

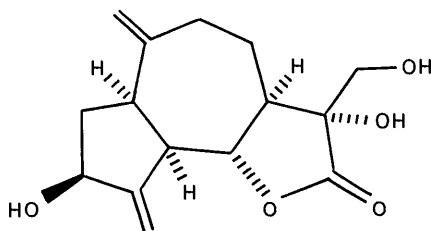
The Structure and Absolute Configuration of Solstitialin, $C_{15}H_{20}O_5$

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The molecular structure of solstitialin, $C_{15}H_{20}O_5$, a new, toxic sesquiterpenoid from *Centaurea solstitialis* L., has been elucidated *via* its crystal structure. Solstitialin crystallizes in the orthorhombic system with $a=10.007$ (4), $b=22.789$ (4), $c=5.844$ (3) Å, space group $P2_12_12_1$ with four molecules in the unit cell. Copper $K\alpha$ data were gathered by use of a Picker automatic diffractometer. The structure was solved by symbolic addition and tangent formula procedures and refined by Fourier and full-matrix least-squares methods to a final R index of 0.026 (1506 reflections). Estimated standard deviations of the bond lengths not involving hydrogen are 0.002–0.003 Å. The absolute configuration was determined by use of the anomalous scattering from oxygen. Solstitialin possesses the guaianolide structure



and has the absolute configuration shown. The lactone carbonyl group is involved in intermolecular hydrogen bonding directed in a plane about 65° from the plane of the lactone group.

Introduction

Continued ingestion of yellow star thistle (*Centaurea solstitialis* L.) by horses has been associated with a syndrome variously called 'chewing disease' or 'star thistle poisoning' (Cordy, 1954; Fowler, 1965) in which the horses have difficulty in eating and drinking, sometimes eventually dying by starvation. Neutral aqueous-ethanolic extracts of the plant have been shown to be toxic in moderate dosage to mice, rats and monkeys (Mettler & Stern, 1963). Application of solvent partition and chromatographic techniques to this fraction has resulted in the isolation of a new sesquiterpene lactone, $C_{15}H_{20}O_5$, called solstitialin (Thiessen, Hope, Zarghami, Heinz, Deuel & Hahn, 1969). This material is lethal to mice at low dosage levels (M. E. Fowler, private communication).

Chemical and spectroscopic investigation of solstitialin accounted for the five oxygen atoms as three hydroxyl groups and a γ -lactone moiety. The carbonyl frequency of 1740 cm^{-1} in the solid state is anomalously low for a γ -lactone, but shifts to the normal 1770 cm^{-1} in pyridine solution. The nature of the carbon skeleton, however, remained unknown although it was clear from spectral data that solstitialin is an unusual sesquiterpenoid in that it contains no methyl groups. Crystallographic analysis was therefore decided upon

and attempts to form a heavy-atom derivative were made. The failure of these attempts (undoubtedly associated with the lability of the material toward acid) led us to apply direct methods of phase determination to the structure of solstitialin itself.

Experimental

The minuscule amount (*ca.* 2 mg) of purified solstitialin available was a deterrent to experiments in recrystallization for the purpose of obtaining well-formed crystals. From the sample at our disposal a single-crystal fragment of approximate dimensions $0.1 \times 0.1 \times 0.3\text{ mm}^3$ was obtained by cutting. The crystal was mounted with its long direction approximately parallel to the ϕ axis of a Picker diffractometer equipped with a full-circle goniostat. The crystal was found to have orthorhombic symmetry with the systematic absences ($h00$, $0k0$, $00l$ absent for odd indices) uniquely determining the space group to be $P2_12_12_1$. Cell dimensions obtained from a least-squares treatment of angles measured on the diffractometer were $a=10.007$ (4), $b=22.789$ (4), $c=5.844$ (3) Å ($t=24^\circ\text{C}$, λ Cu $K\alpha_1=1.54051$ Å). The density calculated for a unit-cell containing four molecules of composition $C_{15}H_{20}O_5$ is 1.395, and the density estimated by flotation is 1.39 g.cm^{-3} .

The intensities of 1659 reflections accessible with Cu $K\alpha$ radiation below $2\theta=160^\circ$ were measured with the diffractometer in automatic mode by use of the

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2 θ - θ scan technique at a scan speed of 1° min⁻¹. Background counts were taken at each end of the scan range. Partial monochromatization was accomplished with a Ni filter and a pulse height analyzer in conjunction with a scintillation detector. An automatic attenuator mechanism was used to keep the count rate below 10⁴ c.p.s. Lorentz and polarization corrections were applied to the observed intensities, but no absorption or secondary extinction corrections were applied. Reflections for which 3 $\sigma(I)$ exceeded $I(\text{net})$ were recorded as 'unobserved', and were given zero weight in subsequent least-squares calculations. The 1506 'observed' reflections were assigned estimated standard deviations based on s values for an observed number of counts according to the expression $s(N) = N^{1/2} + 0.005N$.

Solution and refinement of the structure

Information from various sources indicated that the solution of problems of similar magnitude by direct methods had required nearly an hour of CDC 6600 computer time, and we were initially reluctant to embark on a venture that seemed likely to be rather time-consuming on the less powerful computer available to us. Since the c axis is quite short, and the projection is centrosymmetric, we felt that it might be worthwhile to attempt a two-dimensional solution.

A set of about 40 signs for $E_{hko} > 1.5$ was determined by the Sayre equation, and the corresponding E map calculated. The molecular structure was unknown, so no model was available to fit to the map, and none of the several trial structures more or less compatible with the map could be successfully refined, giving us good reason to abandon the two-dimensional project.

The 122 three-dimensional E 's above 1.65 (about six per 'heavy' atom) were then selected for phase determination by the symbolic addition-tangent formula procedure. The normalized structure factors are given in Table 1.

Examination of the list of 2243 \sum_2 relationships led to the choice of the reflections 520, 014, 405 and 830 for arbitrary choice of phases to specify the origin and enantiomorph (Karle & Hauptman, 1956). Application of the symbolic addition method with three symbols a , b , and c , ($a = \varphi_{12,9,1}$, $b = \varphi_{6,16,0}$, and $c = \varphi_{5,16,1}$) led in sixteen cycles (fewer would have sufficed but an input error was not caught until after the eighth cycle) to phases (absolute and symbolic) for 77 E 's in terms of two symbols, the phase of 6,16,0 having been consistently indicated as π . The sum of the products indicating a certain phase was required to be ≥ 11.4 before it was accepted as known.

Starting with the two remaining symbols set to 0° ten cycles of tangent formula refinement led to a set of 119 phases from which an E map (Fig. 1) was calculated. Only two of the 21 largest peaks in this map were not chemically reasonable. Structure factors based on the other nineteen had an R index of 0.30, and the

Table 1. Normalized structure factors ($\times 100$)

E_o were calculated from F_o by use of the scale factor and overall temperature factor from a Wilson plot, and E_c are derived from the refined structure. Δx is the difference (in millicycles) between phases determined with the tangent formula and those from the final structure. Three reflections, marked with *, were not used in the calculation of the E map.

h	k	l	E_o	E_c	Δx	h	k	l	E_o	E_c	Δx	h	k	l	E_o	E_c	Δx	
10	0	0	166	167	0	7	1	1	167	166	-1	7	0	5	207	206	0	
1	15	0	290	284	0	7	7	1	177	179	-2	7	7	5	163	158	5	
1	0	0	245	251	0	7	15	1	176	175	1	7	0	5	146	146	0	
1	10	0	243	226	0	7	7	1	165	168	-3	7	0	5	197	196	1	
0	0	0	155	205	0	5	5	1	206	155	-51	7	10	5	210	211	-1	
0	15	0	182	206	0	5	15	1	211	155	-56	7	21	5	170	168	2	
0	0	0	166	167	0	5	5	1	176	175	1	7	0	5	194	195	-1	
0	0	0	200	201	0	5	15	1	165	166	-1	5	0	5	211	169	42	
0	0	0	260	261	0	15	0	1	165	155	-10	5	2	5	162	166	-4	
0	0	0	157	185	0	10	0	1	184	150	-34	0	1	4	287	295	-8	
0	0	0	178	178	0	0	15	2	265	266	-1	0	11	4	178	167	11	
0	0	0	172	177	0	0	20	2	181	161	20	0	15	4	171	186	-15	
0	0	0	179	185	0	2	16	2	164	167	-3	0	5	4	210	220	-10	
0	0	0	194	196	0	0	15	2	167	171	-4	0	5	4	206	205	1	
0	0	0	268	252	0	2	19	2	179	184	-5	4	16	4	167	164	3	
0	0	0	220	196	0	2	27	2	156	164	-8	1	1	4	213	204	9	
0	0	0	182	148	0	5	21	2	172	175	-3	5	3	4	259	248	11	
0	0	0	241	235	0	5	7	2	210	215	-5	1	1	5	177	181	-4	
0	0	0	162	155	0	5	12	2	183	184	-1	5	4	4	259	265	-6	
0	0	0	186	181	0	5	17	2	187	187	0	5	15	4	185	185	0	
0	0	0	246	241	0	6	18	2	174	178	-4	6	5	4	240	238	2	
0	0	0	182	174	0	6	18	2	175	175	0	6	11	4	213	200	13	
0	0	0	182	177	0	6	8	2	163	162	1	6	9	7	4	206	191	15
0	0	0	238	228	0	8	3	2	172	170	2	0	8	5	251	228	23	
0	0	0	231	224	0	8	7	2	203	202	1	1	10	5	194	197	-3	
0	0	0	233	225	0	8	7	2	210	228	-18	1	1	5	176	181	-5	
10	0	0	305	279	0	10	9	2	178	165	13	2	2	5	162	169	-7	
11	0	0	215	181	0	11	2	2	184	155	29	2	4	5	159	207	-48	
11	0	0	217	268	0	0	17	3	195	197	-2	2	20	5	201	196	5	
11	0	0	173	184	0	0	15	3	173	183	-10	0	3	5	202	181	21	
11	0	0	200	170	0	*0	24	3	180	169	11	0	4	0	236	250	-14	
1	1	1	164	171	-25	1	2	3	162	165	-3	7	3	5	182	172	10	
1	1	1	163	170	26	1	26	3	229	219	10	7	12	5	164	171	-7	
1	1	1	165	187	-65	2	0	3	166	169	-3	8	2	5	207	184	23	
1	1	1	208	215	-15	3	0	3	213	217	-4	6	5	5	173	152	21	
1	1	1	227	231	-17	3	20	3	159	199	-66	0	4	6	214	208	6	
1	1	1	179	180	80	4	22	3	169	159	10	0	11	6	196	259	-63	
1	1	1	165	167	(M7)	4	23	3	163	183	-90	1	9	5	190	190	0	
1	1	1	173	173	12	5	15	3	202	198	4	1	7	6	150	175	-25	
1	1	1	247	250	-44	6	16	3	212	202	10	5	7	5	197	197	0	

corresponding Fourier synthesis revealed the remaining carbon atom.

The structure arrived at by Fourier methods was refined by use of a full-matrix least-squares program capable of adjusting 163 parameters at a time. The parameters which could not be refined during one cycle were adjusted in the following cycle (the contributions of the corresponding atoms to the structure factors were of course always included). With anisotropic temperature factors for all 'heavy' atoms and excluding hydrogen atoms, three refinement cycles led to an R index of about 0.07. All hydrogen atoms were then located from a difference Fourier map. Inclusion of the contributions of the hydrogen atoms to F_{calc} , with $B(\text{iso}) = 4 \text{ \AA}^2$ immediately lowered R to about 0.03. Several cycles of least-squares refinement were then carried out, during which it was attempted to refine together those atoms whose parameters had the largest covariance coefficients, as determined by inspection of the inverse normal equation matrix. Not surprisingly, it was found that parameters for 'heavy' atoms and their attached hydrogen atoms frequently were fairly strongly correlated.

As an experiment the structure was first refined to convergence by use of the Hughes (1941) weighting scheme [$4F_o(\text{min}) = 6.9$] with the final R index having a value $R = 0.0272$ for 'observed' reflections. The weighting was then changed to a $1/\sigma^2(F)$ scheme, giving a final R index of 0.0264 for 'observed' reflections and 0.0306 for all measured. As a result of the change in weighting, one 'heavy' atom parameter

shifted by as much as 2σ and shifts in a few of the hydrogen parameters approached 3σ , while the remaining parameters changed imperceptibly. The final parameters from the $1/\sigma^2(F)$ refinement are given in Tables 2, 3, and 4. Table 5 gives a comparison of observed and calculated structure factors.

Table 2. Positional parameters (with estimated standard deviations) for carbon and oxygen atoms

	x	y	z
C(1)	0.7289 (2)	0.1630 (1)	0.8309 (4)
C(2)	0.8677 (2)	0.1557 (1)	0.7207 (5)
C(3)	0.8625 (2)	0.1032 (1)	0.5550 (4)
C(4)	0.7224 (2)	0.0786 (1)	0.5800 (3)
C(5)	0.6668 (2)	0.1007 (1)	0.8040 (3)
C(6)	0.5159 (2)	0.0990 (1)	0.8234 (3)
C(7)	0.4545 (2)	0.1346 (1)	1.0193 (3)
C(8)	0.4187 (2)	0.1970 (1)	0.9459 (4)
C(9)	0.5394 (2)	0.2364 (1)	0.8953 (4)
C(10)	0.6419 (2)	0.2110 (1)	0.7326 (3)
C(11)	0.3373 (2)	0.0961 (1)	1.0987 (3)
C(12)	0.3827 (2)	0.0347 (1)	1.0284 (3)
C(13)	0.2050 (2)	0.1097 (1)	0.9782 (4)
C(14)	0.6631 (2)	0.0451 (1)	0.4287 (4)
C(15)	0.6560 (2)	0.2311 (1)	0.5231 (4)
O(16)	0.8898 (2)	0.1208 (1)	0.3246 (3)
O(17)	0.4776 (1)	0.0373 (0)	0.8691 (2)
O(18)	0.3207 (1)	0.0992 (1)	1.3389 (2)
O(19)	0.3406 (1)	-0.0113 (1)	1.1008 (2)
O(20)	0.1022 (1)	0.0715 (1)	1.0546 (3)

Although the methods used in the solution of this structure have been employed successfully in numerous cases, many users approach them with a feeling of un-

certainty regarding the requirements for success. We therefore feel that it may be of value to give some statistical information relating to the present case.

As is indicated by the E map (Fig. 1) about six E 's for each non-hydrogen atom were sufficient for easy recognition of the main features of the molecular structure. An impression of the quality of the E 's and their assigned phases may be obtained by inspection of Table 1. The agreement between 'experimental' E 's and those calculated from the final structure is very good ($R=0.04$). All zero layer E 's were assigned correct phases, whereas for the remaining reflections the phases used in the E map deviate by an average of 40 millicycles (14.7°) from the final ones. The tangent formula refinement had nearly converged, with most shifts being less than 2 millicycles in the final cycle.

We attribute the ease with which the solution emerged mainly to two factors: the relatively large proportion of 'centrosymmetric' reflections, and the inclusion of reflections up to $2\theta=160^\circ$, the latter permitting the establishment of a large number of relationships. The total IBM 7044 time spent for the symbolic addition - tangent formula procedure was about 35 min. As has been suggested by Oh & Maslen (1968), a more economic strategy probably would have been a more moderate use of the Σ_2 procedure and heavier reliance on the tangent formula.

Discussion

Solstitialin represents the first example of a guaianolide, a class characterized by fused five- and seven-

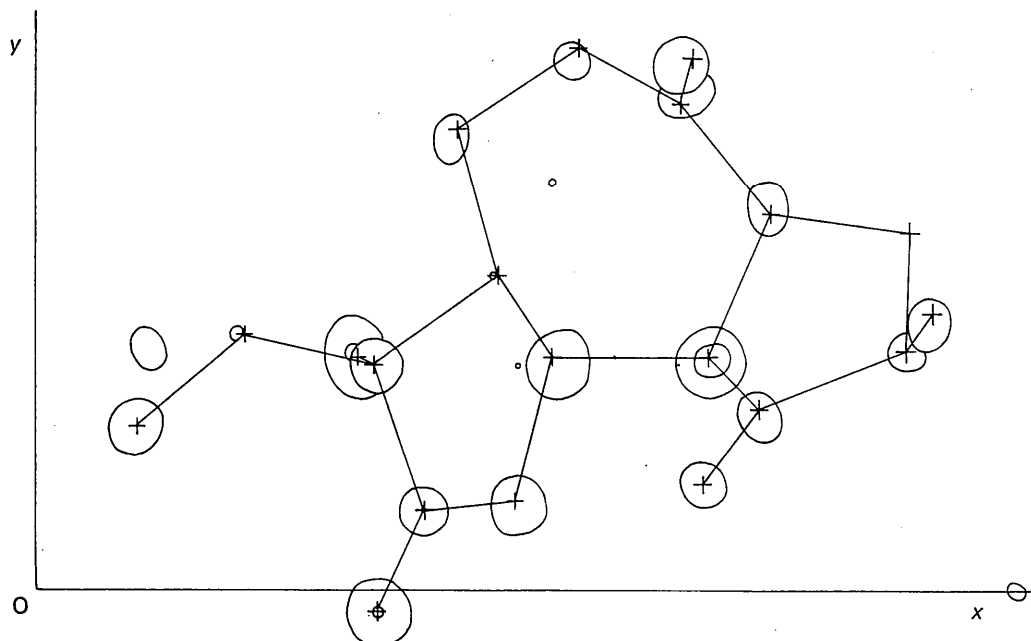


Fig. 1. Composite E map projected along [001]. Crosses indicate the atomic positions in the refined structure.

membered rings in addition to the lactone ring, to be isolated from *Centaurea* spp. The sesquiterpene lactones which have been reported (Suchy, Samek, Herout & Šorm, 1965) are germacranolides, which possess a single ten-membered ring in addition to the lactone ring. The vicinal hydroxylation of C(11) and C(13) has, to our knowledge, not been observed previously in sesquiterpene lactones.

The atomic numbering scheme is shown in Fig. 2(a), and the observed bond distances and angles are given in Fig. 2(b) and (c) and interatomic distances and angles involving hydrogen atoms are given in Tables 6 and 7. The distances and angles for the most part are consistent with common experience. A difference of about 0.1 Å between alkyl and acyl carbon-oxygen distances has been noted several times in the literature

(Karle & Karle, 1966a; Kim, Jeffrey, Rosenstein & Corfield, 1967 and references cited therein). In solstitialin, the alkyl carbon-oxygen distance (1.482 Å) is 0.15 Å greater than the acyl carbon-oxygen distance and 0.06 Å greater than an average carbon-hydroxyl oxygen atom bond-length. β -D-Glucuronolactone (Kim, Jeffrey, Rosenstein & Corfield, 1967) contains both a γ -lactone and the ether linkage of a hemiacetal, also in a five-membered ring; the alkyl carbon-oxygen distance in the lactone group is significantly longer [1.475 (5) *vs.* 1.446 (5) Å]. The even longer bond in solstitialin may reflect the fusion of the γ -lactone to a seven-membered rather than to a five-membered ring. The bond angles of the seven-membered ring are all greater than the tetrahedral angle, indicating a general flattening of the ring.

Table 3. Anisotropic thermal parameters for carbon and oxygen atoms and their estimated standard deviations

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1)	2.23 (7)	2.80 (7)	2.61 (9)	-0.29 (6)	-0.08 (7)	-0.07 (7)
C(2)	2.33 (8)	4.16 (10)	4.61 (12)	-0.30 (7)	0.22 (8)	0.09 (9)
C(3)	2.50 (7)	3.68 (8)	3.64 (10)	0.79 (7)	0.68 (8)	0.65 (8)
C(4)	2.66 (7)	2.36 (7)	2.55 (8)	0.65 (6)	0.34 (7)	0.39 (6)
C(5)	2.09 (6)	2.37 (6)	2.15 (7)	0.23 (5)	-0.05 (6)	0.25 (6)
C(6)	2.22 (6)	1.95 (6)	2.26 (8)	-0.08 (5)	0.05 (6)	0.02 (6)
C(7)	2.02 (6)	2.37 (7)	2.33 (8)	-0.07 (5)	0.03 (6)	-0.13 (6)
C(8)	2.67 (7)	2.29 (7)	3.76 (10)	0.22 (6)	0.45 (8)	-0.11 (7)
C(9)	3.10 (8)	2.12 (7)	3.97 (11)	-0.07 (6)	0.33 (8)	0.10 (8)
C(10)	2.65 (7)	2.43 (7)	2.98 (9)	-0.57 (6)	-0.15 (7)	0.01 (7)
C(11)	2.20 (7)	2.49 (7)	2.13 (8)	-0.06 (6)	0.11 (6)	-0.08 (6)
C(12)	2.03 (6)	2.65 (7)	2.60 (8)	-0.12 (5)	-0.19 (6)	0.08 (7)
C(13)	2.21 (7)	2.72 (7)	3.22 (10)	-0.03 (6)	-0.09 (7)	-0.11 (7)
C(14)	4.05 (9)	3.31 (8)	2.84 (10)	0.43 (8)	0.55 (9)	-0.24 (8)
C(15)	4.96 (11)	4.64 (10)	3.88 (11)	0.93 (9)	0.36 (11)	1.28 (9)
O(16)	5.50 (9)	6.47 (10)	4.22 (8)	0.22 (8)	2.54 (8)	0.82 (8)
O(17)	2.82 (5)	2.06 (5)	3.64 (7)	-0.10 (4)	0.68 (5)	-0.19 (5)
O(18)	3.04 (5)	4.18 (6)	2.31 (6)	-0.77 (5)	0.34 (5)	-0.25 (5)
O(19)	3.55 (6)	2.45 (5)	4.16 (7)	-0.44 (4)	0.49 (6)	0.53 (5)
O(20)	2.24 (5)	4.15 (7)	5.09 (9)	-0.52 (5)	0.20 (6)	0.07 (7)

Table 4. Positional and isotropic thermal parameters (with estimated standard deviations) for the hydrogen atoms

The first two digits of the number for each H atom denote the number of the carbon or oxygen atom to which it is attached.

	x	y	z	B
H(011)	0.7370 (17)	0.1710 (7)	1.0059 (33)	2.04 (38)
H(021)	0.9372 (24)	0.1476 (10)	0.8460 (47)	5.68 (67)
H(022)	0.9000 (25)	0.1910 (10)	0.6475 (46)	5.91 (68)
H(031)	0.9317 (18)	0.0715 (7)	0.6064 (34)	3.38 (46)
H(051)	0.7055 (16)	0.0766 (7)	0.9304 (31)	1.90 (36)
H(061)	0.4694 (16)	0.1101 (7)	0.6741 (29)	1.56 (35)
H(071)	0.5178 (18)	0.1350 (8)	1.1424 (36)	2.73 (43)
H(081)	0.3638 (17)	0.2146 (7)	1.0610 (31)	2.62 (40)
H(082)	0.3608 (18)	0.1957 (7)	0.8054 (31)	2.76 (41)
H(091)	0.5899 (18)	0.2456 (8)	1.0548 (34)	3.22 (45)
H(092)	0.5066 (18)	0.2726 (8)	0.8334 (33)	3.18 (45)
H(131)	0.1813 (17)	0.1488 (7)	1.0242 (34)	2.36 (39)
H(132)	0.2156 (20)	0.1107 (8)	0.8026 (39)	3.58 (50)
H(141)	0.5711 (18)	0.0313 (8)	0.4503 (36)	3.14 (45)
H(142)	0.7114 (21)	0.0339 (8)	0.2917 (37)	4.33 (54)
H(151)	0.6016 (22)	0.2638 (10)	0.4824 (48)	6.17 (66)
H(152)	0.7281 (23)	0.2136 (9)	0.4245 (42)	5.36 (62)
H(161)	0.9485 (24)	0.0964 (11)	0.2885 (47)	5.80 (77)
H(181)	0.2550 (21)	0.0794 (9)	1.3714 (41)	5.66 (58)
H(201)	0.1198 (24)	0.0386 (11)	0.9913 (51)	9.87 (82)

Table 5. Observed and calculated structure factors

The five columns in each group list k, 10F_o, 10F_c, the phase angle (°) and 100/σ(F_o).

h	k	l	10F _o	10F _c	Phase angle (°)	100/σ(F _o)
0	0	0	100	100	0	0
1	0	0	100	100	0	0
2	0	0	100	100	0	0
3	0	0	100	100	0	0
4	0	0	100	100	0	0
5	0	0	100	100	0	0
6	0	0	100	100	0	0
7	0	0	100	100	0	0
8	0	0	100	100	0	0
9	0	0	100	100	0	0
10	0	0	100	100	0	0
11	0	0	100	100	0	0
12	0	0	100	100	0	0
13	0	0	100	100	0	0
14	0	0	100	100	0	0
15	0	0	100	100	0	0
16	0	0	100	100	0	0
17	0	0	100	100	0	0
18	0	0	100	100	0	0
19	0	0	100	100	0	0
20	0	0	100	100	0	0
21	0	0	100	100	0	0
22	0	0	100	100	0	0
23	0	0	100	100	0	0
24	0	0	100	100	0	0
25	0	0	100	100	0	0
26	0	0	100	100	0	0
27	0	0	100	100	0	0
28	0	0	100	100	0	0
29	0	0	100	100	0	0
30	0	0	100	100	0	0
31	0	0	100	100	0	0
32	0	0	100	100	0	0
33	0	0	100	100	0	0
34	0	0	100	100	0	0
35	0	0	100	100	0	0
36	0	0	100	100	0	0
37	0	0	100	100	0	0
38	0	0	100	100	0	0
39	0	0	100	100	0	0
40	0	0	100	100	0	0
41	0	0	100	100	0	0
42	0	0	100	100	0	0
43	0	0	100	100	0	0
44	0	0	100	100	0	0
45	0	0	100	100	0	0
46	0	0	100	100	0	0
47	0	0	100	100	0	0
48	0	0	100	100	0	0
49	0	0	100	100	0	0
50	0	0	100	100	0	0
51	0	0	100	100	0	0
52	0	0	100	100	0	0
53	0	0	100	100	0	0
54	0	0	100	100	0	0
55	0	0	100	100	0	0
56	0	0	100	100	0	0
57	0	0	100	100	0	0
58	0	0	100	100	0	0
59	0	0	100	100	0	0
60	0	0	100	100	0	0
61	0	0	100	100	0	0
62	0	0	100	100	0	0
63	0	0	100	100	0	0
64	0	0	100	100	0	0
65	0	0	100	100	0	0
66	0	0	100	100	0	0
67	0	0	100	100	0	0
68	0	0	100	100	0	0
69	0	0	100	100	0	0
70	0	0	100	100	0	0
71	0	0	100	100	0	0
72	0	0	100	100	0	0
73	0	0	100	100	0	0
74	0	0	100	100	0	0
75	0	0	100	100	0	0
76	0	0	100	100	0	0
77	0	0	100	100	0	0
78	0	0	100	100	0	0
79	0	0	100	100	0	0
80	0	0	100	100	0	0
81	0	0	100	100	0	0
82	0	0	100	100	0	0
83	0	0	100	100	0	0
84	0	0	100	100	0	0
85	0	0	100	100	0	0
86	0	0	100	100	0	0
87	0	0	100	100	0	0
88	0	0	100	100	0	0
89	0	0	100	100	0	0
90	0	0	100	100	0	0
91	0	0	100	100	0	0
92	0	0	100	100	0	0
93	0	0	100	100	0	0
94	0	0	100	100	0	0
95	0	0	100	100	0	0
96	0	0	100	100	0	0
97	0	0	100	100	0	0
98	0	0	100	100	0	0
99	0	0	100	100	0	0
100	0	0	100	100	0	0

lactone group at O...H distances of 2.26 and 2.40 Å respectively.

In solution, intermolecular hydrogen bonds to carbonyl groups are generally supposed to involve the non-bonding ('n') electrons of the carbonyl group, having bonding directions in the plane of the bonds of the carbonyl carbon atom. A study of intramolecular hydrogen bonding in hydroxyketones (Joris & Schleyer, 1968) strongly suggests that 'n'-type bonding occurs when geometry permits. Evidence for hydrogen bonding directed outside the plane of the carbonyl group was found only when molecular geometry required the C=O...H angle to be acute. These kinds of hydrogen bonding are associated with a modest lowering of the carbonyl frequency by 3–25 cm⁻¹ (Bellamy, 1968) even when there is evidence of two hydrogen bonds per carbonyl group (Whetsel & Kagari, 1962).

No such clear directional preferences are evident in hydrogen bonding to carbonyl groups in crystals (Donohue, 1968). In solstitialin the planes defined by C=O...H(181') and C=O...H(201') lie at angles of about 60 and 65° respectively, to the plane of the carbonyl carbon bonds, with the angles C=O...H being obtuse. This situation would be expected to increase the

electron density in the π* molecular orbital by polarization, thereby giving rise to a marked decrease in the carbonyl stretching frequency. That such is the case is attested to by the lowering of this frequency by 30 cm⁻¹ in the crystal relative to that observed in pyridine solution. [The intermolecular O(19)...O(18') distance is 2.99 Å and O(19)...O(20') is 3.04 Å.] The same effect, only more pronounced, is found in 4-hydroxycoumarin hydrate (Gaultier & Hauw, 1966) which shows a similar hydrogen-bonding pattern with intermolecular O...O distances of 2.73 and 2.80 Å; the carbonyl stretching frequency of the solid is 1664 cm⁻¹ as compared with 1730 cm⁻¹ in dioxan solution (Farmer, 1959).

The absolute configuration

It has been shown (Hope & de la Camp, 1969) that the anomalous scattering of Cu Kα radiation by oxygen can be utilized for the determination of absolute configurations of molecules containing only oxygen and lighter elements.

The good agreement between observed and calculated structure factors for the present structure indicated that it would be worthwhile to attempt a deter-

Table 7. Bond angles involving hydrogen atoms

Estimated standard deviations are 1–2°.			
C(2)—C(1)—H(011)	111°	C(9)—C(8)—H(081)	110°
C(5)—C(1)—H(011)	107	C(9)—C(8)—H(082)	108
C(10)—C(1)—H(011)	107	H(081)—C(8)—H(082)	105
C(1)—C(2)—H(021)	109	C(8)—C(9)—H(091)	108
C(1)—C(2)—H(022)	113	C(8)—C(9)—H(092)	108
C(3)—C(2)—H(021)	110	C(10)—C(9)—H(091)	107
C(3)—C(2)—H(022)	112	C(10)—C(9)—H(092)	109
H(021)—C(2)—H(023)	104	H(091)—C(9)—H(092)	109
C(2)—C(3)—H(031)	110	C(11)—C(13)—H(131)	106
C(4)—C(3)—H(031)	109	C(11)—C(13)—H(132)	112
O(16)—C(3)—H(031)	110	O(20)—C(13)—H(131)	108
C(1)—C(5)—H(051)	106	O(20)—C(13)—H(132)	114
C(4)—C(5)—H(051)	108	H(131)—C(13)—H(132)	106
C(6)—C(5)—H(051)	109	C(4)—C(14)—H(141)	122
C(5)—C(6)—H(061)	113	C(4)—C(14)—H(142)	119
C(7)—C(6)—H(061)	109	H(141)—C(14)—H(142)	119
O(17)—C(6)—H(061)	106	C(10)—C(15)—H(151)	116
C(6)—C(7)—H(071)	108	C(10)—C(15)—H(152)	118
C(8)—C(7)—H(071)	111	H(151)—C(15)—H(152)	125
C(11)—C(7)—H(071)	106	C(3)—O(16)—H(161)	101
C(7)—C(8)—H(081)	109	C(11)—O(18)—H(181)	107
C(7)—C(8)—H(082)	110	C(13)—O(20)—H(201)	105

Table 8. Least-squares planes

The normal equations are given. Deviations are in Å. Planes are defined by atoms given before slash (/).

(1) $2.9607x - 13.4955y + 4.3802z = 3.6082$

Deviations:

C(1), -0.010; C(2), 0.016; C(3), -0.016; C(4), 0.010/C(5), 0.529; C(14), -0.376.

(2) $6.8238x - 0.0254y + 4.2745z = 7.0086$

Deviations:

C(6), 0.029; O(17), -0.035; C(12), -0.002; O(19), 0.021; C(11), -0.013/C(7), 0.447.

(3) $1.9460x - 2.1557y + 5.7057z = 5.7279$

Deviations:

C(1), 0.080; C(5), -0.060; C(8), 0.059; C(9), -0.080/C(6), -0.239; C(7), 0.682; C(10), -0.754.

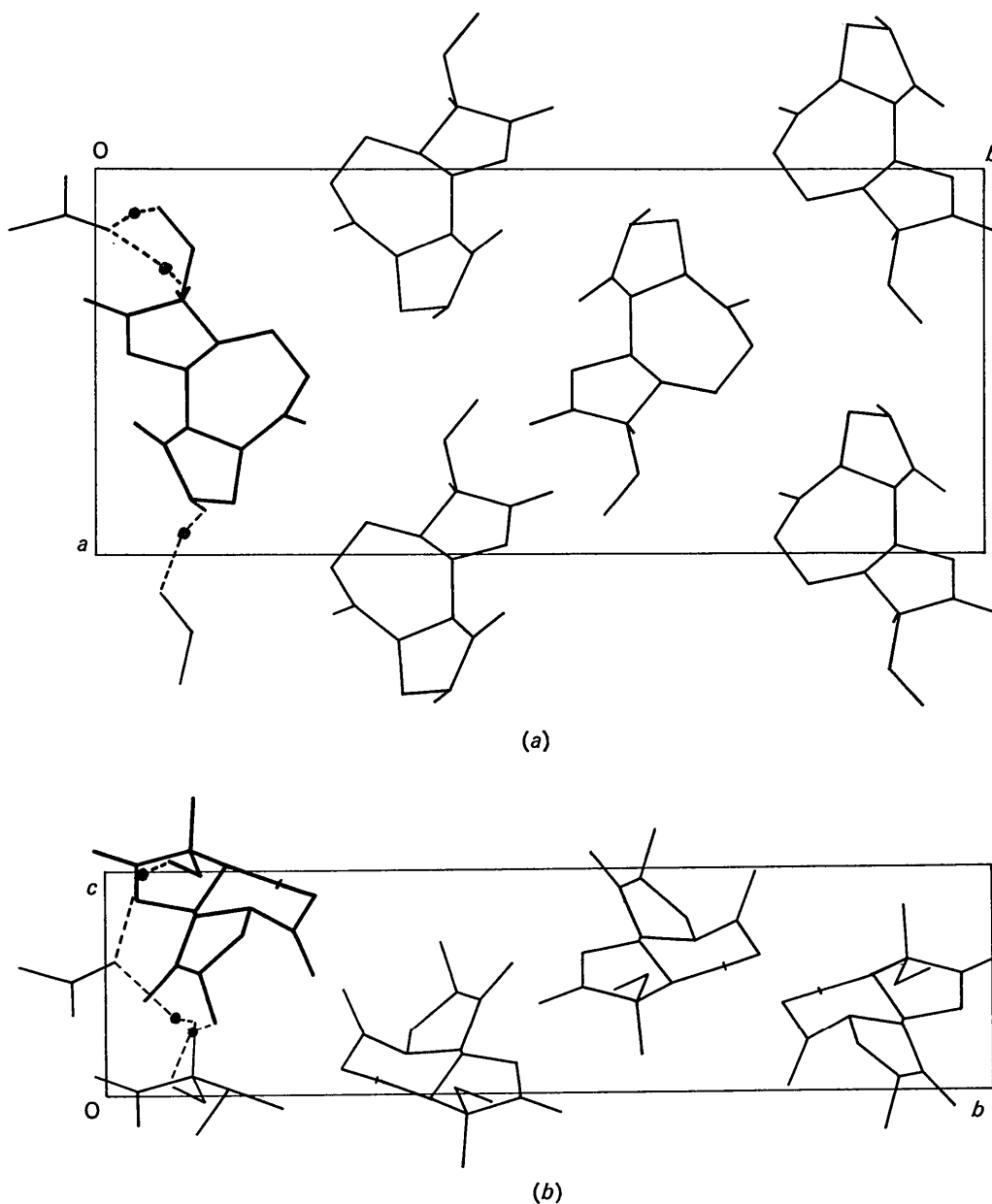


Fig. 3. Packing diagrams: (a) projection along [001]; (b) projection along [100]. Dots represent H atoms and dashed lines bonding or bridging to O atoms.

mination of the absolute configuration of solstitialin.

The function $D = [|F_c(hkl)| - |F_c(\bar{h}\bar{k}\bar{l})|]^2 / \sigma^2 [F_o(hkl)]$ was used to select reflections with the highest probability of observable differences $F(hkl) - F(\bar{h}\bar{k}\bar{l})$ (Hope & de la Camp, 1969). At the time of the data collection we did not find sufficient reason for gathering a complete set of Bijvoet pairs, and we therefore cannot carry out actual comparisons of $F_o(hkl)$ and $F_o(\bar{h}\bar{k}\bar{l})$. We feel, however, that our application of the R index comparison method (Ibers & Hamilton, 1964) provides ample evidence for the correct absolute configuration.

From the observed data were selected two sets of

reflections corresponding to two cut off levels in D , giving the 147 and 49 'most sensitive' reflections respectively. For the 147 reflections R for the two enantiomorphs are 0.0244 and 0.0250 respectively, whereas the corresponding results for the set of 49 reflections are 0.0220 and 0.0235. Since the refinement of the structure had been carried out without the real part ($\Delta f''$) of the anomalous correction terms, these were also not included in the calculations of D . The imaginary terms ($\Delta f''$) were calculated from Hönl's formula, giving $\Delta f''_C = 0.010$, and $\Delta f''_O = 0.032$.

The configuration which in both cases led to the

lower *R* index is given by (1*R*, 3*S*, 5*R*, 6*R*, 7*R*, 11*R*) in the notation of Cahn, Ingold & Prelog (1956). A conventional graphical representation of the configuration is also given in Fig. 4. Thus solstitialin possesses the *R* configuration at C(7) in accordance with the majority of guaiane and eudesmane sesquiterpenoids. Exceptions in both series are known, however (Ishii, Tozyo & Minato, 1968; Meshawari, Jain, Bates & Bhattacharyya, 1963). The junction between the seven- and five-membered carbocyclic rings is *cis* (1*R*, 5*R*) as predicted from the assumption that guaianes are produced in the plant by cyclization of a ten-membered ring precursor (Hendrickson, 1959).

Computing procedures

Most of the computer programs used in this study have been described elsewhere (Hope & Christensen, 1968). The phase determination program *PHASEM*, written by M. G. B. Drew, was used with only a minor modification to allow packing of data. The program can be used to determine initial approximate phases expressed in terms of 'symbols' by use of the symbolic addition method (Karle & Karle, 1966*b*) and can refine a set of phases by the tangent formula, given numerical values for the symbols. The program used to select reflections for the absolute configuration determination was written by H. Hope & U. de la Camp.

The least-squares program minimizes the function $S = \sum w_i (F_o - F_c)^2$ by a full-matrix procedure, where the functional form of the weight *w* is (within limits) determined by input parameters. The form factors for carbon and oxygen are those given by Hanson, Herman, Lea & Skillman (1964), and for hydrogen those of Stewart, Davidson & Simpson (1965). The isotropic temperature factors are of the form $\exp(-B \sin^2 \theta / \lambda^2)$ and the anisotropic of the form $\exp(-\frac{1}{2} h^2 a^{*2} B_{11} - \dots - \frac{1}{2} k l b^* c^* B_{23})$. The *R* index is defined by $R = \frac{\sum |F_o| - |F_c|}{\sum |F_o|}$. All calculations were performed on an IBM 7044 computer.

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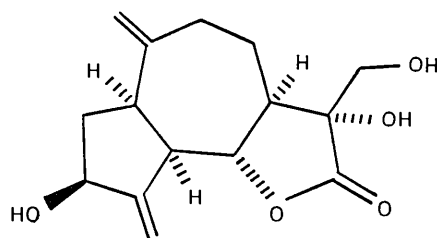


Fig. 4. Conventional structure formula for solstitialin, with indication of absolute configuration.

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