8-Ethylidene-7,8-dihydro-4-methoxypyrano[4,3-*b*]pyran-2,5-dione (Coarctatin), a Metabolite of *Chaetomium coarctatum*

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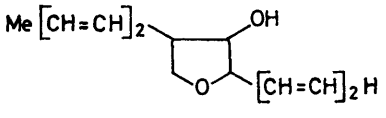
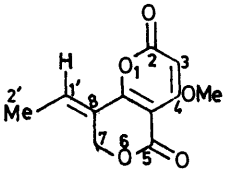
Coarctatin, a metabolite of the fungus *Chaetomium coarctatum*, is shown by its spectroscopic properties to be 8-ethylidene-7,8-dihydro-4-methoxypyrano[4,3-*b*]pyran-2,5-dione (2). This structure has been confirmed by an *X*-ray analysis of the dibromo-derivative (3).

DURING a search for biologically active metabolites of fungi we isolated two inactive metabolites from *Chaetomium coarctatum*. One of these has been shown to be 2-(buta-1,3-dienyl)-3-hydroxy-4-(penta-1,3-dienyl)-tetrahydrofuran (1),[1] and we now present evidence which leads to structure (2) for the second, for which we propose the trivial name coarctatin.

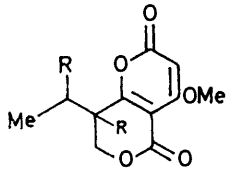
Coarctatin, $C_{11}H_{10}O_5$, shows i.r. bands due to carbonyl groups and double bonds but not to hydroxy-groups, and its u.v. spectrum shows the presence of a conjugated chromophore. Its ^1H n.m.r. spectrum reveals the presence of the part-structure $CH_3{\cdot}CH{=}C{\cdot}CH_2{\cdot}O$ (with



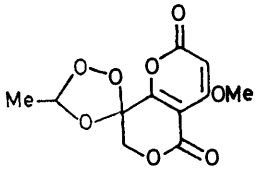
(1)



(2)



(3) R = Br
(4) R = H



(5)

allylic coupling between the vinyl proton and the methylene group and homoallylic coupling between the methylene and methyl groups), a second (uncoupled) vinylic proton, and an *O*-methyl group. The presence of these groups was confirmed by the following reactions to give products with the expected spectroscopic properties (see Experimental section). Bromination yielded the dibromide (3), and hydrogenation yielded dihydrocoarctatin (4). Further hydrogenation gave acidic hydrogenolysis products which we were unable to obtain pure, probably because they exist as mixtures of stereoisomers. Ozonolysis of coarctatin gave a stable ozonide (5), from which only intractable mixtures were obtained by hydrolysis or reduction. (The formation of the ozonide is unusual and we have not found a clear precedent. However, Bailey [2] points out that ozonide formation is favoured by the presence of an ester group α to the double bond undergoing attack, and coarctatin possesses two vinylogous α-ester systems.) The u.v. spectra of the transformation products show a bathochromic shift relative to that of coarctatin indicating that the trisubstituted double bond is part of the chromophore. Other attempts to degrade coarctatin by hydrolysis, reduction, or oxidation gave intractable mixtures.

The nature of the C_5O_3 residue not accounted for by the above results was revealed by the ^{13}C n.m.r. spectrum of coarctatin. In addition to signals due to the *O*-methyl group, the *C*-methyl group, and the methylene group, whose presence in coarctatin was already established, the spectrum showed two signals at about 170 p.p.m. characteristic of ester or lactone carbonyl carbon atoms [3] and six signals in the range 90—155 p.p.m., characteristic of double bond carbon atoms. Of these latter signals two are at about 155 and two are at 90·5 and 101·1 p.p.m., and these four signals could be attributed to two vinyl ether systems (*cf.* methyl vinyl ether, which gives signals at 153·2 and 84·1 p.p.m. from the vinyl carbons [4]); the signal at 90·5 p.p.m. gave a doublet in a single-frequency off-resonance coupling (FORD) experiment and is due to the carbon carrying the proton which gives a signal at τ 4·25. The remaining two signals are at 141·3 and 122·0 p.p.m. and are due to the trisubstituted double bond discussed above; a FORD experiment shows that the former signal is due to the proton-bearing carbon.

[1] B. F. Burrows, *Chem. Comm.*, 1967, 597.
[2] P. S. Bailey, *Chem. Rev.*, 1958, **58**, 925.
[3] G. C. Levy and G. L. Nelson, ' Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley–Interscience, New York, 1972, p. 119.
[4] K. Hatada, K. Nagata, and H. Yuki, *Bull. Chem. Soc. Japan*, 1970, **43**, 3195.

Thus, the ^{13}C n.m.r. spectrum shows the presence of two carbonyl groups and three double bonds in coarctatin, and since the molecule possesses seven degrees of unsaturation two rings must be present. Combining the above information leads to structure (2) for coarctatin. Since our experiments with coarctatin showed that it would be difficult to prove structure (2) by chemical means, we turned to *X*-ray analysis for proof. An analysis of dibromocoarctatin (3) by Drs. A. J. Geddes and B. Sheldrick (Department of Biophysics, Leeds University), while not yet fully refined, confirms structure (2) for coarctatin and establishes the configuration of the exocyclic double bond as shown. The results of this analysis will be published elsewhere.

Coarctatin is presumably derived biosynthetically from a tetraketide chain, providing C-2′ to C-2, with two carbons (C-7 and C-5) derived from the C_1 pool.

EXPERIMENTAL

Unless otherwise stated, ^1H n.m.r. spectra were measured at 100 MHz in deuteriochloroform, u.v. spectra are for methanolic solutions, and i.r. spectra are for Nujol mulls. The ^{13}C n.m.r. spectrum of coarctatin was measured on a Varian HA100D spectrometer with a Varian pulse-box linked to a G.E.C./E.P.A. March computer; 2726 pulses were measured at 1 s intervals, and the chemical shifts are given relative to Me_4Si as internal standard. T.l.c. was carried out in chloroform–acetone (95 : 5) on Merck GF silica gel plates.

Isolation of Coarctatin.—*Chaetomium coarctatum* (I.M.I. 90,491; no. 1714 in our collection) was grown as surface culture in 160 Glaxo vessels each containing Raulin–Thom medium (250 ml). After 15 days the combined content of the flasks was filtered, and the filtrate (37·5 l) was extracted twice with chloroform (4 l) to give a gummy solid (10·9 g). Crystallisation of the crude product from acetone gave needles (3·3 g), m.p. 210—216°, which were recrystallised from acetone to give *coarctatin* (*8-ethylidene-7,8-dihydro-4-methoxypyrano*[4,3-b]*pyran-2,5-dione*) (2), m.p. 221—224° (Found: C, 59·8; H, 4·6%; *m/e* 222. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·6%; *M*, 222), $\nu_{max.}$ 1750sh, 1730s, 1641m, 1604m, and 1542m cm^{-1}, $\lambda_{max.}$ 212 (ε 16,750), 247 (11,800), and 313 nm (7800), τ ($CDCl_3$–$CF_3{\cdot}CO_2H$) 3·00 (1H, qt, *J* 7·5 and 1·8 Hz), 4·25 (1H, s), 4·92 (2H, m), 6·08 (3H, s), and 8·03 (3H, dt, *J* 7·5 and 0·5 Hz), δ_C ($CF_3{\cdot}CO_2H$) 172·9, 167·6, 156·4, 155·8, 141·3, 122·0, 101·1, 90·5, 66·8, 58·7, and 14·5.

Dibromocoarctatin (3).—Bromine (2 g) was added dropwise to a stirred solution of coarctatin (200 mg) in chloroform (5 ml) and stirring was continued for 1 h. The excess of bromine was removed with a stream of nitrogen and the solution was washed with sodium thiosulphate solution, dried, and evaporated. The crude product was purified by preparative t.l.c. and was recrystallised from ethyl acetate–light petroleum to give *dibromocoarctatin* (3), prisms, m.p. 159—160° (Found: C, 35·0; H, 2·6; Br, 41·8. $C_{11}H_{10}Br_2O_5$ requires C, 34·7; H, 2·6; Br, 41·7%), $\nu_{max.}$ 1767, 1637, and 1564 cm^{-1}, $\lambda_{max.}$ 224 (ε 18,000) and 308 nm (3840), $\lambda_{infl.}$ 250 nm (ε 8090), τ 4·44 (1H, s), 4·91 (1H, d, *J* 13 Hz), 5·04 (1H, q, *J* 7 Hz), 5·45 (1H, d, *J* 13 Hz), 6·09 (3H, s), and 8·06 (3H, d, *J* 7 Hz).

Dihydrocoarctatin (4).—A solution of coarctatin (0·6 g) in glacial acetic acid (70 ml) was added to a pre-reduced suspension of 5% palladised charcoal in a little acetic acid. The mixture was shaken with hydrogen until 55 ml had been consumed, filtered, and evaporated to dryness. The residue was dissolved in chloroform and washed with sodium hydrogen carbonate solution, and the chloroform was removed to give a residue (436 mg) which was crystallised from benzene–light petroleum to give *dihydrocoarctatin* (4), rods, m.p. 113—115° (Found: C, 59·0; H, 5·2%; *m/e*, 224. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%; *M*, 224), $\nu_{max.}$ 1750sh, 1725s, 1618m, and 1552 cm^{-1}, $\lambda_{max.}$ 215 (ε 17,800), 250 (8900), and 281 nm (3600), τ 4·46 (1H, s), 5·50 (1H, dd, *J* 4 and 12 Hz), 5·72 (1H, dd, *J* 4 and 12 Hz), 6·07 (3H, s), 7·20 (1H, m), 8·20 (2H, m), and 8·90 (3H, t, *J* 6 Hz).

Ozonolysis of Coarctatin.—A solution of coarctatin (300 mg) in methylene chloride (100 ml) was treated during 18 min at −78° with an excess of ozonised oxygen. The excess of ozone was removed with a stream of oxygen and the solution was allowed to warm to room temperature and was shaken with water and zinc dust. The aqueous layer was extracted with methylene chloride and the combined organic layers were evaporated to give a foam (290 mg) which was chromatographed on silica gel plates. Recovery of the major band (R_F 0·5) and crystallisation of the product from acetone gave the *ozonide* (5) as rods, m.p. 220—225° (decomp.) after a phase change at *ca.* 130° and considerable darkening (Found: C, 48·8; H, 3·7%; *m/e*, 227. $C_{11}H_{10}O_8$ requires C, 48·9; H, 3·7%; *M* − C_2H_3O, 227), $\nu_{max.}$ 1730s, 1640m, and 1565m cm^{-1}, $\lambda_{max.}$ 225 (ε 9500) and 280 nm (3000), τ 4·40 (1H, q, *J* 5 Hz), 4·39 (1H, s), 5·68 (2H, s), 6·12 (3H, s), and 8·50 (3H, d, *J* 5 Hz).

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