Structure and Stereochemistry of Multicolanic, Multicolic, and Multicolosic Acids, 4-Ylidenetetronic Acid Metabolites from *Penicillium multicolor*. Synthesis of Methyl (*E*)-*O*-Methylmulticolanate

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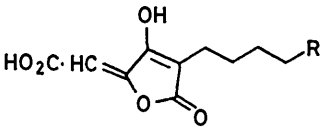
The application of 2-methoxy-3-n-pentylmaleic anhydride (8) in the synthesis of methyl *O*-methylmulticolanate (9) and its geometrical isomer is described. Comparison of ^{1}H and ^{13}C n.m.r. data with those of the dimethyl derivative of natural multicolanic acid (1a) from *Penicillium multicolor* establishes an *E*-geometry for (1a), and for the related multicolic (1b) and multicolosic acids (1c). The alternative bis-butenolide formulation (11) is entertained for the ylidenetetronic acids.

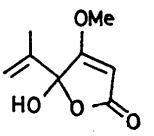
MULTICOLANIC (1a), multicolic (1b), and multicolosic acid (1c) are members of a small, but unique group of tetronic acid metabolites found in Penicillium species (*P. multicolor*).[1] Other members include penicillic acid (2) from *P. cyclopium*, viridicatic acid (3a) from *P. viridicatum*, and carlosic and carolinic acids, (3b) and (3c) respectively from *P. charlesii*.[2] The naturally occurring acetyltetronic acids carolic acid (4a) and terrestric acid (4b), possessing hydroxy groups in their side-chains, exist as mixtures of *Z*- and *E*-isomers of the five-membered ring ether structures (5).[3] This group of natural products commands considerable interest from the point of view of biosynthesis. Both multicolic (1b) [1] and penicillic acid (2) [4] are produced in nature *via* oxidative cleavages of polyketide derived aromatic intermediates, whereas the biosynthesis of carolic acid (4a) and related metabolites from *P. charlesii* has been shown to occur from Kreb's cycle intermediates.[5]

The gross structures of multicolic and multicolosic acids followed largely from hydrogenation and (u.v., n.m.r.) spectroscopic studies, and the detailed structure of multicolic acid (1b) was uniquely worked out from an examination of the ^{13}C couplings observed in the spectrum of the dimethyl derivative of the metabolite enriched with doubly labelled ^{13}C-acetate.[1] Multicolanic acid (1a) has only recently been found in *P. multicolor*, and its structure was deduced from comparison of spectral data with those of (1b) and (1c).[6] The only apparent outstanding doubt concerning these structures is the stereochemistry about the C-4 double bond. Our studies of the synthesis of 4-ylidenetetronic acids and related structures,[7] suggested a simple route to the multicolanic acid carbon skeleton based on regioselective addition of methoxycarbonylmethylenetriphenylphosphorane to the methoxymaleic anhydride (8). In this paper we report the development of this idea leading to a synthesis of the *E*-isomer of methyl *O*-methylmulticolanate (9) in the natural (stereochemical) series.[8]

The 2-hydroxymaleic anhydride derivative (7) was first prepared from condensation between ethyl heptanoate and diethyl oxalate in the presence of sodium ethoxide, followed by treatment of the resulting oxalacetic ester (6) with sulphuric acid.[9] Methylation of the anhydride with ethereal diazomethane or dimethyl sulphate, then led to the methoxy-derivative (8). The



(1)
a; R = Me
b; R = CH_2OH
c; R = CO_2H



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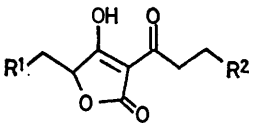
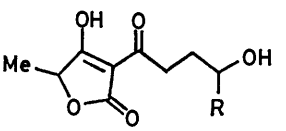
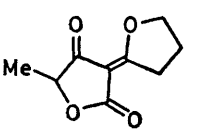


(3)
a; R^1 = Pr^n; R^2 = CO_2H
b; R^1 = Me; R^2 = CO_2H
c; R^1 = CO_2H; R^2 = H

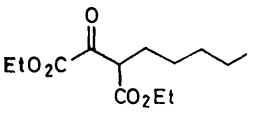


(4)
a; R = H
b; R = Et

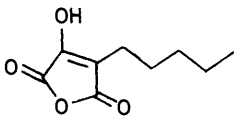


(5)

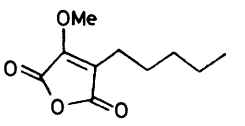
condensation between anhydride (8) and methoxycarbonylmethylenetriphenylphosphorane in chloroform (24 h, 25 °C) was found to be completely regioselective, and led to a 1 : 3 mixture of *E*- and *Z*-isomers (9) and (10) respectively, of methyl *O*-methylmulticolanate, which was separated by chromatography.



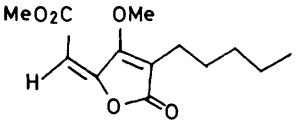
(6)



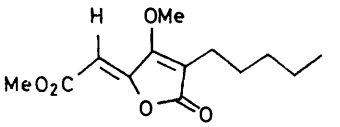
(7)



(8)



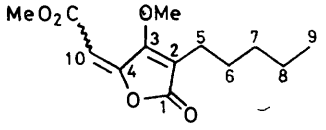
(9)



(10)

The structures and geometries of the isomeric multicolanates, (9) and (10), followed from comparison of their spectroscopic data with those of the 2-methyl substituted analogues whose structures and geometries had been firmly established by *X*-ray measurements.[7,8] The oily *E*-isomer (9) is easily distinguished from the crystalline *Z*-isomer by ^{1}H n.m.r. studies, since the olefinic proton in (9) is considerably deshielded (τ 4.17 against τ 4.37) by virtue of its *cis*-relationship to the butenolide oxygen atom. The corresponding olefinic protons in the fully methylated derivatives of the naturally derived 4-ylidenetetronic acids (1a—c) absorb at τ *ca.* 4.17, which straightaway suggests that they all have the same *E*-stereochemistry. Additional support and confirmation of this stereochemical assignment came from inspection

^{13}C N.m.r. data (δ_C in p.p.m. from Me_4Si) of the isomeric multicolanates (9) and (10) compared with naturally derived methyl *O*-methylmulticolanate

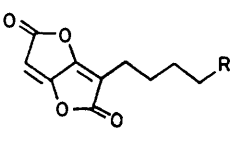


Carbon atom	4-*Z* (10)	4-*E* (9) *
1	169.0	168.7 (168.6)
2	107.3	110.6 (110.4)
3	161.6	161.1 (160.9)
4	152.3	150.9 (150.7)
5	22.3	22.3 (22.4)
6	29.9	29.7 (29.7)
7	23.4	23.5 (23.5)
8	31.6	31.6 (31.6)
9	13.9	13.9 (13.9)
10	95.0	101.1 (101.0)
11	164.0	164.4 (164.3)

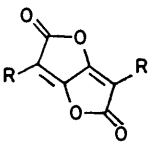
* Data for naturally derived methyl *O*-methylmulticolanate are given in parentheses.

and comparison of the ^{13}C n.m.r. shift data of (9) and (10), with those recorded for naturally derived methyl *O*-methylmulticolanate, which are summarised in the Table. The assignments for synthetic (9) and (10) followed from application of off-resonance techniques and from comparison of ^{13}C data reported for other tetronic acids.[1,4b] The data distinguish clearly the isomeric multicolanates. Furthermore the identical chemical shifts in the *E*-isomer (9) and those of the naturally derived metabolite endorse fully the assignment of an *E*-geometry to the latter, and hence to natural multicolic (1b) and multicolosic (1c) acids.

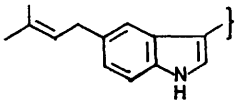
The establishment of an *E*-geometry for (1a), (1b), and (1c) naturally raises the question whether or not the metabolites occur in nature as bis-butenolides [*viz.* (11)], rather than as 'free' ylidenetetronic acids; other examples of natural bis-butenolides are found amongst the well-known pulvinic acid pigments, *e.g.* 'pulvinic anhydride' (12a) of lichens,[2,3] and in 'cochliodinone'



(11)
R = Me, CH_2OH, CO_2H



(12)
a ; R = R = Ph
b ; R = R =



(12b) an orange-coloured fluorescent metabolite, isolated recently from *Chaetomium cochliodes*.[10]

EXPERIMENTAL

For general experimental details see preceding papers.

2-Hydroxy-3-n-pentylmaleic Anhydride (*3-Hydroxy-4-n-pentylfuran-2,5-dione*) (7).—Concentrated sulphuric acid (50 g) was added dropwise during 5 min to ethyl n-pentyloxalacetate (50 g) [9] maintained at 0 °C (ice–salt), and the mixture was then stirred at 25 °C for 60 h. The anhydride which had separated was filtered off and washed thoroughly with cold, light petroleum (b.p. 100—120 °C). Crystallisation of the residue from benzene gave the anhydride (21 g, 58%), as colourless flakes, m.p. 92—94 °C (lit.,[9] m.p. 93—94 °C), $\nu_{max.}$(KBr) 3 380, 1 845, 1 768, and 1 698 cm^{-1}; τ 3.28 (O*H*), 7.39 (t, *J* 7, :C·CH_2CH$_2$), 8.37—8.74 (m, 6 H), and 9.1 (t, *J* *ca.* 7, CH$_2$CH_3) (Found: C, 58.4; H, 6.7%; *m/e*

184.073 8. Calc. for $C_9H_{12}O_4$: C, 58.7; H, 6.6%; *M* 184.073 6).

2-Methoxy-3-n-pentylmaleic Anhydride (*3-Methoxy-4-n-pentylfuran-2,5-dione*) (8).—Methylation of 2-hydroxy-3-n-pentylmaleic anhydride (2.4 g) in ether (30 ml) with diazomethane in ether, in the usual way, gave the anhydride (>90%) as a colourless oil, b.p. 100—110 °C/0.5 mmHg, $\lambda_{max.}$(EtOH) 286 nm (ε 5 600); $\nu_{max.}$ (film) 1 850, 1 760, and 1 660 cm^{-1}; τ 5.74 (OMe), 7.58 (t, *J* 7, :C·CH_2CH$_2$), 8.26—8.8 (m, 6 H), and 9.09 (t, *J ca.* 7, CH$_2$CH_3); *m/e* 198.090 6. $C_{10}H_{14}O_4$ requires *M* 198.089 2.

Methyl (E)-*4-n-Pentyl-5-oxo-2,5-dihydrofuran-2-ylideneacetate* [*Methyl* (E)-O-*Methylmulticolanate*] (9).—A solution of 2-methoxy-3-n-pentylmaleic anhydride (0.96 g) and methoxycarbonylmethylenetriphenylphosphorane (1.67 g) in chloroform (25 ml) was stirred at 25 °C for 24 h, and then evaporated to dryness. Chromatography of the residue in ether–hexane (4 : 1) on silica gel gave: (i) *methyl* (E)-O-*methylmulticolanate* (9) (eluted first), a colourless oil, $\lambda_{max.}$($CHCl_3$) 270 (ε 16 300) nm; $\nu_{max.}$ (film) 1 772, 1 722, and 1 632 cm^{-1}; τ 4.17 (:C*H*), 5.94 (O*Me*), 6.26 (CO_2*Me*), 7.5 (t, *J* 7, :C·CH_2CH$_2$), 8.25—8.77 (m, 6 H), 9.1 (t, *J ca.* 7, CH$_2$CH_3); *m/e* 254.113 7. $C_{13}H_{18}O_5$ requires 254.115 4 [naturally derived methyl *O*-methylmulticolanate shows $\lambda_{max.}$(EtOH) 256 (ε 16 600); $\nu_{max.}$ 1 775, 1 727, and 1 630 cm^{-1}; τ 4.17 (:C*H*), 5.93 (OMe), 6.26 (OMe), 7.52 (t, *J* 7, :C·CH_2CH$_2$), 8.3—8.8 (m, 6 H), 9.08 (t, *J* 7, CH$_2$CH_3)]; and (ii) *methyl* Z-O-*methylmulticolanate* (10) (eluted second), which crystallised from chloroform as colourless needles, m.p. 72—73 °C, $\lambda_{max.}$($CHCl_3$) 271 (ε 16 200) nm; $\nu_{max.}$(KBr) 1 795, 1 702, and 1 620 cm^{-1}; τ 4.37 (:C*H*), 5.83 (OMe), 6.18 (CO_2Me), 7.48 (t, *J* 7, :C·CH_2CH$_2$), 8.25—8.77 (m, 6 H), and 9.10 (t, *J ca.* 7, CH$_2$CH_3) (Found: C, 61.7; H, 7.0; *m/e* 254.114 9. $C_{13}H_{18}O_5$ requires C, 61.4; H, 7.1%).

We thank Dr. J. S. E. Holker (University of Liverpool) for kindly providing spectral data on naturally derived methyl *O*-methylmulticpolanate, and the S.R.C. for a studentship (to D. R. G.).

[7/2128 *Received, 5th December,* 1977]

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