Pyrrolylpolyenes. Part 3.[1] Synthesis of All-(*E*)-wallemia C and Stereochemistry of Natural Wallemia C

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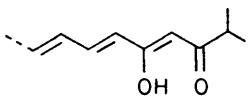
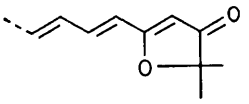
2,2-Dimethyl-5-[(5*E*)-5-methyl-6-pyrrol-2-ylhexa-1,3,5-trienyl]furan-3(2*H*)-one (7) and its lower vinylogue (9) have been synthesised. Comparison of the spectra of compound (7) with those of natural wallemia C (2) has established the *Z*-stereochemistry of the trisubstituted double bond in the natural pigment.

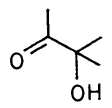
THE pyrrolylpolyene wallemia pigments have been isolated [2] from the fungus *Wallemia sebi* (Fr.) v. Arx. The two main pigments were wallemia A and wallemia C whose structures have been established [2] on the basis of their spectral data, as compounds (1) and (2), respectively. The trisubstituted double bond in wallemia A has been shown [1] to have the *Z*-configuration, by spectroscopy and by the synthesis of all-(*E*)-wallemia A (6). There has, however, been no synthetic confirmation of the stereochemistry of the trisubstituted double bond in wallemia C nor of its conjugated furan-3(2*H*)-one ring. The relative amounts of these two pigments produced by the fungus vary greatly from batch to batch, with neither pigment being the major one in all cases. It seems probable that there is a close biosynthetic relationship between wallemia-A and -C. A possible biosynthetic pathway (Scheme) involves oxidation of wallemia A at C-2, followed by cyclisation of the resulting alcohol to give the furanone ring of wallemia C. We have already reported [3] the synthesis of retinoidal furan-3(2*H*)-ones by a route based on such a scheme. The method has general applicability to the synthesis of conjugated furan-3(2*H*)-ones and, in this paper, we report the syntheses of all-(*E*)-wallemia C (7) and its lower vinylogue (9) using this method.

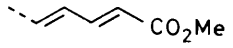
A Claisen-type condensation between the (6*E*)-trienoate ester [2] (4) and 3-hydroxy-3-methylbutan-2-one (3) using freshly prepared lithium amide in dry tetrahydrofuran [1] gave the hydroxylated compound (5), in 64% yield, which has an electronic absorption spectrum identical with that of (10*E*)-wallemia A [1] ($\lambda_{max.}$ 432 nm, shifting to 401 nm upon addition of base) and a ^{1}H n.m.r. spectrum (Table) which confirms it as the C-2 hydroxylated (10*E*)-wallemia A.

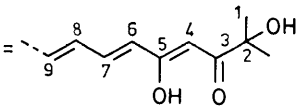
Cyclisation of compound (5) in the presence of aqueous sulphuric acid afforded compound (7), the all-(*E*)-isomer of wallemia C, in 25% yield. The absorption maximum at λ 436 nm in the electronic spectrum did not shift to a lower wavelength on addition of base. Retinoidal furan-3(2*H*)-ones [3] show strong, distinctive bands in the i.r. spectra at ν 1 670 (CO), 1 605, and 1 570 cm^{-1} and, in the n.m.r. spectra, the C-4 protons resonate at δ 5.5 and the C-2 geminal methyl groups give rise to a six-proton singlet at δ 1.4. Comparison of the spectral data of compound (7) (see Experimental section) with those of retinoidal furan-3(2*H*)-ones confirms the presence of the

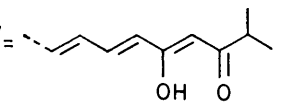
(1) R = 

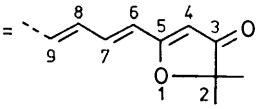
(2) R = 

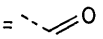
(3) 

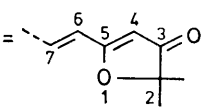
(4) R′ = 

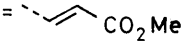
(5) R′ = 

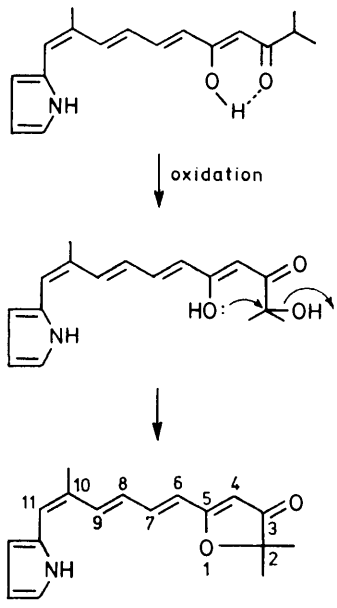
(6) R′ = 

(7) R′ = 

(8) R′ = 

(9) R′ = 

(10) R′ = 



SCHEME

conjugated furan-3(2*H*)-one system. The synthetic wallemia C, prepared using the (*E*)-trienoate ester (4) derived from the aldehyde (8),[1] has the n.m.r. signal at δ 2.13 for a methyl group attached to the double bond, whereas the corresponding signal for natural wallemia C is at δ 2.00. The chemical shifts of this signal in the two compounds therefore differ by δ 0.13; in wallemia A the corresponding signals differ by 0.14. These data, therefore, confirm the *Z*-stereochemistry of the trisubstituted double bond in natural wallemia C.

Chemical shifts (δ) of protons in the ^{1}H n.m.r. spectra of (*E*)-hydroxywallemia A (5) and (*E*)-wallemia A (6) (*J* in Hz)

	(5)	(6) [1]
2-gem-CH_3	1.42 (s)	1.14 (d, *J* 7)
10-CH_3	2.12 (s)	2.08 (s)
2-H		2.52 (m, *J* 7)
2-OH	3.66 (s)	
4-H	5.69 (s)	5.51 (s)
6-H	5.96 (d, *J* 15)	5.90 (d, *J* 15)
7-H	7.38 (dd, *J* 15,11)	7.34 (dd, *J* 15,10)
5-OH	14.45br	15.4br
N-H	8.31br	8.4br

Using a similar route, the lower vinylogue (9) of (*E*)-wallemia C was prepared from the (*E*)-dienoate ester (10), derived from the aldehyde (8),[1] and could be separated into two stereoisomers. The close similarity of the olefinic methyl group signals in the n.m.r. spectra of the two isomers of (9) (δ 2.06 and 2.05), establishes that the trisubstituted double bond has the *E*-configuration in both. Accordingly, we conclude that the isomerism is about the 6,7-double bond; the configurations about that double bond are assigned from the ^{1}H n.m.r. coupling constants (J_E 12, J_Z 10.5 Hz). Work is in progress on the synthesis of the (10*Z*)-isomer of wallemia C.

EXPERIMENTAL

M.p.s are uncorrected. T.l.c. was carried out on Merck silica-gel $60F_{254}$ pre-coated plates of 0.25 or 0.5 mm thickness. Electronic spectra were recorded on a Shimadzu UV 200S instrument and i.r. spectra on a Shimadzu IR-400 spectrometer. N.m.r. spectra at 200 MHz were determined on a Varian XL-200 superconducting (FT)-NMR spectrometer using solutions in deuteriochloroform. Mass spectra were determined on a JEOL JMS-01SG mass spectrometer; high resolution measurements were made relative to perfluorokerosene as reference.

(10E)-2,5-*Dihydroxy*-2,10-*dimethyl*-11-*pyrrol*-2-*ylundeca*-4,6,8,10-*tetraen*-3-*one* (5).—To a suspension of lithium amide [freshly prepared from lithium (169.6 mg) and liquid ammonia (120 cm^3)] in dry tetrahydrofuran (THF) (50 cm^3) were added successively a solution of 3-hydroxy-3-methylbutan-2-one (3) (1.08 g) in dry THF (15 cm^3) and a solution of methyl (6*E*)-6-methyl-7-pyrrol-2-ylhepta-2,4,6-trienoate [2] (4) (230 mg) in dry THF (15 cm^3) and the mixture was heated under reflux for 18 h. The cooled reaction mixture was poured onto ice–water (*ca.* 100 cm^3), the solution was cautiously adjusted to pH 6 with 10% hydrochloric acid, and then extracted with diethyl ether. The ethereal solution was washed with brine, dried (Na_2SO_4), and evaporated to give a gum (862 mg), which, after repeated t.l.c. (silica gel; 20% acetone in benzene), yielded the (10E)-*isomer* (5) of 2-hydroxywallemia A (195.4 mg, 64%); $\lambda_{max.}$ (ethanol) 432 nm; $\lambda_{max.}$ (ethanol–NaOH) 401 nm; δ 1.42 (6 H, s), 2.12 (3 H, s), 3.66 (1 H, s), 5.69 (1 H, s), 5.96 (1 H, d, *J* 15 Hz), 6.32—6.46 (4 H, m), 6.71 (1 H, d, *J* 14.9 Hz), 6.89 (1 H, m), 7.38 (1 H, dd, *J* 15 and 11 Hz), 8.31br (1 H) and 14.45br (1 H) (Found: $M^{+\bullet}$, 287.149. $C_{17}H_{21}NO_3$ requires $M^{+\bullet}$, 287.152).

2,2-*Dimethyl*-5-[(5E)-5-*methyl*-6-*pyrrol*-2-*ylhexa*-1,3,5-*trienyl*]*furan*-3(2H)-*one* (7).—To the undecatetraenone (5) (195.4 mg) in ethanol (10 cm^3) was added a few drops of aqueous sulphuric acid (10%) to give a mixture of pH 2—3 which was stirred under argon at room temperature for 3 h in the dark. After neutralisation of the reaction mixture with sodium hydrogencarbonate solution, the mixture was extracted with an excess of diethyl ether, and the extracts were washed with brine, dried (Na_2SO_4), and evaporated to give a gum (150 mg) which, after repeated t.l.c. (silica gel; 20% acetone in benzene), yielded *all*-(E)-*wallemia C* (7) (45.7 mg, 25%), m.p. 183—185 °C (from diethyl ether); $\lambda_{max.}$ (ethanol) 436 nm (ε 44 800); $\nu_{max.}$ ($CHCl_3$) 3 475, 1 690sh, 1 680, 1 620, 1 610, and 1 580 cm^{-1}; δ 1.43 (6 H, s, 2-gem-Me), 2.13 (3 H, s, 10-Me), 5.47 (1 H, s, 4-H), 6.29 (1 H, d, *J* 16 Hz, 6-H), 6.39—6.49 (4 H, m), 6.73 (1 H, d, *J* 14.6 Hz, 9-H), 6.91br (1 H), 7.26 (1 H, dd, *J* 16 and 11 Hz, 7-H), and 8.42br (1 H, NH) (Found: $M^{+\bullet}$, 269.142. $C_{17}H_{19}NO_2$ requires $M^{+\bullet}$, 269.142).

2,2-*Dimethyl*-5-[(3E)-3-*methyl*-4-*pyrrol*-2-*ylbuta*-1,3-*dienyl*]*furan*-3(2H)-*one* (9).—To a suspension of lithium amide [freshly prepared from lithium (166 mg) and liquid ammonia (100 cm^3)] in dry THF (50 cm^3), were added successively a solution of the butanone (3) (1.068 g) in dry THF (10 cm^3) and a solution of methyl (4*E*)-4-methyl-5-pyrrol-2-ylpenta-2,4-dienoate [2] (10) (200 mg) in dry THF (10 cm^3), and the mixture was heated under reflux for 20 h and then cooled. The reaction mixture was poured onto ice–water and the solution was adjusted to pH 6 with 10% hydrochloric acid and then extracted with diethyl ether. The ethereal solution was washed with brine, dried (Na_2SO_4), and evaporated to give a gum (780 mg) which, after repeated t.l.c. (silica gel; 20% acetone in benzene), yielded the hydroxy-β-diketone (33.5 mg, 12.3%); $\lambda_{max.}$ (ethanol) 413 nm; $\lambda_{max.}$ (ethanol–NaOH) 377 nm. To the hydroxy-β-

diketone (33.5 mg) in ethanol (*ca.* 5 cm^3) was added a few drops of aqueous sulphuric acid (10%) to give a mixture of pH 2—3 which was stirred under argon at room temperature for 3 h in the dark. After neutralisation of the reaction mixture with sodium hydrogencarbonate solution, the mixture was extracted with diethyl ether, and the extract was washed with brine, dried (Na_2SO_4), and evaporated to give a gum (28.5 mg) which, after repeated t.l.c. (silica gel; 20% acetone in benzene), yielded two isomers of compound (**9**) (8 mg) and (15 mg). The (6E)-*isomer* (8 mg) had $\lambda_{max.}$ (ethanol) 412 nm; δ 1.44 (6 H, s), 2.06 (3 H, s), 5.62 (1 H, s), 6.28—6.80 (4 H, m), 6.93br (1 H), 7.70 (1 H, d, *J* 12 Hz), and 8.38br (1 H) (Found: $M^{+\bullet}$, 243.124. $C_{15}H_{17}NO_2$ requires $M^{+\bullet}$, 243.126); the (6Z)-*isomer* (15 mg) had $\lambda_{max.}$ (ethanol) 413 nm; δ 1.43 (6 H, s), 2.05 (3 H, s), 5.56 (1 H, s), 6.30 (1 H, m), 6.46 (1 H, m), 6.71 (1 H, d, *J* 10.5 Hz), 6.76 (1 H, s), 6.90 (1 H, m), 7.19 (1 H, d, *J* 10.5 Hz), and 8.63br (1 H) (Found: $M^{+\bullet}$, 243.126. $C_{15}H_{17}NO_2$ requires $M^{+\bullet}$, 243.126).

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