Isolation and Crystal Structure of Grilactone, a New Guaianolide from *Ferula oopoda*

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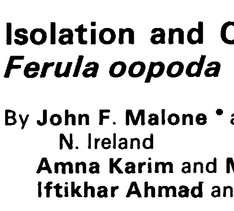
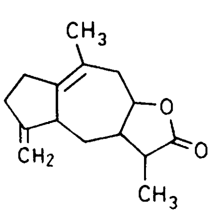
The chief constituent of the essential oils from the roots of the plant *Ferula oopoda* is the sesquiterpene guaianolide, grilactone, whose structure has been determined by an *X*-ray diffraction study. Crystals are orthorhombic, space group $P2_12_12_1$ with four molecules in a cell of dimensions a = 9.90 (2), b = 14.98 (2), c = 8.74 (2) Å. The structure was refined by least squares to R 0.079. Grilactone has a *cis-anti-cis*-configuration at the ring junctions.

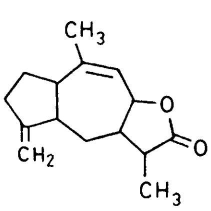
SOME years ago Kir'yalov [1] isolated from the roots of the umbelliferous plant *Ferula grigoriewii* a crystalline substance, $C_{15}H_{20}O_2$, m.p. 79.5—81.0 °C, for which he proposed the name grilactone and the structural expression (1) or (2) (without stereochemical details), having established the presence of the lactone and olefinic functions and isolated guaiazulene and chamazulene from selenium-induced dehydrogenation. In a later publication, Kir'yalov and his co-workers [2] considered yet a third structure (3) for grilactone. A related plant *Ferula oopoda* grows abundantly in the wild in the Hazargangii (Quetta) district of Pakistan where it is used as a vegetable and cattle fodder and is known locally as ' chir '. We have examined the steam distillate of the dried, crushed roots of ' chir ' and have isolated a sesquiterpene guaianolide which is undoubtedly identical with Kir'yalov's grilactone, though none of the proposed structures is correct. The m.p.s of our lactone, its C-11 epimer, and the diol obtained by lithium aluminium hydride reduction of the lactone all agree closely with those reported by Kir'yalov.[1] However, the n.m.r. spectrum of grilactone is inconsistent with structures (1)—(3). Using *X*-ray diffraction we have now established that grilactone has the structure and relative stereochemistry shown in (4); its epimer at C-11 is therefore structure (5).



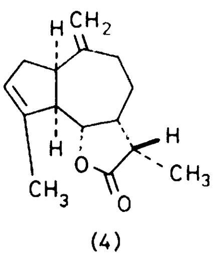
(1)



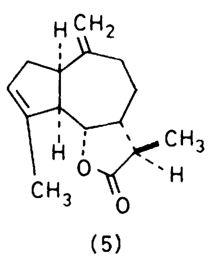
(2)



(3)



(4)



(5)

EXPERIMENTAL

Isolation of Grilactone (4).—The dried, crushed roots of ' chir ' were steam-distilled, yielding a mixture of essential oils (2.5—3.0%). On standing the distillate deposited crystals which on recrystallisation from light petroleum (b.p. 40—60 °C) gave the lactone, m.p. 78—79 °C (lit.,[1] 79.5—81.0 °C) (Found: C, 78.0; H, 8.85. $C_{15}H_{20}O_2$ requires C, 77.6; H, 8.6%); $\nu_{max.}$ (KBr) 3.3, 3.4, 5.7, 6.1, 6.8, 7.3, 7.4, 8.5, 9.8, 10.1, 10.2, 11.2, 12.5, 13.4, and 15.0 μm; τ ($CDCl_3$) 1.1 (3 H, d, $CHCH_3$), 1.8 (3 H, s, $=CCH_3$), 1.5—3.1 (10 H, m), 4.2 (1 H, m, CHO), 4.8 (2 H, s, $>C=CH_2$), and 5.4 (1 H, s, =CH).

Isomerisation of Grilactone to its Epimer (5).—A solution of grilactone (3.0 g) in 0.5M ethanolic potassium hydroxide was heated under reflux for 1.5 h. The mixture was then evaporated to dryness and the residue was dissolved in water and acidified with 0.5M-hydrochloric acid. The mixture was extracted with ether, yielding a solid (2.5 g) which was found by g.l.c. analysis on 2.5% silicone gum rubber at 200 °C to contain two components in the ratio 80 : 20. The minor component corresponded in retention time with grilactone. Crystallisation of the mixture from light petroleum gave the C-11 epimer (5) of grilactone, m.p. 105—107 °C (lit.,[1] 108—109 °C). Reduction of grilactone with lithium aluminium hydride as described by Kir'yalov gave a diol, m.p. 76—77 °C (lit.,[1] 76—77 °C).

Crystal Data.—$C_{15}H_{20}O_2$, M = 323.3. Orthorhombic, a = 9.90 (2), b = 14.98 (2), c = 8.74(2) Å, U = 1 296.1 Å^3, Z = 4, D_c = 1.19 g cm^{-3}, $F(000)$ = 504, Cu-K_α radiation, λ = 1.541 8 Å, μ(Cu-K_α) = 6.2 cm^{-1}. Space group $P2_12_12_1$.

Structure Determination.—Intensity data were recorded on equi-inclination Weissenberg photographs of the reciprocal lattice layers $0kl$ to $8kl$, by use of Cu-K_α radiation. The films were scanned by the S.R.C. microdensitometer service [3] and were corrected for Lorentz and polarization effects yielding 1 459 non-zero structure amplitudes. Symmetry equivalent hkl and $hk\bar{l}$ data were not merged. The non-hydrogen structure was solved by use of MULTAN[4] and was refined by least squares. Atomic scattering factors were taken from ref. 5. Initial full-matrix refinement, allowing isotropic vibration parameters reduced R to 13.8% and subsequent block-diagonal refinement allowing anisotropic vibrations for all atoms produced convergence at R 9.4%. (In a late stage of refinement ten F values were deleted from the F_o list, seven deemed to be suffering from secondary extinction and three measured in error by the densitometer.) A difference Fourier then revealed the positions of 18 of the 20 hydrogen atoms in the molecule. These were included in the refinement and the two missing hydrogen atoms [those on C(14)] were included at their calculated positions. Hydrogen scattering factors were taken from ref. 6, Temperature factors for the hydrogen atoms were fixed at U_{iso} 0.15 Å^2. Following a single cycle of refinement of the co-ordinates of the 37 atoms, temperature factors for the non-hydrogen atoms and nine inter-layer scale factors, a structure factor calculation gave R 7.9%. The final weighting scheme used was $W = (5 + |F_o| + 0.025|F_o|^2 + 0.03|F_o|^3)^{-1}$. The final atomic co-ordinates are listed in Table 1. Tables of anisotropic temperature factors and observed and calculated structure factors are given in Supplementary Publication No. SUP 22854 (11 pp.).* All estimated standard deviations have been corrected to allow for the fact that unmerged symmetry-equivalent data were used.

TABLE 1

(a) Atomic fractional co-ordinates for non-hydrogen atoms (with estimated standard derivations in parentheses)

	x	y	z
O(1)	0.130 8(5)	0.093 8(3)	−0.012 5(5)
O(2)	0.347 5(6)	0.084 4(4)	0.047 0(7)
C(1)	−0.230 2(7)	0.173 1(4)	0.051 3(9)
C(2)	−0.318 2(8)	0.104 8(5)	−0.030 4(10)
C(3)	−0.249 2(8)	0.095 9(5)	−0.182 1(9)
C(4)	−0.125 7(7)	0.126 6(4)	−0.178 6(7)
C(5)	−0.088 8(6)	0.160 9(4)	−0.020 4(7)
C(6)	−0.000 6(6)	0.093 6(4)	0.064 5(7)
C(7)	0.034 2(7)	0.111 8(4)	0.233 4(7)
C(8)	0.019 1(8)	0.211 2(4)	0.277 3(9)
C(9)	−0.132 1(10)	0.239 1(6)	0.294 0(9)
C(10)	−0.233 6(8)	0.179 2(5)	0.222 7(9)
C(11)	0.177 2(6)	0.076 2(5)	0.247 5(7)
C(12)	0.231 4(6)	0.084 2(5)	0.088 5(8)
C(13)	0.271 1(11)	0.115 6(6)	0.368 1(10)
C(14)	−0.327 0(12)	0.137 0(7)	0.307 2(13)
C(15)	−0.025 4(11)	0.125 7(7)	−0.308 3(10)

(b) Hydrogen parameters

Bonded to	x	y	z	C–H (Å)
C(1)	−0.258(14)	0.234(10)	0.015(19)	1.00(11)
C(2)	−0.326(15)	0.045(9)	0.040(18)	1.09(10)
C(2)	−0.405(15)	0.116(8)	−0.050(18)	0.89(10)
C(3)	−0.300(14)	0.071(10)	−0.254(17)	0.89(11)
C(5)	−0.038(15)	0.225(7)	−0.007(20)	1.10(9)
C(6)	−0.029(14)	0.042(8)	0.067(19)	0.82(10)
C(7)	−0.031(15)	0.075(10)	0.331(17)	1.20(11)
C(8)	0.071(14)	0.244(9)	0.184(19)	1.08(11)
C(8)	0.080(14)	0.218(8)	0.396(19)	1.20(12)
C(9)	−0.138(16)	0.300(9)	0.258(16)	0.97(10)
C(9)	−0.162(14)	0.240(10)	0.398(17)	0.96(11)
C(11)	0.164(14)	0.003(9)	0.275(17)	1.14(10)
C(13)	0.294(14)	0.174(10)	0.356(17)	0.91(11)
C(13)	0.371(15)	0.103(9)	0.365(17)	1.00(11)
C(13)	0.225(15)	0.108(8)	0.478(16)	1.07(10)
C(14)	−0.412(14)	0.108(9)	0.260(17)	1.03(10)
C(14)	−0.332(14)	0.150(9)	0.412(18)	0.94(11)
C(15)	0.030(13)	0.189(10)	−0.328(17)	1.11(11)
C(15)	−0.083(15)	0.104(8)	−0.401(19)	1.05(12)
C(15)	0.103(14)	0.106(8)	−0.307(18)	1.31(10)

RESULTS AND DISCUSSION

Bond lengths and interbond angles are listed in Table 2 and torsion angles in Table 3. An ORTEP[7] picture of the molecule is shown in the Figure. Grilactone has the constitution and relative configuration shown in (4). The absolute configuration was not determined.

TABLE 2

Bond lengths and angles

(a) Bonds (Å)

C(1)–C(2)	1.522(10)	C(7)–C(8)	1.545(9)
C(1)–C(5)	1.545(9)	C(7)–C(11)	1.519(9)
C(1)–C(10)	1.500(11)	C(8)–C(9)	1.560(13)
C(2)–C(3)	1.498(12)	C(9)–C(10)	1.485(12)
C(3)–C(4)	1.307(10)	C(10)–C(14)	1.342(14)
C(4)–C(5)	1.519(9)	C(11)–C(12)	1.494(9)
C(4)–C(15)	1.507(12)	C(11)–C(13)	1.524(12)
C(5)–C(6)	1.527(8)	C(12)–O(1)	1.339(8)
C(6)–C(7)	1.540(9)	C(12)–O(2)	1.205(8)
C(6)–O(1)	1.465(7)		

(b) Angles (°)

C(2)–C(1)–C(5)	104.4(5)	C(6)–C(7)–C(11)	102.9(5)
C(2)–C(1)–C(10)	119.7(6)	C(8)–C(7)–C(11)	114.1(5)
C(5)–C(1)–C(10)	115.7(5)	C(7)–C(8)–C(9)	111.9(6)
C(1)–C(2)–C(3)	102.4(6)	C(8)–C(9)–C(10)	116.7(6)
C(2)–C(3)–C(4)	112.0(6)	C(9)–C(10)–C(1)	116.1(6)
C(3)–C(4)–C(5)	111.4(6)	C(9)–C(10)–C(14)	121.3(7)
C(3)–C(4)–C(15)	126.6(6)	C(1)–C(10)–C(14)	122.5(7)
C(5)–C(4)–C(15)	121.9(6)	C(7)–C(11)–C(12)	103.4(5)
C(1)–C(5)–C(4)	101.1(5)	C(7)–C(11)–C(13)	119.3(6)
C(1)–C(5)–C(6)	113.6(5)	C(12)–C(11)–C(13)	113.1(6)
C(4)–C(5)–C(6)	110.9(5)	C(11)–C(12)–O(1)	110.7(5)
C(5)–C(6)–C(7)	118.5(4)	C(11)–C(12)–O(2)	128.5(6)
C(5)–C(6)–O(1)	106.5(4)	O(1)–C(12)–O(2)	120.8(6)
C(7)–C(6)–O(1)	104.0(4)	C(12)–O(1)–C(6)	111.0(5)
C(6)–C(7)–C(8)	112.8(5)		

Both ring junctions in the tricyclic molecule are *cis* and the full configuration is *cis-anti-cis*. The conformation of the seven-membered ring approximates to a twist-chair form. The symmetrical distribution of torsion angles (Table 3) is indicative of an approximate C_2 axis passing

TABLE 3

Torsion angles (°)

Seven-membered ring	
C(10)–C(1)–C(5)–C(6)	+42.9
C(1)–C(5)–C(6)–C(7)	−60.4
C(5)–C(6)–C(7)–C(8)	−21.1
C(6)–C(7)–C(8)–C(9)	+75.0
C(7)–C(8)–C(9)–C(10)	−17.9
C(8)–C(9)–C(10)–C(1)	−65.8
C(9)–C(10)–C(1)–C(5)	+46.0
Five-membered ring	
C(5)–C(1)–C(2)–C(3)	−27.8
C(1)–C(2)–C(3)–C(4)	+17.5
C(2)–C(3)–C(4)–C(5)	+0.9
C(3)–C(4)–C(5)–C(1)	−18.5
C(4)–C(5)–C(1)–C(2)	+28.0
Lactone ring	
O(1)–C(6)–C(7)–C(11)	−26.7
C(6)–C(7)–C(11)–C(12)	+26.5
C(7)–C(11)–C(12)–O(1)	−17.6
C(11)–C(12)–O(1)–C(6)	+0.2
C(12)–O(1)–C(6)–C(7)	+17.2

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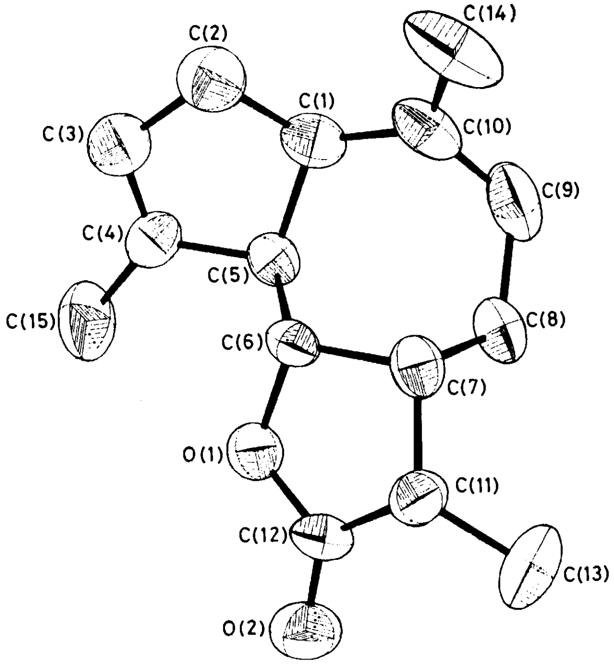
* For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1979, Index issue.

through C-1 and the mid point of the C-7–C-8 bond. This is consistent with molecular mechanics calculations which indicate that the most stable form of a methylenecycloheptane is a twist-chair in which an approximate C_2 axis of the ring passes through the carbon atom adjacent to that bearing the exocyclic methylene group.[8] Both five-membered rings have envelope conformations. The average C–H distance is 1.04 Å (average of 20 bonds) and there are no intermolecular contacts <3.4 Å between non-hydrogen atoms.



Molecular structure of grilactone, showing 50% probability thermal ellipsoids

Exposure of grilactone to alcoholic potassium hydroxide followed by acidification gives a 1 : 4 mixture of grilactone and its epimer (5) at C-11. The epimer was obtained in a pure state by recrystallisation from light petroleum.

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