X-Ray Determination of the Structure and Conformation of an Oxide from Helenalin

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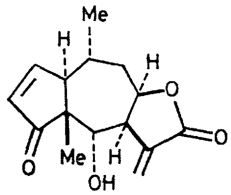
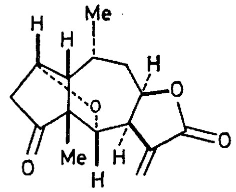
The crystal and molecular structure of the oxide (II) produced by the reaction of helenalin (I) with hydrogen chloride–chloroform and deactivated neutral alumina has been established by *X*-ray analysis from photographic data. Crystals are orthorhombic, space group $P2_12_12_1$, with $a = 8{\cdot}57(1)$, $b = 15{\cdot}79(2)$, $c = 9{\cdot}95(1)$ Å, $Z = 4$. The structure was solved by direct phase-determining methods and the molecular parameters refined by full-matrix least-squares calculations to R 0·117 over 1303 independent observed reflections. The cycloheptane ring adopts a conformation intermediate between the twist-chair and chair forms.

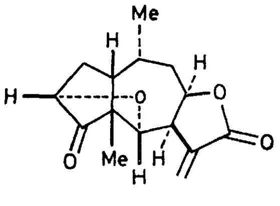
IN the course of their reinvestigations on the reactions of helenalin (I) with hydrogen chloride–chloroform and deactivated alumina, Lee *et al.*[1] obtained a new product for which spectral data and chemical reactions suggested either (II) or (III) as the structure. We undertook a single-crystal *X*-ray diffraction study of this product to establish unambiguously the constitution and to provide details of the molecular conformation. A preliminary account of this work has appeared.[2]



(I)



(II)



(III)

EXPERIMENTAL

Crystals grown from methylene chloride–ethanol were obtained as thin plates, m.p. 188—190 °C.

Crystal Data.—$C_{15}H_{18}O_4$, $M = 262{\cdot}3$. Orthorhombic, $a = 8{\cdot}57(1)$, $b = 15{\cdot}79(2)$, $c = 9{\cdot}95(1)$ Å, $U = 1346$ Å^3, $D_m = 1{\cdot}29$, $Z = 4$, D_c (flotation) $= 1{\cdot}29$, $F(000) = 560$, Cu-K_α radiation, $\lambda = 1{\cdot}542$ Å, $\mu(\text{Cu-}K_\alpha) = 7{\cdot}6$ cm^{-1}. Space group $P2_12_12_1$ (D_2^4) from systematic absences: $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, and $00l$ when $l \neq 2n$.

Crystallographic Measurements.—Unit-cell dimensions and space group data were obtained from rotation and Weissenberg photographs taken with Cu-K_α radiation and from precession photographs taken with Mo-K_α ($\lambda = 0{\cdot}7107$ Å) radiation.

Three-dimensional intensity data for the $hk0$—9 reciprocal lattice levels were collected by the equi-inclination, multiple-film Weissenberg technique by use of Cu-K_α radiation. The intensities of 1303 independent observed reflections

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[1] K. H. Lee, H. Furukawa, S. H. Kim, and C. Piantadosi, *J. Pharm. Sci.*, 1973, **62**, 987.

[2] A. T. McPhail, K. D. Onan, K. H. Lee, H. Furukawa, S. H. Kim, and C. Piantadosi, *Tetrahedron Letters*, 1973, 4641.

were estimated visually by comparison with a calibrated intensity scale and corrected for spot-shape variation, Lorentz and polarization factors; absorption was neglected. Initially the various layers were assumed to be on a common scale, and the individual absolute layer scales were obtained at the end of the isotropic refinement by correlation of $\Sigma|F_o|$ with $\Sigma|F_c|$.

Structure Analysis.—The structure was solved by direct phase-determining methods using MULTAN[3] and 294 reflections with $|E| \geqslant 1{\cdot}2$. Reflections selected for the starting set were 2,0,7; 5,0,3; 7,3,0; 1,1,9; 6,2,3; 8,3,1; and 2,1,7; the first three of these were used for origin definition and the fourth for enantiomer specification. (Attempts to phase the structure with fewer than four reflections in addition to the three origin-defining reflections did not produce meaningful E-maps.) An E-map computed with that set of phases which gave the highest figure of merit and the lowest residual revealed clearly positions for all non-hydrogen atoms. For structure factors calculated using these positions and an overall isotropic temperature factor B 3·5 Å^2, R was 0·276.

TABLE 1

Fractional atomic co-ordinates ($\times 10^4$) and anisotropic thermal parameters * ($\times 10^4$), with estimated standard deviations in parentheses

Atom	x	y	z	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
C(1)	3948(7)	1097(4)	−1093(7)	61(7)	26(2)	91(7)	9(7)	−3(12)	−8(6)
C(2)	4757(7)	821(4)	197(6)	78(6)	27(2)	76(6)	4(7)	43(12)	−6(6)
C(3)	4882(9)	1663(4)	976(8)	115(9)	38(3)	79(7)	0(9)	10(14)	−19(7)
C(4)	5264(8)	2273(4)	−172(7)	88(7)	29(2)	89(7)	25(8)	2(14)	−12(7)
C(5)	5237(7)	1743(3)	−1473(7)	63(6)	23(2)	74(6)	16(7)	−9(12)	7(6)
C(6)	6711(6)	1181(4)	−1319(6)	47(6)	28(2)	70(6)	−1(7)	−4(10)	1(6)
C(7)	7345(7)	624(4)	−2481(6)	56(6)	28(2)	74(6)	11(7)	15(11)	10(6)
C(8)	6187(8)	35(4)	−3184(7)	82(7)	26(2)	79(7)	−6(7)	10(12)	−8(7)
C(9)	4698(8)	−248(4)	−2468(7)	91(7)	26(2)	80(7)	−30(8)	32(14)	−27(6)
C(10)	3467(7)	409(4)	−2112(7)	56(6)	40(3)	82(7)	−20(8)	13(12)	1(7)
C(11)	7970(8)	1140(4)	−3627(7)	80(7)	37(3)	94(8)	4(8)	31(14)	1(8)
C(12)	6897(8)	1030(5)	−4787(8)	96(8)	38(3)	93(8)	4(9)	43(14)	10(8)
C(13)	9272(9)	1615(5)	−3701(9)	101(9)	46(3)	134(10)	−57(9)	48(16)	−2(10)
C(14)	5042(9)	2284(4)	−2716(7)	114(8)	25(2)	89(7)	22(8)	−20(14)	28(6)
C(15)	2042(8)	−51(6)	−1523(9)	81(8)	65(4)	118(9)	−71(10)	29(16)	−28(10)
O(16)	5497(7)	3019(3)	−81(6)	162(8)	32(2)	124(6)	−21(7)	32(14)	−38(6)
O(17)	6320(5)	598(3)	−237(5)	80(5)	36(2)	67(4)	−21(5)	5(8)	9(5)
O(18)	5787(6)	461(3)	−4457(5)	85(6)	47(2)	83(5)	−7(7)	−1(9)	−12(6)
O(19)	6918(8)	1374(4)	−5785(6)	176(9)	64(3)	86(6)	−5(10)	11(14)	31(7)

* In the form: $B \sin^2\theta/\lambda^2 = b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl$.

TABLE 2

Calculated hydrogen atom fractional co-ordinates ($\times 10^3$), labelled according to their bonded carbon atoms

	x	y	z		x	y	z
H(1)	289	141	−84	H(10)	312	73	−300
H(2)	421	33	76	H(13α)	971	199	−448
H(3α)	579	166	169	H(13β)	996	171	−286
H(3β)	383	183	144	H(14α)	405	267	−283
H(6)	758	159	−103	H(14β)	513	273	−299
H(7)	822	26	−205	H(14γ)	503	193	−361
H(8)	682	−52	−342	H(15α)	120	39	−130
H(9α)	507	−54	−156	H(15β)	170	−53	−224
H(9β)	418	−72	−308	H(15γ)	237	−38	−64

Refinement of the atomic parameters by full-matrix least-squares calculations proceeded smoothly. With individual isotropic temperature factors R was reduced to 0·151 and subsequent variation of anisotropic thermal parameters decreased R to 0·131. Calculated hydrogen atom positions (assuming C–H 1·05 Å) were confirmed to correspond with sites of significant positive electron-density in a difference map, and inclusion of their contributions in a structure-factor calculation reduced R to 0·122. Further least-squares iterations on the non-hydrogen atom parameters brought the refinement to convergence at R 0·117.

For all structure-factor calculations scattering factor curves from ref. 4 were used. The weighting scheme adopted in the least-squares refinement [$\sqrt{w} = 1$ for $|F_o| \leqslant 7{\cdot}5$, and $\sqrt{w} = |F_o|/7{\cdot}5$ for $|F_o| > 7{\cdot}5$] showed no systematic dependence of $\langle w\Delta^2\rangle$ when analysed in ranges of $|F_o|$.

Final atomic positional and anisotropic thermal parameters are given in Table 1 for the carbon and oxygen atoms. Calculated hydrogen atom positions are listed in Table 2. Observed and calculated structure factors are listed in Supplementary Publication No. SUP 21235 (9 pp., 1 microfiche).*

RESULTS AND DISCUSSION

The X-ray analysis establishes the structure and stereochemistry of the oxide as (II) wherein the cyclopentanone and α-methylene-γ-lactone rings are fused *cis-anti-cis* to the cycloheptane ring and the ether bridge is formed on the α-face of the molecule between C(2) and C(6). Figure 1 shows the solid-state conformation and atom numbering scheme. Interatomic distances

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* See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1974, Index issue.

[3] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.

[4] 'International Tables for X-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962.

TABLE 3

Interatomic distances (Å) and angles (deg.), with estimated standard deviations in parentheses

(*a*) Bond lengths

C(1)–C(2)	1·523(9)	C(6)–O(17)	1·455(8)
C(1)–C(5)	1·550(8)	C(7)–C(8)	1·530(9)
C(1)–C(10)	1·542(9)	C(7)–C(11)	1·500(9)
C(2)–C(3)	1·542(9)	C(8)–C(9)	1·528(9)
C(2)–O(17)	1·451(7)	C(8)–O(18)	1·475(8)
C(3)–C(4)	1·530(10)	C(9)–C(10)	1·522(9)
C(4)–C(5)	1·541(9)	C(10)–C(15)	1·537(10)
C(4)–O(16)	1·198(8)	C(11)–C(12)	1·486(10)
C(5)–C(6)	1·551(8)	C(11)–C(13)	1·346(10)
C(5)–C(14)	1·512(9)	C(12)–O(18)	1·349(9)
C(6)–C(7)	1·551(9)	C(12)–O(19)	1·211(10)

(*b*) Valency angles

C(2)–C(1)–C(5)	94·0(5)	C(6)–C(7)–C(8)	117·2(5)
C(2)–C(1)–C(10)	118·3(5)	C(6)–C(7)–C(11)	112·6(5)
C(5)–C(1)–C(10)	119·6(5)	C(8)–C(7)–C(11)	102·4(5)
C(1)–C(2)–C(3)	102·0(5)	C(7)–C(8)–C(9)	120·5(6)
C(1)–C(2)–O(17)	103·8(5)	C(7)–C(8)–O(18)	105·5(5)
C(3)–C(2)–O(17)	107·1(5)	C(9)–C(8)–O(18)	109·9(5)
C(2)–C(3)–C(4)	100·5(6)	C(8)–C(9)–C(10)	119·2(5)
C(3)–C(4)–C(5)	106·4(5)	C(1)–C(10)–C(9)	116·7(5)
C(3)–C(4)–O(16)	126·8(7)	C(1)–C(10)–C(15)	107·1(6)
C(5)–C(4)–O(16)	126·8(6)	C(9)–C(10)–C(15)	108·5(6)
C(1)–C(5)–C(4)	99·4(5)	C(7)–C(11)–C(12)	107·8(5)
C(1)–C(5)–C(6)	100·3(4)	C(7)–C(11)–C(13)	129·8(7)
C(1)–C(5)–C(14)	119·5(5)	C(12)–C(11)–C(13)	122·4(7)
C(4)–C(5)–C(6)	102·5(5)	C(11)–C(12)–O(18)	109·0(6)
C(4)–C(5)–C(14)	112·5(5)	C(11)–C(12)–O(19)	129·2(7)
C(6)–C(5)–C(14)	119·6(5)	O(18)–C(12)–O(19)	121·8(7)
C(5)–C(6)–C(7)	122·4(5)	C(2)–O(17)–C(6)	106·2(4)
C(5)–C(6)–O(17)	104·3(4)	C(8)–O(18)–C(12)	110·4(5)
C(7)–C(6)–O(17)	105·9(5)		

(*c*) Intermolecular distances <3·70 Å

O(17) ··· C(12^{I})	3·02	O(17) ··· O(19^{I})	3·52
O(17) ··· O(18^{I})	3·09	O(17) ··· C(7^{I})	3·54
O(17) ··· C(8^{I})	3·12	C(7) ··· O(19^{I})	3·59
O(17) ··· C(11^{I})	3·24	C(8) ··· O(19^{I})	3·59
C(15) ··· O(18^{II})	3·24	C(3) ··· O(19^{IV})	3·62
O(16) ··· C(1^{III})	3·47	O(19) ··· C(14^{V})	3·69

Roman numeral superscripts refer to the following transformations of the co-ordinates of Table 1:

I $\frac{3}{2} - x, -y, \frac{1}{2} + z$
II $\frac{1}{2} - x, -y, \frac{1}{2} + z$
III $\frac{1}{2} + x, \frac{1}{2} - y, -z$
IV $x, y, 1 + z$
V $\frac{1}{2} + x, \frac{1}{2} - y, -1 - z$

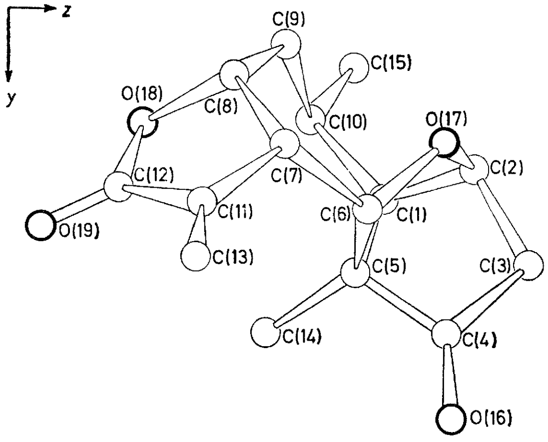


FIGURE 1 Molecular conformation and atom numbering scheme

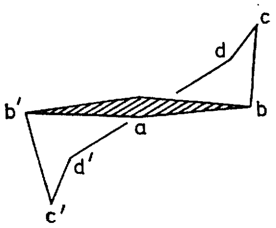
and valency angles are in Table 3, and torsion angles[5] in Table 4.

On the basis of thermodynamic considerations Hendrickson[6] has suggested that the C_2 cycloheptane twist-chair conformation is more stable than the C_s chair form. In addition, from assessment of the torsional strain involved he concluded that *cis*-fusion of a five-membered ring to a cycloheptane ring in the C_2 conformation (IV) may occur only at a–b or d–d′ bonds. Clearly intermediate forms may be encountered in molecules where the rings are heavily substituted or additional constraining ring-fusions are present. Recent calculations[7] which permit discrimination to be made between the C_2 and C_s conformations lend support to these suggestions for they demonstrate that the cycloheptane rings in a number of sesquiterpene lactones, whose structures have been established by

TABLE 4

Torsion angles (deg.); standard deviation *ca.* 1°

C(5)–C(1)–C(2)–C(3)	59	C(14)–C(5)–C(6)–C(7)	−45
C(5)–C(1)–C(2)–O(17)	−53	C(14)–C(5)–C(6)–O(17)	−165
C(10)–C(1)–C(2)–C(3)	−175	C(5)–C(6)–C(7)–C(8)	−51
C(10)–C(1)–C(2)–O(17)	74	C(5)–C(6)–C(7)–C(11)	67
C(2)–C(1)–C(5)–C(4)	−55	O(17)–C(6)–C(7)–C(8)	68
C(2)–C(1)–C(5)–C(6)	50	O(17)–C(6)–C(7)–C(11)	−174
C(2)–C(1)–C(5)–C(14)	−177	C(5)–C(6)–O(17)–C(2)	−1
C(10)–C(1)–C(5)–C(4)	180	C(7)–C(6)–O(17)–C(2)	−131
C(10)–C(1)–C(5)–C(6)	−76	C(6)–C(7)–C(8)–C(9)	−23
C(10)–C(1)–C(5)–C(14)	57	C(6)–C(7)–C(8)–O(18)	102
C(2)–C(1)–C(10)–C(9)	−48	C(11)–C(7)–C(8)–C(9)	−147
C(2)–C(1)–C(10)–C(15)	74	C(11)–C(7)–C(8)–O(18)	−22
C(5)–C(1)–C(10)–C(9)	65	C(6)–C(7)–C(11)–C(12)	−111
C(5)–C(1)–C(10)–C(15)	−173	C(6)–C(7)–C(11)–C(13)	71
C(1)–C(2)–C(3)–C(4)	−39	C(8)–C(7)–C(11)–C(12)	16
C(1)–C(2)–O(17)–C(6)	35	C(8)–C(7)–C(11)–C(13)	−162
C(3)–C(2)–O(17)–C(6)	−73	C(7)–C(8)–C(9)–C(10)	65
C(2)–C(3)–C(4)–C(5)	3	O(18)–C(8)–C(9)–C(10)	−58
C(2)–C(3)–C(4)–O(16)	−179	C(7)–C(8)–O(18)–C(12)	21
C(3)–C(4)–C(5)–C(1)	33	C(9)–C(8)–O(18)–C(12)	152
C(3)–C(4)–C(5)–C(6)	−70	C(8)–C(9)–C(10)–C(1)	−64
C(3)–C(4)–C(5)–C(14)	160	C(8)–C(9)–C(10)–C(15)	175
O(16)–C(4)–C(5)–C(1)	−145	C(7)–C(11)–C(12)–O(18)	−4
O(16)–C(4)–C(5)–C(6)	112	C(7)–C(11)–C(12)–O(19)	175
O(16)–C(4)–C(5)–C(14)	−18	C(13)–C(11)–C(12)–O(18)	174
C(1)–C(5)–C(6)–C(7)	87	C(13)–C(11)–C(12)–O(19)	−7
C(1)–C(5)–C(6)–O(17)	−32	C(11)–C(12)–O(18)–C(8)	−11
C(4)–C(5)–C(6)–C(7)	−170	O(19)–C(12)–O(18)–C(8)	170
C(4)–C(5)–C(6)–O(17)	70		



(IV)

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[5] W. Klyne and V. Prelog, *Experientia*, 1960, **16**, 521.

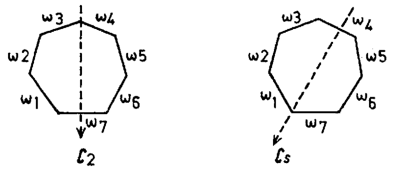
[6] J. B. Hendrickson, *Tetrahedron*, 1963, **19**, 1387.

[7] A. T. McPhail and G. A. Sim, *Tetrahedron*, 1973, **29**, 1751.

diffraction methods, more frequently approximate to a C_2 rather than a C_s conformation and the *cis,trans*-nature of the ring-fusions also accord with the proposed possible locations. Similar analysis of the torsion angles (Table 5) of the cycloheptane rings in (II), shows that $\Sigma_2 \simeq \Sigma_s$ thereby indicating that this ring exists in an intermediate form. Such a conformation positions the approximate C_2 symmetry axis at C(7), a result which is incompatible with the Hendrickson proposals for allowed locations of ring junctions since it places *cis*-fusions at a–b and c′–d′ cycloheptane bonds. Inspection of Dreiding molecular models reveals that if the C_2 axis carbon were at C(1) or C(8), either of which would result in allowed relative positions of *cis*-junctions, then severe non-bonded transannular interactions between the axial C(10)-methyl group and the oxide bridge would result. In the conformation adopted, relief from non-bonded interactions is attained through increase of the C(11) $\cdots$ C(14) and C(12) $\cdots$ C(14) distances to 3·22 and 3·27 Å from the more sterically compressed values of *ca.* 2·5 Å measured on a Dreiding molecular model. The mean endocyclic valency angle in the cycloheptane ring (116·5°) compares well with the corresponding values in euparotin bromoacetate (115°),[7] bromohelenalin (116°),[8] and bromomexicanin E (116°).[9] The small C(1)–C(5)–C(6) angle (100·3°) differs significantly from the other ring angles owing to the fact that C(5) is also a vertex of the cyclopentanone and tetrahydrofuran rings.

TABLE 5

Comparison of the torsion angles (deg.) in (II) with calculated values [a]



	Twist chair (C_2)	Chair (C_s)	(II)
ω_1	−72	−64	−76
ω_2	88	84	87
ω_3	−39	−66	−51
ω_4	−39	0	−23
ω_5	88	66	65
ω_6	−72	−84	−64
ω_7	54	64	65
Σ_2 [b]	0	104	62
Σ_s [c]	122	0	71
$\Sigma_2/(\Sigma_2 + \Sigma_s)$	0	1	0·47

[a] J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1967, **89**, 7036.

[b] $\Sigma_2 = (|\omega_1 - \omega_6| + |\omega_2 - \omega_5| + |\omega_3 - \omega_4|)$.

[c] $\Sigma_s = (|\omega_1 + \omega_7| + |\omega_2 + \omega_6| + |\omega_3 + \omega_5| + |\omega_4|)$.

The presence of an oxide bridge between C(2) and C(6) makes the C(1)—(6), O(17) portion of the sesquiterpene conformationally rigid. The C(2)—(6), O(17) six-membered ring adopts a boat conformation with C(2)–C(5) 2·247(9) Å, significantly shorter than in an ideal boat (2·57 Å) but close to the experimental value (2·27 Å) in tricyclo[4.4.0.0^{2,8}]dec-3-ene-7,10-dione.[10] The mean endocyclic valency angles in the two five-membered rings are 100·5 and 101·7°, and the rings adopt envelope conformations in which the torsion angles around the C(3)–C(4) and C(6)–O(17) bonds are not significantly different from the ideal value of zero; C(1) is displaced by 0·88 and 0·83 Å from the respective least-squares mean planes through the other four ring atoms. The dihedral angle between the planes through the four coplanar atoms of each of these five-membered rings is 109·8°, and the two planes make angles of 122·6 and 127·7° with the C(2)–C(1)–C(5) plane. These values compare favourably with the corresponding angles (111, 123, and 126°) found for the norbornene system in *anti*-7-norbornenyl *p*-bromobenzoate.[11]

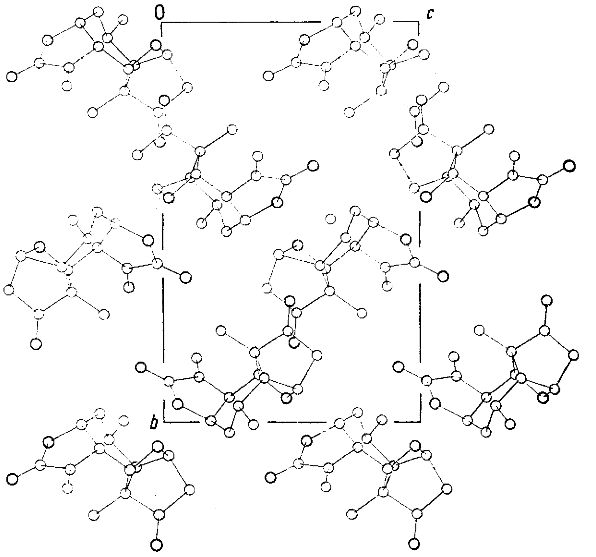


FIGURE 2 The crystal structure, viewed in projection along the *a* axis

The α-methylene-γ-lactone ring with C(7) and C(8) displaced by 0·12 and 0·24 Å, respectively, to opposite sides of the mean plane through C(11), C(12), O(18), and O(19), more closely approximates to a half-chair conformation than to an envelope form. Thus the conformation in (II) is very similar to that found in bromogaillardin [12] where the corresponding displacements are 0·16 and 0·26 Å. In accord with the results of diffraction studies of other α-methylene-γ-lactone sesquiterpenes, the carbonyl and ethylene groups depart by a small

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[8] M. T. Emerson, C. N. Caughlan, and W. Herz, *Tetrahedron Letters*, 1964, 621; Mazhar-Ul-Haque and C. N. Caughlan, *J. Chem. Soc.* (*B*), 1969, 956.

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amount from coplanarity. In (II), the C(13)–C(11)–C(12)–O(19) torsion angle is −7° and the C(11)–C(7)–C(8)–O(18) torsion angle (−22°) is *ca.* 3 times this value. These may be compared with the corresponding values (−3 and −11°) in euparotin bromoacetate,[7] and (−14 and −41°) in vernolepin *p*-bromobenzenesulphonate.[13]

Individual bond lengths do not depart significantly from the corresponding means of chemically equivalent bonds, all of which compare well with expected values: [14] $C(sp^3)$–$C(sp^3)$ 1·535, $C(sp^3)$–$C(sp^2)$ 1·527, $C(sp^2)$–$C(sp^2)$ 1·486, $C(sp^2)$=$C(sp^2)$ 1·346, $C(sp^3)$–O 1·460, $C(sp^2)$–O 1·349, C=O 1·205 Å.

The arrangement of molecules in the crystal, as viewed along the *a* axis, is shown in Figure 2. The shorter intermolecular contacts (Table 3) all involve oxygen atoms and correspond to normal van der Waals interactions.

We thank Dr. K. H. Lee for the crystals and discussions, and Duke University for the award of a James B. Duke Fellowship (to K. O.). Calculations were performed on an IBM 370 165 at the Triangle Universities Computation Centre, Research Triangle Park, North Carolina.

[4/1798 *Received, 29th August,* 1974]

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