (1·40 g.) with palladised charcoal in tetrahydrofuran (15 ml.) gave virtually quantitative yields of the *acid* [Found: equiv. (by titration), 334. Calc. for $C_{17}H_{25}O_4(CO_2H)$: 338], $\nu_{max.}$ (liquid film) 1725 (ester) and 1706 (acid) cm.$^{-1}$. This acid could not be crystallised and was used in the subsequent reaction without further purification.

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[8] A. J. Birch and F. W. Donovan, *Austral. J. Chem.*, 1953, **6**, 373.

[9] W. Theilacker and W. Schmid, *Annalen*, 1950, **570**, 15.

[10] J. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, 1955, **77**, 1067.

(±)-*Di*-O-*methylcurvularin*.—The acid (IV; R = H) (237 mg.) was dissolved in a mixture of trifluoroacetic acid (10 ml.) and trifluoroacetic anhydride (2 ml.) and the solution was left at room temperature for 4 hr. It was poured into an excess of sodium hydrogen carbonate and the product was isolated with ether. The combined ether extracts were washed with water and dried ($MgSO_4$), and the solvent was removed. A solution of the residue in benzene was chromatographed on acid-washed alumina (Spence, H). The column was eluted with benzene–ether (9 : 1 v/v) followed by ether alone. Removal of the solvent from the latter eluate yielded an oil which gave (±)-di-*O*-methylcurvularin (32 mg., 14%), m. p. 105—108° (from aqueous methanol) [(—)-di-*O*-methylcurvularin, m. p. 72°] [Found: C, 67·8; H, 7·30%; *M* (mass spectrum), 320. $C_{18}H_{24}O_5$ requires C, 67·5; H, 7·55%; *M*, 320]. The synthetic and the natural product had identical infrared absorption spectra ($CHCl_3$) and R_F values (t.l.c., silica plates) in three different solvent systems. $\lambda_{max.}$ (synthetic) 221, 269, and 293 mμ (log ε 4·08, 3·76, and 3·61); (*ex* natural) 221, 268, and 290 mμ (log ε 4·08, 3·76, and 3·62).

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