Crystal and Molecular Structure of Schkuhriolid Monohydrate, a *cis, trans*-Germacra-1(10),4-dien-*cis*-8,12-olide

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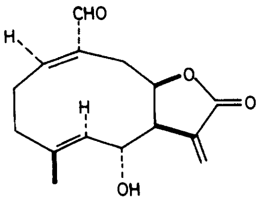
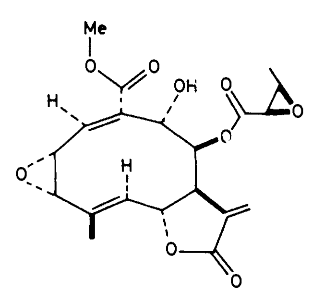
The crystal structure of the title compound (I) has been determined from three-dimensional *X*-ray diffractometer data by direct methods. Crystals are orthorhombic, space group $P2_12_12_1$, with $Z = 4$ in a cell of dimensions. $a = 6.968(1)$, $b = 9.603(1)$, $c = 22.478(3)$ Å. Schkuhriolid is a representative of the germacra-*cis*-1(10), *trans*-4-diene class of sesquiterpene, sub-group melampolide. The ten-membered ring conformation in schkuhriolid is similar to that found in crystal structures of other malampolides though the mode of the attachment of the γ-lactone ring is different. Schkuhriolid, with a lactone ring closed at C(8) and *cis*-annelated to the homocyclic ring is the first such melampolide studied by *X*-ray diffraction.

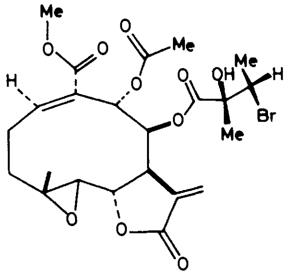
The isolation of schkuhriolid from *Schkuhria schkuhrioides* (Link and Otto) Thellung (genus Heliantheae, sub-genus Heleniineae) followed by chemical and spectroscopic investigations led to the assignment of structure (I); the molecule was shown to be a melampolide sesquiterpene lactone with an exceptional (among melampolides) *cis*-lactone ring closed at C(8).[1] This compound was chosen for further studies for two reasons. First, confirmation of the structure (I) by *X*-ray crystallography would strengthen the evidence for the proposed use of ^{1}H n.m.r. spectra in determining of the stereochemistry of α-methylene-γ-lactones.[2] Secondly, from the structural point of view it was of interest to compare the conformation of schkuhriolid with other melampolides studied so far by the *X*-ray method. Since all the published *X*-ray studies on melampolides refer to compounds with lactone rings *trans*-fused at C(6) and C(7), it was expected to elucidate whether a change in the position and stereochemistry of the lactone ring would result in significant changes in the ten-membered ring conformation.



(I)



(II)



(III)

Experimental

Crystal Data.—$C_{15}H_{18}O_4,H_2O$. Orthorhombic, $P2_12_12_1$, $a = 6.968(1)$, $b = 9.603(1)$, $c = 22.478(3)$ Å, $U = 1\,504.0(3)$ Å^3, $D_m = 1.23$, $D_c = 1.24$ g cm^{-3}, $Z = 4$.

Crystallographic Measurements.—A crystal of dimensions 0.3 × 0.4 × 0.4 mm was used to collect intensity data on a Syntex P2$_1$ diffractometer by the θ–2θ scanning technique using a variable scan speed and a graphite-monochromated Cu-K_α radiation. The cell dimensions were refined by a least-squares procedure utilizing 15 reflections whose angles were measured by a centring routine associated with the Syntex diffractometer. 1 206 independent reflections were measured out to 2θ 115°. The background and integrated intensity for each reflection were evaluated from a profile analysis according to the Lehmann and Larsen method[3] using the PRAN program.[4] Those 1 141 reflections for which $I/\delta(I) \geqslant 1.96$ were regarded as observed. Lorentz and polarization corrections were applied but no absorption corrections were made [μ(Cu-K_α) 0.78 mm^{-1}]. Anomalous dispersion corrections were applied to the scattering factors of the oxygen and carbon atoms.

Structure Analysis.—The structure was solved with MULTAN.[5] After several cycles of full-matrix least-squares refinement 16 hydrogen atoms out of 20 were located from a difference electron-density map by means of nineteen-point electron-density interpolation. The positions of four hydrogen atoms [attached to C(3) and C(15)] were calculated using a C–H distance of 1.05 Å and a tetrahedral angle of 109.5°. Hydrogen atoms were included to a full-matrix least-squares refinement as a fixed contributions. The isotropic temperature factor assigned to each hydrogen was the isotropic B value for the atom to which it was bonded plus 1.0 Å^2. Statistical weights, $w = 1/\delta_F{}^2$, were initially used, but in the last cycles of the refinement the following weighting scheme was applied: $w = F_o{}^2/a^2$ if $|F_o| < a$, $w = 1$ if $a \leqslant |F_o| \leqslant b$, $w = b^2/F_o{}^2$ if $|F_o| >$ b, where $a = 3.5$ and $b = 12.5$. The quantity minimized in the least-squares calculations was $\Sigma w(|F_o| - |F|_c)^2$. Five of the most intense reflections showed significant secondary extinction and were dropped from the final refinement. The final R value was 0.053 for 1 136 reflections.

An attempt was made to verify the assumed absolute configuration by means of the Hamilton test.[6] Both enantiomers were refined with weights based on counting statistics. The R_G [$=(\Sigma w||F_o| - |F_c||^2/\Sigma w|F_o|^2)^{1/2}$] values for the two enantiomers were $R_G(1)$ 0.0647 and $R_G(2)$ 0.0650. The configuration with a slightly lower R_G value has a probability of being correct at a significance level of 0.005, a result in accordance with the prior assumption.

Table 1. Fractional co-ordinates for non-hydrogen atoms (× 10^4) and for hydrogen atoms (× 10^3)

	x	*y*	*z*
C(1)	6 815(8)	2 697(5)	3 017(2)
C(2)	7 375(8)	3 894(5)	3 395(2)
C(3)	7 107(10)	3 577(5)	4 065(2)
C(4)	8 632(8)	2 583(5)	4 265(2)
C(5)	8 377(7)	1 211(4)	4 217(2)
C(6)	9 888(6)	121(4)	4 262(2)
C(7)	9 996(6)	−759(4)	3 687(2)
C(8)	10 619(6)	−27(5)	3 106(2)
C(9)	10 044(6)	1 448(4)	2 927(2)
C(10)	7 908(6)	1 629(4)	2 820(2)
C(11)	11 603(7)	−1 803(4)	3 734(2)
C(12)	13 299(7)	−1 152(5)	3 458(2)
C(13)	11 611(8)	−3 063(5)	3 974(2)
C(14)	6 910(7)	641(5)	2 430(2)
C(15)	10 524(12)	3 274(6)	4 423(3)
O(1)	12 741(4)	−33(3)	3 140(1)
O(2)	14 968(5)	−1 492(4)	3 486(2)
O(3)	9 533(5)	−781(3)	4 761(1)
O(4)	7 641(5)	−291(4)	2 150(2)
O(W)	6 814(6)	−2 677(5)	4 488(2)
H(11)	529	275	292
H(21)	887	413	334
H(22)	667	472	333
H(31)	567	304	412
H(32)	704	449	433
H(51)	667	83	417
H(61)	1 125	66	434
H(71)	867	−113	354
H(81)	1 030	−75	273
H(91)	1 073	163	247
H(92)	1 056	217	325
H(131)	1 049	−340	428
H(132)	1 284	−362	402
H(141)	542	83	236
H(151)	1 093	261	480
H(152)	1 043	433	454
H(153)	1 160	315	407
HO(3)	833	−139	458
HW(1)	630	−274	417
HW(2)	622	−332	468

Table 2. Bond lengths (Å), with estimated standard deviations in parentheses

C(1)-C(2)	1.483(7)	C(7)-C(11)	1.507(6)
C(1)-C(10)	1.352(6)	C(11)-C(12)	1.474(6)
C(2)-C(3)	1.548(7)	C(11)-C(13)	1.324(6)
C(3)-C(4)	1.497(8)	C(12)-O(1)	1.347(6)
C(4)-C(5)	1.335(6)	C(12)-O(2)	1.209(6)
C(4)-C(15)	1.518(9)	C(8)-O(1)	1.481(5)
C(5)-C(6)	1.487(6)	C(8)-C(9)	1.526(6)
C(6)-C(7)	1.546(5)	C(9)-C(10)	1.517(6)
C(6)-O(3)	1.438(5)	C(10)-C(14)	1.468(6)
C(7)-C(8)	1.546(6)	C(14)-O(4)	1.206(6)

The computations were performed on a Nova minicomputer using original and locally modified Syntex XTL programs, except for the calculations concerned with the assignment of absolute configuration, which were carried out using the SHELX program system.[7]

Table 3. Valency angles (°), with estimated standard deviations in parentheses

C(10)-C(1)-C(2)	128.9(4)	C(7)-C(11)-C(13)	129.7(4)
C(1)-C(2)-C(3)	111.9(4)	C(13)-C(11)-C(12)	123.8(4)
C(2)-C(3)-C(4)	109.4(4)	C(11)-C(12)-O(1)	109.3(4)
C(3)-C(4)-C(5)	120.7(5)	C(11)-C(12)-O(2)	129.4(4)
C(3)-C(4)-C(15)	114.1(5)	O(2)-C(12)-O(1)	121.3(4)
C(5)-C(4)-C(15)	124.5(5)	C(12)-O(1)-C(8)	108.6(3)
C(4)-C(5)-C(6)	126.5(4)	O(1)-C(8)-C(7)	103.6(3)
C(5)-C(6)-C(7)	111.2(3)	O(1)-C(8)-C(9)	106.3(3)
C(5)-C(6)-O(3)	110.8(3)	C(7)-C(8)-C(9)	124.8(4)
O(3)-C(6)-C(7)	109.3(3)	C(8)-C(9)-C(10)	113.9(3)
C(6)-C(7)-C(8)	118.1(3)	C(9)-C(10)-C(1)	126.0(4)
C(6)-C(7)-C(11)	110.0(3)	C(9)-C(10)C-(14)	119.0(4)
C(8)-C(7)-C(11)	98.8(3)	C(14)-C(10)-C(1)	114.8(4)
C(7)-C(11)-C(12)	106.5(4)	C(10)-C(14)-O(4)	126.2(4)

Table 4. The ten-membered ring torsion angles (°) for schkuhriolid (I) (present work), melampodin (II),[9] and enhydrin (III) [10]

	(I)	(II)	(III)
C(10)-C(1)-C(2)-C(3)	−90	−56	−97
C(1)-C(2)-C(3)-C(4)	73	14 *	75
C(2)-C(3)-C(4)-C(5)	−87	−54	−92
C(3)-C(4)-C(5)-C(6)	165	155	147 *
C(4)-C(5)-C(6)-C(7)	−121	−101	−119
C(5)-C(6)-C(7)-C(8)	65	76	95
C(6)-C(7)-C(8)-C(9)	−38	−71	−63
C(7)-C(8)-C(9)-C(10)	−65	−44	−56
C(8)-C(9)-C(10)-C(1)	136	125	132
C(9)-C(10)-C(1)-C(2)	−3	4	13

* Torsion angles associated with bonds in the epoxide groups.

Results and Discussion

Lists of structure factors and anisotropic thermal parameters have been deposited as Supplementary Publication No. SUP 23396 (25 pp.).* The positional parameters for all atoms are given in Table 1. The molecule is depicted in Figure 1. Bond lengths and angles are listed in Tables 2 and 3, respectively.

The stereochemistry of the schkuhriolid molecule has been established as having *cis*-fusion of the lactone ring, a result in accordance with the predictions based on Samek's lactone rule.[1] The complete stereochemistry of the molecule is as shown in (I).† All drawings are presented with respect to a right handed set of crystal axes and show the absolute configuration.

The conformation of the ten-membered ring in schkuhriolid is closely related to that found in crystal structures of other melampolides, *e.g.* melampodin (II)[9] and enhydrin (III).[10] The torsion angles for these ten-membered rings are listed in Table 4, and the results show that the cyclodecadiene ring in (I) differs from the conformations found in melampodin and enhydrin only by the distortions at the ring fusion and around these bonds which are part of the epoxide system in both melampodin and enhydrin. This indicates that melampolides have an inherent tendency to adopt a particular conformation independent on orientation and stereochemistry of the lactone ring. This conformation can be described as a distorted chair-boat with an *anti*-orientation for the substituents at C(4) and C(10).

It has been established that the conformations of the various types of germacranolides depend mainly on the *cis*- or *trans*-nature of the 1(10) and 4(5) double bonds.[11] The

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* For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc. Perkin Trans. 2*, 1981, Index issue.

† Drawn according to the convention of Rogers *et al.*[8]

Table 5. The lactone ring torsion angles (°) and the asymmetry parameters for schkuhriolid (I) (present work) and the corresponding values for melampodin (II)[9]

Torsion angles

(I)	
C(11)–C(7)–C(8)–O(1)	−35.3
C(7)–C(8)–O(1)–C(12)	29.2
C(8)–O(1)–C(12)–C(11)	−9.5
O(1)–C(12)–C(11)–C(7)	−14.6
C(12)–C(11)–C(7)–C(8)	30.4

(II)	
C(11)–C(7)–C(6)–O(1)	−35.0
C(7)–C(6)–O(1)–C(12)	28.1
C(6)–O(1)–C(12)–C(11)	−8.6
O(1)–C(12)–C(11)–C(7)	−15.3
C(12)–C(11)–C(7)–C(6)	30.5

Asymmetry parameters

(I)	(I)
$\Delta C_2^{7,8} = 3.7$	$\Delta C_2^{6.7} = 5.0$
$\Delta C_s^{7} = 10.9$	$\Delta C_s^{7} = 9.6$
$\Delta C_s^{8} = 15.4$	$\Delta C_s^{6} = 16.2$

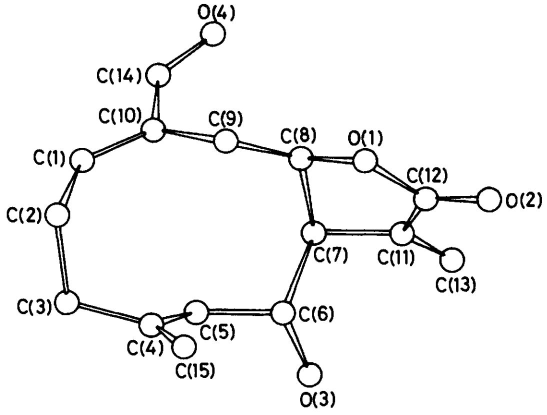

Figure 1. View of the β-face of the molecule and atom numbering scheme

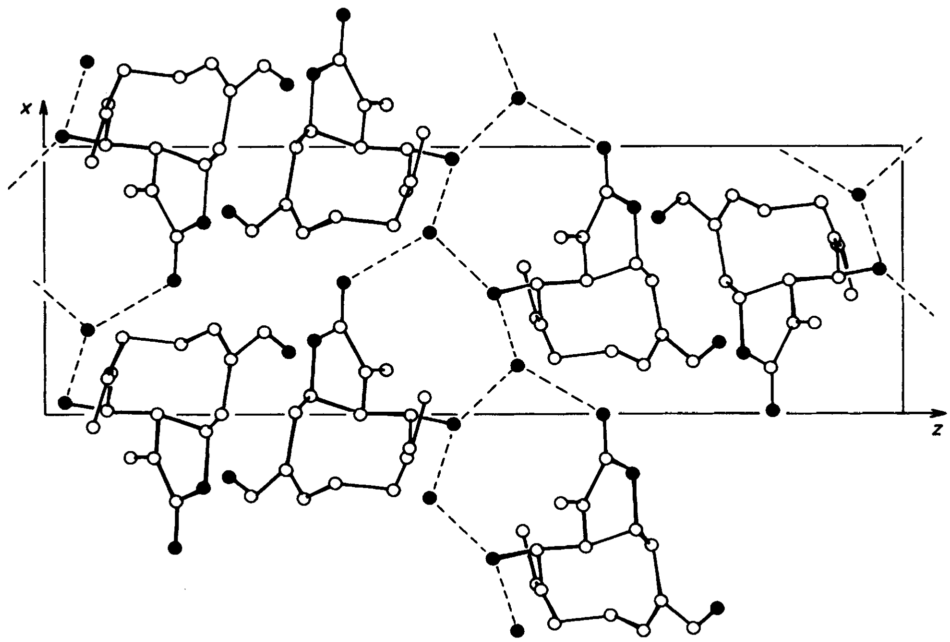

Figure 2. Crystal structure viewed in projection along the *b* axis showing the hydrogen bonding scheme

preference for one conformation observed in the melampolides is in line with these findings. It should be mentioned, however, that the ten-membered ring conformation representative of melampolides does not correspond to the minimum energy form of the *cis,trans* isomer of the cyclodeca-1,5-diene obtained from the force-field calculations[12] which in turn closely resembles the conformation of heliangolides, *trans*-1(10)-*cis*-4-germacranolides.[13,14]

cis-Fusion of the lactone ring in schkuhriolid causes some minor conformational changes within the macrocycle; because of the *cis*-ring junction the cyclodecadiene torsion angle C(6)–C(7)–C(8)–C(9) (−38°) is smaller than in other melampolides and have nearly identical value with the lactone torsion angle C(11)–C(7)–C(8)–O(1) (−35°). Also the internal angle at C(8) (125°) reflects a deformation which may be due to the strain caused by the *cis*-fusion of the γ-lactone.

The conformation of the γ-lactone ring can best be described as a half-chair with a pseudo-diad passing through C(12) and the midpoint of the C(7)–C(8) bond. The conformations of the γ-lactone rings in melampodin and schkuhriolid might be expected to differ owing to the different fusion with the homocyclic ring, but actually the puckering and the type of deformation of the two rings is very similar. This can be seen from comparison of the torsion angles and asymmetry parameters,[15] given in Table 5.

In view of the observed conformational similarity between melampodin and schkuhriolid (Tables 4 and 5) it is likely that relactonization of a 7,8-*cis*-lactonized melampolide to a 6,7-*trans*-lactonized compound proceeds without much conformational changes within the molecule.

The crystal structure is stabilized by an extensive hydrogen-bonding network (Figure 2). The water molecule acts both as a

Table 6. Distances (Å) and angles (°) in the hydrogen-bonding system

D-H···A	Acceptor position	D-H	H···A	D···A	D-H···A
O(3)-HO(3)···O(W)	x, y, z	1.09	1.64	2.697(5)	160
O(W)-HW(1)···O(2)	$x - 1, y, z$	0.80	2.17	2.833(5)	142
O(W)-HW(2)···O(3)	$x - \frac{1}{2}, -\frac{1}{2} - y, -z$	0.86	1.92	2.753(5)	161

donor in two hydrogen bonds with a translation-equivalent (x direction) lactone carbonyl oxygen and a screw-axis-related (x direction) hydroxy oxygen, and as an acceptor in a hydrogen bond with a hydroxy oxygen of the reference molecule. In this way the hydroxy oxygen also acts both as a donor and as an acceptor in hydrogen bonds with two symmetry related (screw axis) water molecules. The packing thus appears to be governed by hydrogen bonds running in a helical form along x direction. Table 6 gives relevant hydrogen-bond distances and angles.

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