1026. *The Biosynthesis of Phenols. Part VIII.*[1] *The Synthesis of (2-Carboxy-3,5-dihydroxyphenyl)propan-2-one (C-Acetyl-o-orsellinic Acid).*

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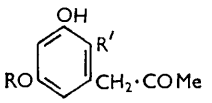
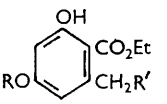
The fungal metabolite (2-carboxy-3,5-dihydroxyphenyl)propan-2-one (I) has been prepared by a series of reactions starting from ethyl 2-ethoxycarbonyl-3,5-dihydroxyphenylacetate (III).

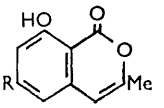
In a previous publication in this series [2] it was suggested that the biosynthesis of citrinin [3] proceeded through dihydrocitrinone,[2] and (2-carboxy-3,5-dihydroxyphenyl)propan-2-one [*C*-acetyl-*o*-orsellinic acid (I)], a compound which has also been proposed [4] as a precursor of oospolactone [4] and mellein.[5] Although the phenol (I) has been isolated as a metabolite of *Penicillium brevi-compactum* [6] it is not readily obtainable from this source. We have, therefore, undertaken a synthesis to make it available for further studies relating to the biosynthesis of citrinin.



(I) R = H; R′ = CO_2H
(IV) R = CH_2Ph; R′ = CO_2Et
(VIII) R = CH_2Ph; R′ = CO_2H
(IX) R = H; R′ = CO_2Et



(II) R = CH_2Ph; R′ = CO_2H
(III) R = H; R′ = CO_2Et
(VII) R = CH_2Ph; R′ = CO_2Et



(V) R = O·CH_2Ph
(VI) R = H
(X) R = OH

5-Benzyloxy-2-ethoxycarbonyl-3-hydroxyphenylacetic acid (II) was prepared from ethyl 2-ethoxycarbonyl-3,5-dihydroxyphenylacetate [7] (III) by benzylation followed by mild alkaline hydrolysis. When the acid chloride derived from the 5-benzyl ether (II) was treated with dimethylcadmium, three phenolic products were formed. Spectroscopic and chemical evidence led to the identification of one of these, m. p. 114—115°, as (5-benzyloxy-2-ethoxycarbonyl-3-hydroxyphenyl)propan-2-one (IV). The ultraviolet absorption spectrum was very similar to that of the acid (II); the bands at 1724 and 1658 $cm.^{-1}$ in the infrared absorption spectrum were assigned, respectively, to an isolated carbonyl group, and to an ethoxycarbonyl function in an ethyl salicylate derivative. Moreover, the n.m.r. spectrum had signals at τ 6·06 (singlet, two protons) and 7·87 (singlet, three protons) due to the system, aryl–CH_2·CO·CH_3.

[1] Part VII, Hassall and Lawrence, *J. Gen. Microbiol.*, 1964, **35**, 483.
[2] Hassall and Jones, *J.*, 1962, 4189.
[3] Brown, Robertson, Whalley, and Cartwright, *J.*, 1949, 867.
[4] Yamamoto, Nitta, and Yamamoto, *Agric. and Biol. Chem.* (*Japan*), 1961, **25**, 405.
[5] Nishikawa, *J. Agric. Chem. Soc. Japan*, 1933, **9**, 772.
[6] Oxford and Raistrick, *Biochem. J.*, 1933, **27**, 634, 1473.
[7] Nogami, *J. Pharm. Soc. Japan*, 1941, **61**, 56.

When the mixture containing the two additional products of the reaction with dimethylcadmium was hydrolysed by very mild treatment with alkali, a neutral and an acidic compound were obtained. The neutral compound, $C_{17}H_{14}O_4$, was evidently 6-benzyloxy-8-hydroxy-3-methylisocoumarin (V). This followed from the close similarity of the ultraviolet spectrum to that of 8-hydroxy-3-methylisocoumarin [8] (VI), and the occurrence in the infrared spectrum of bands at 1686 (*o*-hydroxyphenyl-lactone) and 1635 cm.$^{-1}$ (conjugated C=C), values identical with those recorded for the isocoumarin (VI). The n.m.r. spectrum included signals at τ 3·83 (singlet, one proton; CH=C<) and 7·78 (singlet, three protons; CH_3). The same compound (V) was obtained from (5-benzyloxy-2-ethoxycarbonyl-3-hydroxyphenyl)propan-2-one (IV) by alkaline hydrolysis followed by treatment with acid. The acid from the reaction mixture was identified as (II). This must have arisen from the corresponding ester (VII) produced presumably by ester exchange during the formation of the acid chloride from the acid (II).

(5-Benzyloxy-2-carboxy-3-hydroxyphenyl)propan-2-one (VIII) was prepared from the isocoumarin derivative (V) by treatment with very dilute sodium hydroxide followed by carefully controlled acidification; debenzylation by hydrogenolysis gave *C*-acetyl-*o*-orsellinic acid (I) in excellent yield. The isocoumarin (X) was similarly prepared from the ether (V).

Unsuccessful attempts were made to synthesise the phenol (I) by treatment of the acid (II) with methyl-lithium. Although methyl ketones have been prepared in this way from benzoic, phenylacetic, phenylpropionic,[9] and 3,5-dimethoxyphenylacetic [10] acids, they could not be obtained when 3,5-dihydroxyphenylacetic acid [11] or the acid (II) were treated with methyl-lithium using a wide variety of conditions.

Experimental

Melting points were determined on a Kofler hot-stage apparatus. Ultraviolet absorption spectra were measured in ethanol on a Unicam S.P. 500 or an Optica CF 4 recording spectrophotometer, and infrared absorption spectra for potassium bromide discs on a Perkin-Elmer Infracord. N.m.r. spectra were determined in deuterated chloroform using tetramethylsilane as an internal standard with a Perkin-Elmer 40 Mc./sec. spectrometer. Peak positions are recorded on the τ scale. Potentiometric titrations were carried out in 50% aqueous methanol using a Radiometer pH meter TTT1, and pK_a values are corrected for methanol content.[12] Silica gel for chromatography was washed with 5% aqueous acetic acid and methanol in turn. It was dried at 90°/15 mm. for 4 hr. Thin-layer chromatography was described in Part V.[13]

Ethyl 5-Benzyloxy-2-ethoxycarbonyl-3-hydroxyphenylacetate (VII).—Ethyl 2-ethoxycarbonyl 3,5-dihydroxyphenylacetate (III) [7] (15 g.), anhydrous potassium carbonate (10 g.), and benzyl chloride (30 g.) in dry acetone (200 ml.) were heated under reflux for 8 hr. The *product* (VII), obtained by working up in the usual way, crystallised from light petroleum (b. p. 60—80°) as lustrous needles (12 g.), m. p. 69°, $\lambda_{max.}$ 265, 306 mμ (log ε 4·18, 3·84) (Found: C, 67·5; H, 6·5. $C_{20}H_{22}O_6$ requires C, 67·0; H, 6·2%), $\nu_{max.}$ 1727 (phenylacetate-CO_2Et) and 1646 cm.$^{-1}$ (*o*-hydroxyphenyl-CO_2Et). The compound gave a weak brown colour with ethanolic ferric chloride.

5-Benzyloxy-2-ethoxycarbonyl-3-hydroxyphenylacetic Acid (II.)—The preceding diester (6·3 g.) and sodium hydroxide (10 g.) in aqueous methanol (methanol–water, 9 : 1; 100 ml.) was allowed to stand at 16—18° for 2 hr. After dilution with ice (50 g.) and water (100 ml.), the solution was acidified to pH 2. After 15 min. solid was collected by filtration and dried (5·5 g.). The solution remaining when methanol had been removed from the filtrate under reduced pressure was extracted with chloroform (4 × 100 ml.), to give further product (0·4 g.) which was crystallised from acetone–light petroleum (b. p. 60—80°) to give the *acid* (II) (5·4 g.) as needles, m. p.

[8] Bendz, *Arkiv Kemi*, 1959, **14**, 511.
[9] Tegnér, *Acta Chem. Scand.*, 1952, **6**, 782.
[10] Birch and Donovan, *Austral. J. Chem.*, 1953, **6**, 373.
[11] Theilacker and Schmid, *Annalen*, 1950, **570**, 15.
[12] Halford, *J. Amer. Chem. Soc.*, 1933, **55**, 2272.
[13] Curtis, Harries, Hassall, and Levi, *Biochem. J.*, 1964, **90**, 43.

169°, $\lambda_{max.}$ 263, 303 mμ (log ε 4·13, 3·85), pK_a 5·21 [Found: C, 65·4; H, 5·7%; Equiv., 332. $C_{18}H_{18}O_6$ requires C, 65·4; H, 5·5%; *M* and Equiv. (monobasic acid), 330], $\nu_{max.}$ 1695 (phenylacetic-CO_2H) and 1656 cm.$^{-1}$ (*o*-hydroxyphenyl-CO_2Et). The compound gave a brown colour with ethanolic ferric chloride.

The corresponding *diacid* was obtained by boiling the diester (VII) (171 mg.) in 2N-sodium hydroxide (10 ml.) for 15 min. under nitrogen. Acidification and recrystallisation from acetone–light petroleum (b. p. 60—80°) gave *5-benzyloxy-2-carboxy-3-hydroxyphenylacetic acid* (120 mg.) as a microcrystalline powder, m. p. 170—174° (decomp.), $\lambda_{max.}$ 262, 303 mμ (log ε 4·16; 3·80), pK_a 3·05, 5·29 [Found: C, 62·9; H, 4·95%; Equiv., 151. $C_{16}H_{14}O_6,0{\cdot}25H_2O$ requires C, 62·7; H, 4·8%; Equiv. (dibasic acid), 151], $\nu_{max.}$ 1689 (phenylacetic-CO_2H) and 1631 cm.$^{-1}$ (*o*-hydroxyphenyl-CO_2H). The compound gave a brown colour with ethanolic ferric chloride.

(*5-Benzyloxy-2-ethoxycarbonyl-3-hydroxyphenyl*)*propan-2-one* (IV).—The acid (II) was neutralised with 0·1N-sodium hydroxide. Water was removed at 40° and the glass-like product was ground in a mortar and dried to constant weight. This sodium salt (5·33 g.), in dry benzene (50 ml.) containing two drops of pyridine, was treated with oxalyl chloride (2·8 g.) at 20°. After 20 min. the solution was decanted from sodium chloride and evaporated under reduced pressure to give a pale yellow gum (5·4 g.) which was dissolved in dry benzene (50 ml.) and used without purification.

A solution of dimethylcadmium (10 mol.) in benzene (130 ml.) was prepared in an atmosphere of nitrogen by adding anhydrous cadmium chloride (14 g.) during 5 min. to an ethereal solution (100 ml.) of methylmagnesium bromide [from magnesium (3·7 g.) and excess of methyl bromide]. After refluxing or 15 min., the ether was replaced by dry benzene.

The mixture of acid chloride and dimethylcadmium solution was heated under reflux, with stirring, for 20 min., and poured into 2N-hydrochloric acid containing crushed ice. The benzene layer was separated, the aqueous phase was extracted with ether, and the combined extract was washed with 5% sodium carbonate, dried, and distilled. The residue (3·14 g.) contained three phenolic components when examined by thin-layer chromatography (system IV, dianisidine spray [13]).

Chromatography on silica gel (25 × 1·5 cm.) using benzene–chloroform (9 : 1) and then benzene–chloroform (1 : 1) gave two main fractions. The later eluate (1 l.) (one component on chromatograms) yielded a pale yellow oil (1·3 g.) which crystallised from light petroleum (b. p. 60—80°) to give (*5-benzyloxy-2-ethoxycarbonyl-3-hydroxyphenyl*)*propan-2-one* (IV) (420 mg.), plates, m. p. 114—115°, $\lambda_{max.}$ 263, 303 mμ (log ε 4·16, 3·85) (Found: C, 69·4; H, 6·1. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%), $\nu_{max.}$ 1724 (aliphatic >CO) and 1658 cm.$^{-1}$ (*o*-hydroxyphenyl-CO_2Et). N.m.r. spectrum (with numbers of protons in parentheses): τ = 5·65 (2, quartet, ester-CH_2); 6·06 (2, singlet, aryl-CH_2); 7·87 (3, singlet, CH_3·CO); 8·67 (3, triplet, ester-CH_3). The compound gave a brown colour with ethanolic ferric chloride.

The first eluate (850 ml.) (two components in chromatograms) gave a pale yellow gum (1·52 g.). This was allowed to stand in aqueous methanol (methanol–water, 95 : 5; 25 ml.) and sodium hydroxide (2·5 g.) for 2 hr. The solution was acidified at 0° and extracted with ether (4 × 100 ml.) which was shaken with 2N-sodium carbonate solution (4 × 15 ml.). Distillation of the ether gave a light brown gum (980 mg.) which crystallised from light petroleum (b. p. 60—80°) to give *6-benzyloxy-8-hydroxy-3-methylisocoumarin* (V) (300 mg.) as needles, m. p. 136—137°, $\lambda_{max.}$ 235 (infl.) 244, 259 (infl.), 277, 326 mμ (log ε 4·66, 4·77, 4·18, 4·05, 3·80) (Found: C, 72·4; H, 5·1. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%), $\nu_{max.}$ 1686 (*o*-hydroxylactone >CO) and 1635 cm.$^{-1}$ (conjugated C=C). N.m.r. spectrum: τ = 3·83 (1, singlet, olefinic H); 7·78 (3, singlet, CH_3). The compound gave a green colour with ethanolic ferric chloride.

Acidification of the sodium carbonate extract gave 5-benzyloxy-2-ethoxycarbonyl-3-hydroxyphenylacetic acid (II) (352 mg.), m. p. and mixed m. p. 163—168°.

6-Benzyloxy-8-hydroxy-3-methylisocoumarin (V).—The foregoing ester (IV) (60 mg.) in aqueous methanol (methanol–water; 9 : 1; 3 ml.) containing sodium hydroxide (300 mg.) was allowed to stand at room temperature for 2·5 hr. The solution was diluted (20 ml.), and acidified with 2N-hydrochloric acid. Extraction with ether gave a neutral fraction (45 mg.) which yielded the isocoumarin (V) (10 mg.) as needles from light petroleum (b. p. 60—80°), m. p. 134—137° undepressed on admixture with the material described above.

(*5-Benzyloxy-2-carboxy-3-hydroxyphenyl*)*propan-2-one* (VIII).—The isocoumarin derivative (150 mg.) in aqueous 0·02N-sodium hydroxide (50 ml.) was boiled for 20 min. Acidification with dilute hydrochloric acid at 0° to pH 6 and working up in the usual way gave the *ketone*

(VIII) (80 mg.), rhombs from benzene, m. p. 139—141°, $\lambda_{max.}$ 263, 302 mμ (log ε 4·11, 3·79), pK_a 3·67 [Found: C, 68·4; 5·5%; Equiv., 302. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%; *M* and Equiv. (monobasic acid), 300], $\nu_{max.}$ 3320 (enolic OH) and 1629 cm.$^{-1}$ (*o*-hydroxyphenyl-CO_2H).

(2-*Carboxy*-3,5-*dihydroxyphenyl*)*propan*-2-*one* (C-*Acetyl*-o-*orsellinic Acid*) (I).—The preceding acid (VIII) (120 mg.) in ethanol (14 ml.) was shaken for 2·5 hr. with hydrogen at atmospheric pressure and freshly reduced 5% palladium chloride–charcoal (120 mg.). After the uptake of 1·1 mol. of hydrogen, catalyst was removed and the product was worked up in the usual way to give a gum (84 mg.), which crystallised from benzene–acetone to give (2-*carboxy*-3,5-*dihydroxyphenyl*)*propan*-2-*one* (I), needles (44 mg.), m. p. 155—157° (solidifying and remelting, 225—230°), $\lambda_{max.}$ 270, 305 mμ (log ε 4·11, 3·79), pK_a 4·2 (lit.,[6] m. p. 152—156°, 220—230°) [Found: C, 57·2; H, 5·2%; Equiv., 207. Calc. for $C_{10}H_{10}O_5$: C, 57·1; H, 4·8%; *M* and Equiv. (monobasic acid), 210], $\nu_{max.}$ 3330 (enolic OH), 1647 (conjugated C=C), and 1631 cm.$^{-1}$ (*o*-hydroxyphenyl-CO_2H). The compound gave a blue-violet colour with ethanolic ferric chloride.

The ester (IV) was hydrogenated under the same conditions to give the corresponding *ethyl ester* (IX), prisms from benzene, m. p. 145—146°, $\lambda_{max.}$ 267,297 mμ (log ε 4·15, 3·82) (Found: C, 60·8; H, 5·95. $C_{12}H_{14}O_5$ requires C, 60·5; H, 5·9%), $\nu_{max.}$ 1706 (aliphatic >CO) and 1645 cm.$^{-1}$ (*o*-hydroxyphenyl-CO_2Et). The compound gave a blue colour with ethanolic ferric chloride.

6,8-*Dihydroxy*-3-*methylisocoumarin* (X).—6-Benzyloxy-8-hydroxy-3-methylisocoumarin (V) (80 mg.) in ethanol (7 ml.) was hydrogenated in the same way for 36 hr. (1 mol. uptake), to give 6,8-dihydroxy-3-methylisocoumarin (X), (54 mg.), fine needles from aqueous acetone, m. p. 245—248° (lit.,[6] m. p. 244—248°), $\lambda_{max.}$ 237 (infl.), 244, 260, 276, 317 mμ (log ε 4·65, 4·75, 4·49, 4·47, 3·80) (Found: C, 62·3; H, 4·1. Calc. for $C_{10}H_8O_4$: C, 62·5; H, 4·2%), $\nu_{max.}$ 1685 (*o*-hydroxylactone >CO) and 1640 cm.$^{-1}$ (conjugated C=C). The compound gave a dark green colour with ethanolic ferric chloride.

We are grateful to British Petroleum Ltd., and Shell Research Ltd., for financial support and to the D.S.I.R. for a research studentship (P. C. H.)

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