218. *Curvularin. Part II.* The Constitution of an Aromatic Degradation Product and the Partial Structure of Curvularin.*

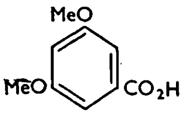
By O. C. Musgrave.

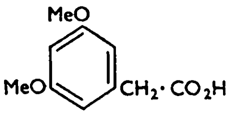
Alkaline hydrolysis of *OO*-dimethylcurvularin followed by permanganate oxidation gives oxalic and succinic acid, and 2-carboxymethyl-4 : 6-dimethoxyphenylglyoxylic acid, the structure of which is confirmed by synthesis. Curvularin is shown to have the partial structure (VII) in which the neighbouring carbonyl group is not coplanar with the benzene ring.

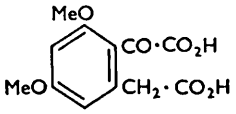
It was shown in Part I * that the mould metabolic product curvularin contains a dihydroxybenzoyl system in which the two hydroxyl groups are *ortho* or *meta* to one another. To orient this group it was desirable to obtain a degradation product containing it intact. Mild alkaline hydrolysis of curvularin gave an acidic material but no homogeneous product could be isolated. Fusion with potassium hydroxide and oxidation with alkaline permanganate solution gave intractable products. *OO*-Dimethylcurvularin, in which the aromatic ring might be expected to be less sensitive than that in curvularin, is insoluble in water, so it was first hydrolysed with alkali and then oxidised in the cold with aqueous potassium permanganate: oxalic and succinic acid and an acid $C_{12}H_{12}O_7$, m. p. 212—212·5°, were isolated by crystallisation. The last-named compound is dibasic, has two methoxyl groups, and therefore contains the aromatic nucleus of *OO*-dimethylcurvularin. In curvularin itself two hydrogen atoms are attached directly to the benzene ring and these are presumably still present in the $C_{12}H_{12}O_7$ acid which accordingly may be written as (I).

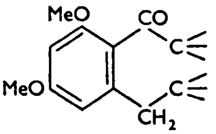
$(MeO)_2C_6H_2\{C_2H_2O\}(CO_2H)_2$ (I)

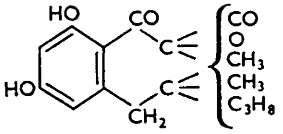
$2:4\text{-}(MeO)_2C_6H_2{\cdot}CO\{(CH_2)(CO_2H)_2\}$ (II)


(III)


(IV)


(V)


(VI)


(VII)

The ultraviolet absorption of the acid resembles that of 2 : 4-dimethoxyacetophenone (for these and other $\lambda_{max.}$ and ε see the Table) suggesting that it contains the 2 : 4-dimethoxybenzoyl chromophore. The infrared absorption of the acid is compatible with this, three strong bands being at 1704, 1667, and 1597 cm.$^{-1}$ The first of these is attributed to the carboxylic acid groups (aliphatic acids [1] absorb at *ca.* 1715 cm.$^{-1}$, phenylacetic acid [2] at 1697 cm.$^{-1}$). The second corresponds to the carbonyl group conjugated with the aromatic nucleus, and the third to the conjugated system of such an aromatic ketone. 2 : 4-Dimethoxyacetophenone itself gives strong bands at 1645 (aromatic carbonyl) and 1580 cm.$^{-1}$ (conjugated aromatic system). The displacement of the carbonyl band in the $C_{12}H_{12}O_7$ acid suggests that the group is closely associated with one or both of the carboxylic acid groups (see below). The expression (I) for the $C_{12}H_{12}O_7$ acid may therefore be expanded to (II). Of the compounds having this partial structure only 2-carboxymethyl-4 : 6-dimethoxyphenylglyoxylic acid (V) appears to be compatible

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* Part I, *J.*, 1956, 4301.

[1] Grove and Willis, *J.*, 1951, 877.

[2] Flett, *ibid.*, p. 962.

with the chemical and spectral evidence. The formulation as a substituted phenylglyoxylic acid is supported by the resemblance (*a*) of its ultraviolet spectrum to those of 2 : 4-dimethoxy- and 2 : 4-dimethoxy-6-methyl-phenylglyoxylic acid, and (*b*) of its infrared spectrum in the 6 μ region to that of 2 : 4-dimethoxyphenylglyoxylic acid [strong bands at 1715 (carboxylic acid), 1656 (aromatic carbonyl), and 1608 cm.$^{-1}$ (conjugated aromatic system)].

The structure of the $C_{12}H_{12}O_7$ acid was confirmed by synthesis. 3 : 5-Dimethoxybenzoic acid (III) was converted into the acid chloride which by the Arndt–Eistert synthesis[3] gave 3 : 5-dimethoxyphenylacetic acid (IV). The derived methyl ester with ethoxalyl chloride in the presence of anhydrous aluminium chloride[4, 5] afforded 2-carboxymethyl-4 : 6-dimethoxyphenylglyoxylic acid, identical (mixed m. p. and infrared spectrum) with the $C_{12}H_{12}O_7$ acid obtained by degradation. [As very few instances[6] of the Friedel–Crafts acylation of esters of phenylacetic acids had been reported it was desirable to ascertain that the reaction would take the normal course. The easily accessible isomeric ester, methyl 3 : 4-dimethoxyphenylacetate, was readily converted into the expected 2-carboxymethyl-4 : 5-dimethoxyphenylglyoxylic acid, the structure of which follows from its analysis and the resemblance of its ultraviolet spectrum to that of 3 : 4-dimethoxyacetophenone.]

*Ultraviolet absorption spectra (in ethanol).**

	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε	$\lambda_{max.}$ (Å)	ε
$C_{12}H_{12}O_7$ acid	2300	11,800	2750	8500	3075	6750
2 : 4-Dimethoxyacetophenone	2275	9500	2695	9550	3050	5650
2 : 4-Dimethoxyphenylglyoxylic acid	2295	11,300	2725	10,800	3095	7800
2 : 4-Dimethoxy-6-methylphenylglyoxylic acid [a] †	*ca.* 2300	9350	2870	10,000	3160	7850
2-Carboxymethyl-4 : 5-dimethoxyphenylglyoxylic acid	2310	19,300	2790	10,200	3065	6450
3 : 4-Dimethoxyacetophenone	2280	16,100	2725	10,600	3035	7550
OO-Dimethylcurvularin	2230	10,500	2675	5100	(2910)	(3600)
2 : 4-Dimethoxy-6-methylacetophenone	2215	10,200	2675	6130	(2920)	(3530)
2-Acetoxyacetophenone	2390	9000	2840	1200	—	—
2-Methylacetophenone [b]	2420	8700	2810	1200	(3310)	(50)
	2450	8300				
4-Acetoxyacetophenone	2480	14,000	—	—	—	—
4-Methylacetophenone [b]	2520	15,100	—	—	—	—
2 : 4-Diacetoxyacetophenone	2480	13,500 [c]	(2830)	(1550)	—	—
2 : 4-Dimethylacetophenone [b]	2510	14,100	2820	1700	—	—
	(2560)	(12,300)	2910	1300		
2 : 4 : 6-Triacetoxyacetophenone [c]	2390	6500	—	—	—	—
2 : 4 : 6-Trimethylacetophenone [d], ‡	(2390)	(2600)	—	—	—	—
Curvularin diacetate	(2350)	(5600)	—	—	—	—
2 : 4-Dihydroxy-6-methylacetophenone	(2335)	(7600)	2825	9750	3200	6000
2 : 4-Dihydroxyacetophenone	2310	9150	2770	15,300	3145	7900
Curvularin	(2290)	(10,150)	2720	6350	3045	5100

[a] Cram, *J. Amer. Chem. Soc.*, 1950, **72**, 1028. [b] Braude and Sondheimer, *J.*, 1955, 3754. [c] Barton and Bruun, *J.*, 1953, 603. [d] Schwartzman and Corson, *J. Amer. Chem. Soc.*, 1954, **76**, 781.

* Values in parentheses are those of inflections. † In 1 : 1 ethanol–0·1N-hydrochloric acid.
‡ In *cyclo*hexane.

The isolation of 2-carboxymethyl-4 : 6-dimethoxyphenylglyoxylic acid from the degradation of *OO*-dimethylcurvularin implies that the latter contains the arrangement (VI), and the two compounds therefore appear to possess the same ultraviolet-light absorbing system. The absorption intensities of *OO*-dimethylcurvularin are, however, much lower than those of the acid. Such a decrease without significant displacement of the maxima frequently indicates considerable non-planarity in the light-absorbing system

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[3] Cf. Bachmann and Struve, *Organic Reactions*, 1942, **1**, 38.
[4] Kindler, Metzendorf, and Dschi-yin-Kwok, *Ber.*, 1943, **76**, *B*, 308.
[5] Cf. Sprenger, Ruoff, and Frazer, *J. Amer. Chem. Soc.*, 1950, **72**, 2874.
[6] *E.g.*, Kunckell, *Ber.*, 1905, **38**, 2609.

caused by the steric requirements of the attached groups.[7] Scale diagrams in which the values for the interference radii suggested by Braude and Sondheimer [7] were used reveal that the hindrance to planarity of the 2 : 4-dimethoxybenzoyl chromophore in the $C_{12}H_{12}O_7$ acid is weak, because of the relatively small steric requirements of the glyoxylic carboxyl group, and is comparable with that in 2 : 4-dimethoxyacetophenone. When the glyoxylic carboxyl group is replaced by the more bulky methyl group, as in 2 : 4-dimethoxy-6-methylacetophenone, steric interference is much increased; the carbonyl group is forced out of the plane of the aromatic ring and, in agreement, this compound shows considerably lower absorption intensities than does its less-hindered analogue 2 : 4-dimethoxyacetophenone. The ultraviolet spectrum of *OO*-dimethylcurvularin bears a very close resemblance to that of the above highly hindered ketone and it is concluded that in this case also the carbonyl group and the aromatic ring are not coplanar. The distortion of the light-absorbing system with consequent reduction in the degree of conjugation is reflected in the high infrared frequency (1695 $cm.^{-1}$) for this carbonyl group, similar to that (1681 $cm.^{-1}$) of 2 : 4-dimethoxy-6-methylacetophenone but much higher than that (1645 $cm.^{-1}$) of 2 : 4-dimethoxyacetophenone.

The ultraviolet spectrum of curvularin diacetate may also be accounted for on this basis. The effects of acetoxyl groups on the absorption of acetophenone are observed to resemble closely those of methyl groups. Thus the spectra of 2- and 4-mono-, 2 : 4-di-, and 2 : 4 : 6-tri-acetoxyacetophenone are similar to those of the corresponding mono-, di-, and tri-methylacetophenones. Curvularin diacetate possesses a spectrum comparable with those of the highly sterically hindered 2 : 4 : 6-triacetoxy- and 2 : 4 : 6-trimethylacetophenone.

While the ultraviolet spectra of *OO*-dimethylcurvularin and 2 : 4-dimethoxy-6-methylacetophenone closely resemble each other, considerable differences in intensities are observed for the corresponding phenols. The absorption of 2 : 4-dihydroxy-6-methylacetophenone is generally similar to that of 2 : 4-dihydroxyacetophenone. This is attributed to the reduction in the degree of distortion of the conjugated system in the highly hindered ketone brought about by hydrogen-bonding between the carbonyl and the *o*-hydroxyl group. In the case of curvularin, hydrogen-bonding is apparently not sufficient to reduce this distortion appreciably. The lower degree of conjugation in curvularin is also seen in its high infrared carbonyl frequency (1653 $cm.^{-1}$) compared with those of 2 : 4-dihydroxy-6-methylacetophenone (1631 $cm.^{-1}$) and 2 : 4-dihydroxyacetophenone (1621 $cm.^{-1}$). It may be concluded that the lack of planarity of the conjugated system in curvularin is caused by large or rigid substituent groups.

Curvularin has been shown previously to contain, in addition to a dihydroxybenzoyl system, a second carbonyl group and two *C*-methyl groups. As *OO*-dimethylcurvularin has now been proved to contain the arrangement (VI), curvularin may be assigned the partial structure (VII) in which the carbonyl group is not coplanar with the aromatic nucleus. The isolation of succinic acid from the oxidation of *OO*-dimethylcurvularin implies that the group $\vdots C{\cdot}CH_2{\cdot}CH_2{\cdot}C\vdots$ is present in the latter and also, presumably, in curvularin itself.

EXPERIMENTAL

Analyses are by the microanalytical laboratory of this Department; molecular weights were determined ebullioscopically in acetone. Ultraviolet absorption spectra were determined with a Hilger " Uvispek " spectrophotometer. Infrared absorption spectra were determined, for thin films (of liquids) or Nujol mulls, with a double-beam spectrophotometer with rock-salt optics; the concentrations and thickness of the mulls were not measured.

Hydrolysis and Oxidation of OO-*Dimethylcurvularin*.—*OO*-Dimethylcurvularin (8·9 g.) was heated under reflux in an atmosphere of nitrogen for 1 hr. with sodium hydroxide (4·0 g.) in methanol (50 ml.) and water (50 ml.). Water (50 ml.) was then added and the methanol

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[7] Braude and Sondheimer, *J.*, 1955, 3754.

removed by distillation. A solution of potassium permanganate (54 g.) in water (1100 ml.) was added slowly to the aqueous solution with stirring and cooling (≯17°). After being kept overnight the mixture was heated to the b. p. and filtered. The colourless filtrate was concentrated under reduced pressure to 400 ml. and acidified to pH 2. Continuous ether-extraction for 24 and 48 hr. periods afforded extracts 1 (5·38 g.) and 2 (2·22 g.) as crystalline solids heavily contaminated with brown oils. Treatment of extract 1 with boiling ethyl acetate (100 ml.) left undissolved a colourless solid (*a*) (0·163 g.; m. p. 212° with gas evolution). The solution on cooling deposited crystals (*b*) (0·635 g.; m. p. 180—185°). Concentration of the mother-liquor to 20 ml. (charcoal) gave crystals (*c*) (0·296 g.; 186° with gas evolution). After the evaporation of all the solvent the oily residue was extracted with ether (80 ml.). Evaporation of the solution afforded a colourless solid (*d*) (0·725 g.; m. p. *ca.* 100°). No further crystalline material could be obtained by solvent treatment.

Fraction (*a*) was identical (mixed m. p.) with the less-soluble portion of fraction (*c*) (see below). Crystallisation of the combined solids from ethyl acetate gave 2-*carboxymethyl*-4 : 6-*dimethoxyphenylglyoxylic acid* (0·193 g.) as plates, m. p. 212—212·5° (with gas evolution) [Found : C, 53·45; H, 4·65; MeO, 20·2%; equiv. (by titration), 131·9; *M*, 270. $C_{12}H_{12}O_7$ requires C, 53·75; H, 4·5; MeO, 23·1%; equiv. (as dibasic acid), 134·1; *M*, 268·2]. Crystallisation of fraction (*b*) from ethyl acetate gave succinic acid (0·414 g.) as plates, m. p. 184—185°, which did not depress the m. p. (185—186°) of an authentic specimen. The infrared spectra of the two compounds were identical. Crystallisation of fraction (*c*) from ethyl acetate afforded a crystalline solid (0·095 g.), m. p. 212° (with gas evolution), identical with fraction (*a*). Concentration of the mother-liquor gave more succinic acid (0·086 g.). Fraction (*d*) on crystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave oxalic acid (0·374 g.) as thick needles, m. p. 102° (with loss of water) [Found : equiv. (by titration), 62·1. Calc. for $C_2H_6O_6$: equiv. (as dibasic acid), 63·05]. The behaviour on melting and the infrared spectrum were identical with those of an authentic specimen. Addition of light petroleum (b. p. 60—80°) to a solution of extract 2 in ethyl acetate gave oxalic acid (0·246 g.), m. p. 100—102° (with loss of water) (Found : equiv., 63·4), as the sole crystalline product.

3 : 5-*Dimethoxyphenylacetic Acid.*—To a suspension of 3 : 5-dimethoxybenzoic acid (18·2 g.) in dry benzene (60 ml.) was added pure thionyl chloride (47·6 g.) and dry pyridine (0·25 ml.), and the mixture was kept at 50° for 3 hr. The solvent was removed under reduced pressure, finally at 50°; dry benzene (2 × 30 ml.) was added and the distillation was repeated. A solution of the crude acid chloride in dry ether (75 ml.) was added to a dry solution of distilled diazomethane [from *N*-nitrosomethylurea (65 g.), ether (600 ml.), and 50% aqueous potassium hydroxide (190 ml.)] in ether (500 ml.) at 5—10°. After being kept overnight at room temperature the solution was filtered and evaporated under reduced pressure, finally at 30°. A solution of the residual crystalline diazo-ketone in pure dioxan (120 ml.) was added dropwise with stirring to a mixture of silver oxide (2·5 g.), sodium carbonate (7 g.), and sodium thiosulphate (4 g.) in water (250 ml.) at 50—60°. After 1 hr., more silver oxide (4·6 g.) was added and the mixture was stirred at 70° for a further 6 hr., after which there was no evolution of nitrogen on testing with hydrochloric acid. The mixture was cooled, filtered, acidified with dilute nitric acid, and kept at 0° overnight, a crystalline solid (2·1 g.; m. p. 101—102°) separating. Ether-extraction of the filtrate gave a solid (9·4 g.; m. p. 87—92°). Repeated crystallisation of the combined solids from water gave 3 : 5-dimethoxyphenylacetic acid (7·12 g.), m. p. 104—104·5 [Found: C, 61·15; H, 6·3; MeO, 29·9%; equiv. (by titration), 198·3; *M*, 189. Calc. for $C_{10}H_{12}O_4$: C, 61·2; H, 6·15; MeO, 31·65%; equiv., 196·2; *M*, 196·2], ultraviolet absorption max. in EtOH at 2765 Å (ε 1600), inflection at 2210 Å (ε 9100), strong infrared absorption band at 1694 cm.$^{-1}$ (carbonyl group of substituted phenylacetic acid). A m. p. of 100—102° is recorded [8] for a specimen prepared from 3 : 5-dimethoxybenzoic acid by a different homologation route.

2-*Carboxymethyl*-4 : 6-*dimethoxyphenylglyoxylic Acid.*—3 : 5-Dimethoxyphenylacetic acid (3·6 g.) was added to a solution of distilled diazomethane [from *N*-nitrosomethylurea (7·5 g.), 50% aqueous potassium hydroxide (25 ml.), and ether (75 ml.)] in ether (75 ml.). After ½ hr. the solution was filtered and evaporated. The residue was dried by adding benzene (20 ml.) and removing this by distillation, finally under reduced pressure. Freshly powdered anhydrous aluminium chloride (5 g.) was added during ½ hr. in small portions with stirring and ice-cooling to a solution of the methyl ester and ethoxalyl chloride [4] (2·5 g.) in nitrobenzene (25 ml.).

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[8] Shepard, Porter, Noth, and Simmans, *J. Org. Chem.*, 1952, **17**, 568.

The dark-red mixture was stirred at 0° for a further ½ hr., kept overnight at room temperature, and decomposed with ice and concentrated hydrochloric acid. After distillation with steam to remove nitrobenzene the cooled solution was extracted thoroughly with ether. The extract was washed with sodium hydrogen carbonate solution and the latter separated and made acid. Thorough ether-extraction gave a solid (3·3 g.) which after crystallisation from ethyl acetate containing a little ethanol gave 2-carboxymethyl-4 : 6-dimethoxyphenylglyoxylic acid as colourless plates, m. p. 211—211·5° (with gas evolution), ultraviolet absorption max. in EtOH at 2320, 2760, and 3080 Å (ε 10,700, 8300, and 6800) which did not depress the m. p. (212—212·5° with gas evolution) of the specimen obtained by the oxidation of *OO*-dimethylcurvularin. The infrared spectra of the two compounds were identical in every respect.

2-*Carboxymethyl*-4 : 5-*dimethoxyphenylglyoxylic Acid*.—Homoveratric acid on treatment as in the previous experiment gave 2-*carboxymethyl*-4 : 5-*dimethoxyphenylglyoxylic acid* (46%) as laths (from ethyl acetate), m. p. 198·5—199° (with gas evolution) [Found: C, 53·45; H, 4·4%; equiv. (by titration), 133; *M*, 270. $C_{12}H_{12}O_7$ requires C, 53·75; H, 4·5%; equiv. (as dibasic acid), 134·1; *M*, 268·2]. No reaction occurred when anhydrous stannic chloride was substituted for aluminium chloride as catalyst, presumably because of complex formation [9] with the ester groups of the reactants.

2 : 4-*Dimethoxy*-6-*methylacetophenone*.—A solution of anhydrous stannic chloride (32·6 g.) in dry benzene (100 ml.) was added dropwise with stirring at 0° to a solution of *OO*-dimethylorcinol (15 g.) and acetyl chloride (7·75 g.) in the same solvent (120 ml.) during 1 hr. After being stirred for 2 hr. at 0° and for 4 hr. at room temperature, the mixture was decomposed with ice and concentrated hydrochloric acid. Ether-extraction afforded, after removal of the solvents, 2 : 4-dimethoxy-6-methylacetophenone (13·2 g.), b. p. 98·5—99·5°/0·2 mm., n_D^{18} 1·5357, which solidified and then crystallised from light petroleum (b. p. 40—60°) in rods, m. p. 41·5—41·7° (Found: C, 68·05; H, 7·25; MeO, 32·55%; *M*, 180. Calc. for $C_{11}H_{14}O_3$: C, 68·05; H, 7·25; MeO, 31·95%; *M*, 194·2). Tambor [10] records m. p. 48° for a specimen prepared in unspecified yield by using anhydrous aluminium chloride as catalyst.

Miscellaneous Derivatives.—2 : 4-Dimethoxyacetophenone (b. p. 97—98°/0·2 mm.) was prepared by the methylation of 2 : 4-dihydroxyacetophenone (m. p. 145—146°). 2 : 4-Dimethoxyphenylglyoxylic acid [11] and 2 : 4-dihydroxy-6-methylacetophenone [12] had m. p.s 109—110·5° and 159—160° respectively. 3 : 4-Dimethoxyacetophenone (b. p. 174·5—175°/16 mm., m. p. 45—46°) was obtained from the stannic chloride-catalysed reaction between acetyl chloride and veratrole (cf. the preparation of 2 : 4-dimethoxy-6-methylacetophenone). 2- and 4-Acetoxyacetophenone [13, 14] had m. p.s 88·5—89° and 53—54° respectively.

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[9] *E.g.*, Heiber and Reindl, *Z. Elektrochem.*, 1940, **46**, 559.
[10] Tambor, *Ber.*, 1908, **41**, 793.
[11] Bouveault, *Bull. Soc. chim. France*, 1897, **17**, 946.
[12] Hoesch, *Ber.*, 1915, **48**, 1122.
[13] Friedlaender and Neudörfer, *Ber.*, 1897, **30**, 1077.
[14] Irvine and Robinson, *J.*, 1927, 2086.