41. *Curvularin. Part IV.*[1] *Synthesis of a Degradation Product.*

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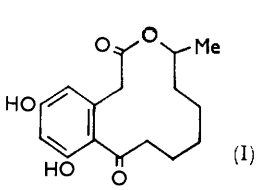
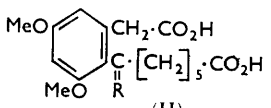
The structure (I) of curvularin has been confirmed by synthesis of a degradation product (II; R = H_2).

Curvularin, isolated originally [2] from a *Curvularia* species and more recently [3] from *Penicillium steckii*, was assigned [1] the structure (I) on the basis of degradative evidence. In view of the unusual medium-sized lactone ring present, confirmation of this formulation seemed desirable. This has now been provided by the synthesis of 7-(2-carboxymethyl-4,6-dimethoxyphenyl)heptanoic acid (II; R = H_2), the di-*p*-bromophenacyl ester of which is identical with that of a degradation product of curvularin.

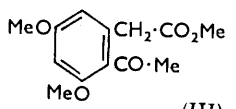
Friedel–Crafts condensation of ethyl 6-chloroformylhexanoate with methyl 3,5-dimethoxyphenylacetate gave the diester of the keto-dicarboxylic acid (II; R = O). Few instances of Friedel–Crafts acylation of substituted phenylacetic esters are known.[4] The orientation of the introduced acyl group follows from comparison of the ultraviolet absorption ($\lambda_{max.}$ 265, 289 mμ; log ε 3·78, 3·61) of this diester with that ($\lambda_{max.}$ 265, 292 mμ; log ε 3·81, 3·65) of the corresponding acetylation product of methyl 3,5-dimethoxyphenylacetate. The latter product was shown to have structure (III) by alkaline hydrolysis and reduction with potassium borohydride to a hydroxy-acid which readily formed a δ-lactone. In addition, 2,4-dimethoxy-6-methylacetophenone [4] has $\lambda_{max.}$ 267, 292 (infl.) mμ (log ε 3·79, 3·55) in contrast to 2,6-dimethoxy-3-methylacetophenone [5] [$\lambda_{max.}$ 238 (infl.), 282 mμ; log ε 3·43, 3·27].



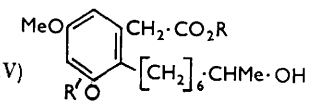
(I)



(II)



(III)



(IV)

Catalytic hydrogenolysis of the diester of (II; R = O) over platinum in the presence of perchloric acid, followed by alkaline hydrolysis, afforded 7-(2-carboxymethyl-4,6-dimethoxyphenyl)heptanoic acid (II; R = H_2). The hydroxy-acid (IV; R = R′ = H),[1] obtained on hydrolysis of deoxydihydro-*O*-methylcurvularin, with diazomethane in methanol gave the ester (IV; R = R′ = Me). This ester on hydrolysis and oxidation with alkaline hypoiodite yielded an acid whose di-*p*-bromophenacyl ester was identical with the corresponding derivative of the synthetic dicarboxylic acid (II; R = H_2).

The acyl side chain of curvularin is cleaved under strongly acidic conditions [1] with the formation, after methylation, of 3,5-dimethoxyphenylacetic acid and derivatives of octanoic acid. It is of interest that, under parallel conditions, 2,4-dihydroxyacetophenone is recovered unchanged. The presence of a substituent group in the 6-position facilitates the reaction sterically, as in 2,4-dihydroxy-6-methylacetophenone which is completely deacylated to orcinol.[6]

[1] Part III, Birch, Musgrave, Rickards, and Smith, *J.*, 1959, 3146.
[2] Musgrave, *J.*, 1956, 4301.
[3] Fennell, Raper, and Stodola, *Chem. and Ind.*, 1959, 1382.
[4] Musgrave, *J.*, 1957, 1104.
[5] Cram and Cranz, *J. Amer. Chem. Soc.*, 1950, **72**, 598.
[6] Cf. Hill and Short, *J.*, 1935, 1123.

Experimental

Ultraviolet spectra were measured for ethanol solutions. Light petroleum refers to the fraction of b. p. 60—80°.

Methyl 3,5-Dimethoxyphenylacetate.—The diazo-ketone prepared by Musgrave's procedure [4] from 3,5-dimethoxybenzoyl chloride was rearranged by Newman and Beal's method.[7] To the diazo-ketone (20 g.) in absolute methanol (100 ml.) was added dropwise, in 30 min., silver benzoate (3 g.) in triethylamine (35 ml.). After 15 minutes' refluxing, charcoal was added and the solution filtered. The residue obtained on removal of solvent was taken up in ether, washed with sodium hydrogen carbonate solution, dried, and distilled, yielding methyl 3,5-dimethoxyphenylacetate (13·2 g., 63% yield from the benzoic acid), b. p. 94°/0·04 mm., $\nu_{max.}$ (liquid film) 1744 cm.$^{-1}$.

Ethyl 7-(2,4-Dimethoxy-6-methoxycarbonylmethylphenyl)-7-oxoheptanoate.—To methyl 3,5-dimethoxyphenylacetate (4·2 g.) and ethyl 6-chloroformylhexanoate (4·2 g.) in nitrobenzene (25 ml.) powdered anhydrous aluminium chloride (5 g.) was added with stirring during 30 min. at 0°. After a further 30 minutes' stirring the mixture was left overnight at room temperature, then decomposed by the addition of ice and concentrated hydrochloric acid. After steam distillation the residue was extracted with ether. Distillation of the extract, after washing with sodium hydrogen carbonate and drying, gave methyl 3,5-dimethoxyphenylacetate (0·46 g.), b. p. 94°/0·04 mm., and *ethyl 7-(2,4-dimethoxy-6-methoxycarbonylmethylphenyl)-7-oxoheptanoate* (1·9 g.), b. p. 190—192°/0·05 mm. (Found: C, 63·25; H, 7·3. $C_{20}H_{28}O_7$ requires C, 63·1; H, 7·4%), $\lambda_{max.}$ 265, 289 mμ (log ε 3·78, 3·61), $\nu_{max.}$ (in CS_2) 1741, 1690 cm.$^{-1}$.

7-(2-Carboxymethyl-4,6-dimethoxyphenyl)heptanoic acid (II; R = H_2). The above keto-ester (0·33 g.) in acetic acid (15 ml.) containing 60% perchloric acid (0·1 ml.) was hydrogenated over Adams catalyst (0·10 g.); 1 mol. was absorbed in 10 min. After filtration from the catalyst, the solvent was removed *in vacuo* and the residue hydrolysed in methanol (5 ml.) and 5% aqueous potassium hydroxide (10 ml.) overnight. Acidification and extraction with ether afforded the *dicarboxylic acid* (II; R = H_2) (0·24 g.), needles, m. p. 108—109° (from benzene) (Found: C, 62·8; H, 7·5. $C_{17}H_{24}O_6$ requires C, 62·9; H, 7·5%), $\lambda_{max.}$ 285 mμ (log ε 3·48), $\nu_{max.}$ (in $CHCl_3$) 3124, 1714 cm.$^{-1}$. The *di-p-bromophenacyl ester*, purified by chromatography on " Florisil " in 1 : 4 ether–light petroleum and crystallised from ethanol, aqueous ethanol, or ether–light petroleum, had m. p. 104—109° (Found: Br, 22·9. $C_{33}H_{34}Br_2O_8$ requires Br, 22·3%), $\nu_{max.}$ (in CS_2) 1751, 1709 cm.$^{-1}$.

Degradation of Curvularin.—The hydroxy-acid (IV; R = R′ = H) (183 mg.), obtained by alkaline hydrolysis of deoxydihydro-*O*-methylcurvularin,[1] with an excess of diazomethane in methanol (2 ml.) and ether (5 ml.) for 48 hr. gave the methyl ester (IV; R = R′ = Me), $\nu_{max.}$ (in CCl_4) 3604 (alcoholic OH), 1740 (ester C=O), which was hydrolysed overnight with aqueous-methanolic 3% potassium hydroxide to the hydroxy-acid (IV; R = H, R′ = Me) (94 mg.). To this acid (94 mg.) in 10% aqueous sodium hydroxide (7 ml.) was added an excess of iodine–potassium iodide. After 4 hr. the solution was centrifuged to remove iodoform, acidified with dilute sulphuric acid, freed from liberated iodine with sodium hydrogen sulphite, and extracted with ether. The extracted acid (60 mg.), after chromatography in ether–light petroleum (1 : 2) on silica gel, yielded a di-*p*-bromophenacyl ester, m. p. 104—109°, identical (mixed m. p. and infrared spectrum) with the corresponding derivative of the synthetic acid (II; R = H_2).

Methyl (2-Acetyl-3,5-dimethoxyphenyl)acetate (III).—To methyl 3,5-dimethoxyphenylacetate (2·2 g.) and acetyl chloride (1·0 g.) in nitrobenzene (15 ml.) at 0° was added powdered anhydrous aluminium chloride (2 g.) with stirring during 15 min. After a further 2 hours' stirring, ice and concentrated hydrochloric acid were added and the mixture was extracted with ether. Distillation of the extract, after drying and removal of the solvents under a vacuum, gave *methyl (2-acetyl-3,5-dimethoxyphenyl)acetate* (2·2 g.), b. p. 140—142°/0·03 mm., rods, m. p. 61—62° (from light petroleum) (Found: C, 61·7; H, 6·4. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%), $\lambda_{max.}$ 265, 292 mμ (log ε 3·81, 3·65), $\nu_{max.}$ (in CS_2) 1745, 1686 cm.$^{-1}$.

6,8-Dimethoxy-1-methylisochroman-3-one.—Methyl (2-acetyl-3,5-dimethoxyphenyl)acetate (205 mg.) and potassium hydroxide (500 mg.) in 1 : 1 aqueous methanol (10 ml.) were left overnight at room temperature. The resulting crude acidic fraction (170 mg.), m. p. 117—121°, was reduced without further purification. Potassium borohydride (2 g.) was added portionwise

[7] Newman and Beal, *J. Amer. Chem. Soc.*, 1950, **72**, 5163.

during 4 hr. to the keto-acid (170 mg.) in refluxing methanol (15 ml.) and water (3 ml.). After being set aside overnight, the solution was diluted with water (50 ml.) and acidified with dilute sulphuric acid. Extraction with ether gave a gum (102 mg.), which on sublimation and crystallisation from light petroleum yielded needles of the *isochromanone*, m. p. 61—63° (Found: C, 64·65; H, 6·65. $C_{12}H_{14}O_4$ requires C, 64·85; H, 6·35%), $\lambda_{max.}$ 281 mμ (log ε 3·33), $\nu_{max.}$ (in CS_2) 1751 cm.$^{-1}$.

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