cavity (1·7 Å out of the mean plane of ether O atoms), because it is not anchored in the crown-ether cavity by hydrogen bonds to three ether O atoms as in the structures of strong acids.

$H_3O^+$ has a pyramidal geometry with HOH valence angles [117 (7), 111 (8) and 113 (8)°] close to tetrahedral ones. The distances of O(1)—H(1)···O(2), O(1)—H(2)···O(10) and O(1)—H(3)···O(9) bonds are 1·0 (2), 1·51 (7), 0·97 (9), 1·84 (9) and 0·78 (9), 2·16 (6) Å respectively. The angles at the H atoms are 143 (8), 166 (7) and 137 (6)° respectively. They are not so widely spread as those reported by Behr, Dumas & Moras (1982).

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# The Structures of Two Sesquiterpene Lactones

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**Abstract.** Helenalin, 6α,8β-dihydroxy-4-oxoambrosa-2,11(13)-dien-12-oic acid 12,8-lactone, (1), $C_{15}H_{18}O_4$, $M_r = 262{\cdot}31$, monoclinic, $P2_1$, $a = 7{\cdot}469\ (2)$, $b = 8{\cdot}568\ (2)$, $c = 10{\cdot}094\ (1)$ Å, $\beta = 90{\cdot}30\ (1)°$, $V = 645{\cdot}4\ (2)$ Å$^3$, $Z = 2$, $D_x = 1{\cdot}348$ g cm$^{-3}$, $\lambda(\text{Mo } K\alpha) = 0{\cdot}71072$ Å, $\mu = 0{\cdot}91$ cm$^{-1}$, $F(000) = 280$, $T = 298$ K, $R = 0{\cdot}0351$ for 1446 observed reflections. Mexicanin I, 6β,8α-dihydroxy-4-oxoambrosa-2,11(13)-dien-12-oic acid 12,8-lactone, (2), $C_{15}H_{18}O_4$, $M_r = 262{\cdot}31$, triclinic, $P1$, $a = 6{\cdot}549\ (1)$, $b = 6{\cdot}649\ (1)$, $c = 8{\cdot}063\ (1)$ Å, $\alpha = 77{\cdot}91\ (1)$, $\beta = 81{\cdot}59\ (1)$, $\gamma = 70{\cdot}67\ (1)°$, $V = 322{\cdot}9\ (1)$ Å$^3$, $Z = 1$, $D_x = 1{\cdot}349$ g cm$^{-3}$, $\lambda(\text{Mo } K\alpha)$, $\mu = 0{\cdot}91$ cm$^{-1}$, $F(000) = 140$, $T = 298$ K, $R = 0{\cdot}0410$ for 1431 reflections. Compounds (1) and (2) are diastereoisomers which are reported to differ significantly in melting points and solubilities in $CHCl_3$. Both compounds reported herein form hydrogen-bonded chains involving the hydroxyl group and the lactone carbonyl of an adjacent molecule; however, there is a reported polymorphic form of (1) with intermolecular H bonds between the hydroxyl and the ketone O atom of the five-membered ring. In (2) the molecules exhibit a flattened conformation and the H-bonded chain is almost linear while (1) adopts a more bent conformation and the H-bonded chains zigzag through the solid. Differences in solvent interactions are estimated to be small and the melting point and solubility differences must be related to the different polymeric forms of (1)

**Introduction.** While investigating *Hymenoxy scaposa* var. *villosa* (Gao, Wang, Mabry & Bierner, 1990), it was noted that the C(6) and C(8) diastereoisomers helenalin (1) and mexicanin I (2) differed significantly in melting points and in their solubilities in $CDCl_3$. Compound (1) (Herz, Romo de Vivar, Romo & Viswanathan, 1963) has a reported melting point of 439–440 K and is readily soluble in $CDCl_3$ while compound (2) (Dominguez & Romo, 1963) melts at 530–533 K and is only slightly soluble in $CDCl_3$. X-ray analysis of samples supplied by Professor Mabry gave calculated densities of 1·348 and 1·349 g cm$^{-3}$ for (1) and (2), respectively. The X-ray structure of (1) has been reported previously (Fronczek, Ober & Fischer, 1987); however, unit-cell dimensions and a calculated density of 1·271 g cm$^{-3}$ indicated a polymorphic relationship. The structure of (2) and the new polymorph of (1) are described in this paper.

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0108-2701/90/081524-05$03.00

Table 1. *Crystal, data collection and refinement data*

| | (1) | (2) |
|---|---|---|
| Crystal data | | |
| Crystal size (mm) | 0·38 × 0·25 × 0·18 | 0·33 × 0·23 × 0·13 |
| Color | Colorless | Colorless |
| Lattice parameters | | |
| $2\theta$ range (°) | 22·04–28·82 | 22·33–29·01 |
| Systematic extinctions | $0k0$ $k = 2n + 1$ | None |
| Data collection | | |
| $2\theta$ range (°) | 3–55 | 3–55 |
| *hkl* | 0,9;0,11; − 13,13 | 0,8; − 8,8; − 10,10 |
| Monitored reflections | $\bar{2}20,13\bar{2}$ | $\bar{1}13,120$ |
| Total reflections | 1708 | 1612 |
| Independent reflections | 1585 | 1612 |
| $R_{\text{int}}$ | 0·008 | 0·006 |
| Reflections with $I > 3\sigma(I)$ | 1446 | 1431 |
| Transmission factors | 0·883–0·855 | 0·960–0·910 |
| Refinement | | |
| $R$ ($R$ all data) | 0·035 (0·0391) | 0·0410 (0·0484) |
| $wR$ ($wR$ all data) | 0·0428 (0·0435) | 0·0505 (0·0522) |
| Number of parameters | 244 | 244 |
| $S$ | 1·114 | 1·013 |
| $(\Delta/\sigma)_{\text{max}}$ | 0·008 | 0·011 |
| Largest peaks in final difference maps (e Å$^{-3}$) | 0·14, − 0·14 | 0·20, − 0·22 |
| $g$ (weighting scheme) | 0·00076 | 0·00145 |

Table 2. *Atomic coordinates* (× 10$^4$) *and equivalent isotropic thermal parameters* (Å$^2$ × 10$^3$) *for* (1)

$U_{\text{eq}}$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

| | $x$ | $y$ | $z$ | $U_{\text{eq}}$ |
|---|---|---|---|---|
| C(1) | 2470 (3) | 3699 (3) | 1306 (2) | 32 (1) |
| C(2) | 3363 (3) | 3570 (3) | −0 (2) | 44 (1) |
| C(3) | 5003 (4) | 4154 (4) | 38 (3) | 48 (1) |
| C(4) | 5496 (3) | 4690 (3) | 1372 (2) | 37 (1) |
| O(4) | 6832 (2) | 5392 (2) | 1740 (2) | 49 (1) |
| C(5) | 4044 (2) | 4100 (3) | 2287 (2) | 30 (1) |
| C(6) | 3539 (3) | 5402 (3) | 3239 (2) | 28 (1) |
| O(6) | 3143 (2) | 6731 (2) | 2436 (2) | 39 (1) |
| C(7) | 1988 (3) | 5044 (2) | 4140 (2) | 29 (1) |
| C(8) | 312 (2) | 4154 (3) | 3612 (2) | 33 (1) |
| O(8) | − 656 (2) | 3931 (2) | 4862 (1) | 41 (1) |
| C(9) | 557 (3) | 2517 (3) | 3077 (2) | 37 (1) |
| C(10) | 1236 (3) | 2350 (3) | 1664 (2) | 37 (1) |
| C(11) | 2345 (3) | 4224 (3) | 5442 (2) | 33 (1) |
| C(12) | 542 (3) | 3781 (3) | 5877 (2) | 38 (1) |
| O(12) | 94 (2) | 3357 (3) | 6958 (2) | 53 (1) |
| C(13) | 4904 (3) | 2690 (3) | 2989 (2) | 38 (1) |
| C(14) | − 324 (4) | 2256 (4) | 644 (3) | 63 (1) |
| C(15) | 3817 (3) | 3898 (3) | 6139 (2) | 45 (1) |

Table 3. *Atomic coordinates* (× 10$^4$) *and equivalent isotropic thermal parmeters* (Å$^2$ × 10$^3$) *for* (2)

$U_{\text{eq}}$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

| | $x$ | $y$ | $z$ | $U_{\text{eq}}$ |
|---|---|---|---|---|
| C(1) | 4418 (4) | 7041 (4) | 13708 (3) | 30 (1) |
| C(2) | 3269 (5) | 8426 (5) | 15050 (4) | 41 (1) |
| C(3) | 2148 (5) | 10411 (5) | 14403 (4) | 42 (1) |
| C(4) | 2334 (5) | 10673 (4) | 12545 (4) | 32 (1) |
| O(4) | 1852 (4) | 12350 (3) | 11531 (3) | 40 (1) |
| C(5) | 3290 (4) | 8410 (4) | 12083 (3) | 25 (1) |
| C(6) | 4838 (5) | 8429 (4) | 10424 (3) | 29 (1) |
| O(6) | 3767 (4) | 8732 (4) | 8954 (3) | 47 (1) |
| C(7) | 6720 (4) | 6323 (4) | 10461 (3) | 28 (1) |
| C(8) | 6078 (4) | 4251 (4) | 11022 (4) | 31 (1) |
| O(8) | 7652 (4) | 2657 (3) | 10076 (3) | 38 (1) |
| C(9) | 6207 (5) | 3317 (4) | 12889 (4) | 36 (1) |
| C(10) | 4542 (5) | 4642 (5) | 14125 (3) | 34 (1) |
| C(11) | 8099 (5) | 5963 (5) | 8815 (4) | 36 (1) |
| C(12) | 8782 (5) | 3605 (5) | 8815 (4) | 38 (1) |
| O(12) | 10132 (4) | 2570 (4) | 7870 (3) | 53 (1) |
| C(13) | 1260 (4) | 7813 (4) | 11885 (4) | 32 (1) |
| C(14) | 5141 (7) | 3602 (6) | 15938 (4) | 54 (1) |
| C(15) | 8716 (7) | 7307 (6) | 7597 (5) | 61 (1) |

**Experimental.** Compounds (1) and (2) were isolated from *Hymenoxy scaposa* var. *villosa* (Gao, Wang, Mabry & Bierner, 1990) and a few crystals of each were supplied by Professor Mabry. Crystallization records are not available. All X-ray data were collected on a Nicolet $R3m/\mu$ update of a $P2_1$ diffractometer using the $\omega$-scan mode, variable scan rate (4 to 28·2° min$^{-1}$) and graphite-monochromated Mo $K\alpha$ radiation. Lattice parameters were obtained from a least-squares refinement of 25 reflections. The data were corrected for Lorentz–polarization contributions and a $\psi$-scan-based empirical absorption correction was applied. The structures were solved by direct methods and refined by a block-cascade least-squares technique. H atoms were located in difference maps and were refined with isotropic thermal parameters. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with $w = [\sigma^2(F_o) + gF_o^2]^{-1}$. Crystal, data collection and refinement parameters are given in Table 1. All computer programs were supplied by Nicolet for Desktop 30 Microeclipse and Nova 4/*C* configuration (Nicolet Instrument Corporation, 1986). Atomic scattering factors and anomalous-dispersion corrections from *International Tables for X-ray Crystallography* (1974). Tables 2 and 3 contain atomic positional parameters for compounds (1) and (2) while Tables 4 and 5 list interatomic distances and selected valence and torsion angles.* Molecular mechanics calculations (Serena Software, 1988) were made on a Compaq 286 using program default parameters.

**Discussion.** Figs. 1 and 2 are of the isolated molecules (1) and (2) while Figs. 3 and 4 are packing diagrams for (1) and (2), respectively. The changes in configuration at C(6) and C(8) lead to different conformations for the isomers with the individual ring systems of (2) more planar and the C(13) methyl and the O(6) hydroxy group lying on the same face. Isomer (1) has a bent conformation with C(13) and O(6) pointing from opposite faces (see Figs. 1 and 2 and torsion angles in Table 5). Although it might appear that the hydroxyl in (2) should be more

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* Lists of structure factors, anisotropic thermal parameters, polymorphic comparisons and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52817 (27 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 4. *Bond distances* (Å) *for compounds* (1), (2) *and a polymorph of* (1)

| | (1) | (1)* | (2) |
|---|---|---|---|
| C(1)—C(2) | 1·505 (3) | 1·505 (3) | 1·518 (4) |
| C(1)—C(5) | 1·546 (3) | 1·545 (3) | 1·558 (3) |
| C(1)—C(10) | 1·530 (3) | 1·530 (3) | 1·537 (4) |
| C(2)—C(3) | 1·323 (4) | 1·338 (3) | 1·318 (4) |
| C(3)—C(4) | 1·456 (3) | 1·457 (4) | 1·463 (4) |
| C(4)—O(4) | 1·211 (3) | 1·226 (3) | 1·213 (3) |
| C(4)—C(5) | 1·537 (3) | 1·529 (3) | 1·529 (4) |
| C(5)—C(6) | 1·529 (3) | 1·517 (3) | 1·557 (3) |
| C(5)—C(13) | 1·529 (3) | 1·538 (3) | 1·546 (5) |
| C(6)—O(6) | 1·422 (3) | 1·429 (3) | 1·409 (4) |
| C(6)—C(7) | 1·532 (3) | 1·542 (3) | 1·527 (3) |
| C(7)—C(8) | 1·543 (3) | 1·547 (4) | 1·532 (4) |
| C(7)—C(11) | 1·505 (3) | 1·500 (3) | 1·508 (4) |
| C(8)—O(8) | 1·491 (2) | 1·474 (3) | 1·467 (3) |
| C(8)—C(9) | 1·516 (3) | 1·520 (4) | 1·506 (4) |
| O(8)—C(12) | 1·339 (2) | 1·355 (3) | 1·341 (4) |
| C(9)—C(10) | 1·540 (3) | 1·514 (4) | 1·540 (4) |
| C(10)—C(14) | 1·525 (3) | 1·520 (5) | 1·528 (4) |
| C(11)—C(12) | 1·482 (3) | 1·483 (3) | 1·481 (4) |
| C(11)—C(15) | 1·312 (3) | 1·311 (4) | 1·297 (5) |
| C(12)—O(12) | 1·210 (3) | 1·197 (4) | 1·206 (4) |

* Polymorph (Fronczek, Ober & Fischer, 1987).

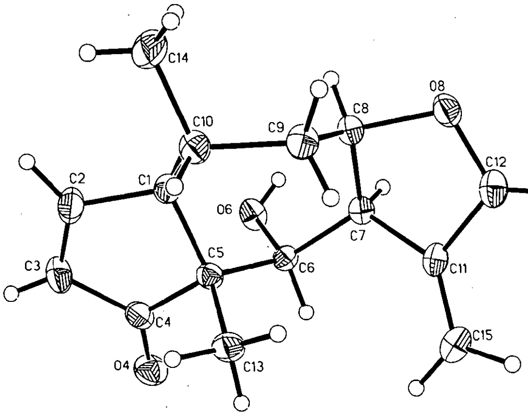

Fig. 1. Compound (1) with thermal ellipsoids at the 35% probability level and H atoms represented by spheres of arbitrary size.

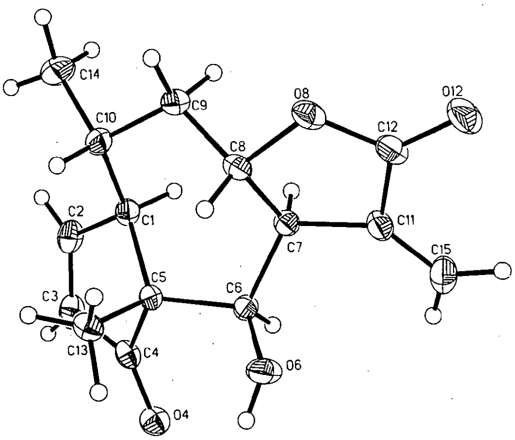

Fig. 2. Compound (2) with thermal ellipsoids at the 35% probability level and H atoms represented by spheres of arbitrary size.

Table 5. *Bond angles* (°) *and torsion angles* (°) *for* (1), (2) *and a polymorph of* (1)

| | (1) | (1)* | (2) |
|---|---|---|---|
| C(2)—C(1)—C(5) | 103·2 (2) | 103·4 (2) | 102·1 (2) |
| C(2)—C(1)—C(10) | 116·3 (2) | 117·6 (2) | 117·1 (2) |
| C(5)—C(1)—C(10) | 117·8 (2) | 117·8 (3) | 117·0 (3) |
| C(1)—C(2)—C(3) | 112·9 (2) | 113·2 (3) | 113·3 (2) |
| C(2)—C(3)—C(4) | 110·2 (2) | 108·9 (3) | 109·7 (3) |
| C(3)—C(4)—O(4) | 127·9 (2) | 127·8 (2) | 127·6 (3) |
| C(3)—C(4)—C(5) | 107·1 (2) | 108·7 (3) | 107·2 (2) |
| O(4)—C(4)—C(5) | 124·9 (2) | 123·4 (2) | 125·2 (3) |
| C(1)—C(5)—C(4) | 103·0 (1) | 102·9 (3) | 102·7 (2) |
| C(1)—C(5)—C(6) | 111·4 (2) | 110·6 (3) | 114·6 (2) |
| C(4)—C(5)—C(6) | 109·6 (2) | 108·6 (3) | 111·1 (2) |
| C(1)—C(5)—C(13) | 114·6 (2) | 116·0 (3) | 111·3 (2) |
| C(4)—C(5)—C(13) | 104·2 (2) | 104·3 (3) | 103·3 (2) |
| C(6)—C(5)—C(13) | 113·2 (2) | 113·4 (4) | 112·8 (2) |
| C(5)—C(6)—O(6) | 106·1 (1) | 105·2 (2) | 112·6 (2) |
| C(5)—C(6)—C(7) | 116·0 (2) | 116·6 (3) | 111·8 (2) |
| O(6)—C(6)—C(7) | 110·7 (2) | 108·6 (2) | 107·4 (2) |
| C(6)—C(7)—C(8) | 121·1 (2) | 122·2 (3) | 115·2 (2) |
| C(6)—C(7)—C(11) | 120·0 (2) | 118·5 (3) | 117·0 (2) |
| C(8)—C(7)—C(11) | 100·6 (2) | 101·7 (3) | 103·2 (2) |
| C(7)—C(8)—O(8) | 100·7 (1) | 101·9 (3) | 105·3 (2) |
| C(7)—C(8)—C(9) | 118·2 (2) | 120·1 (3) | 114·8 (3) |
| O(8)—C(8)—C(9) | 104·6 (2) | 105·6 (3) | 107·5 (2) |
| C(8)—O(8)—C(12) | 109·2 (1) | 110·4 (3) | 111·3 (2) |
| C(8)—C(9)—C(10) | 117·7 (2) | 116·9 (3) | 116·4 (2) |
| C(1)—C(10)—C(9) | 111·9 (2) | 111·7 (3) | 111·6 (2) |
| C(1)—C(10)—C(14) | 109·4 (2) | 110·1 (3) | 112·6 (3) |
| C(9)—C(10)—C(14) | 111·1 (2) | 111·1 (3) | 108·1 (2) |
| C(7)—C(11)—C(12) | 104·3 (2) | 106·1 (3) | 106·2 (2) |
| C(7)—C(11)—C(15) | 133·1 (2) | 131·6 (3) | 131·0 (3) |
| C(12)—C(11)—C(15) | 122·6 (2) | 122·1 (3) | 122·8 (3) |
| O(8)—C(12)—C(11) | 109·7 (2) | 108·6 (2) | 110·0 (2) |
| O(8)—C(12)—O(12) | 121·2 (2) | 122·2 (2) | 121·4 (3) |
| C(11)—C(12)—O(12) | 129·2 (2) | 129·1 (2) | 128·6 (3) |
| | | | |
| C(1)—C(2)—C(3)—C(4) | 2·7 (3) | 3·6 (5) | 0·8 (5) |
| C(2)—C(3)—C(4)—C(5) | 10·1 (3) | 7·7 (5) | 13·6 (4) |
| C(3)—C(4)—C(5)—C(1) | −17·9 (2) | −15·1 (5) | −21·3 (3) |
| C(4)—C(5)—C(1)—C(2) | 18·5 (2) | 16·1 (4) | 20·5 (3) |
| C(5)—C(1)—C(2)—C(3) | −14·1 (3) | −13·1 (4) | −14·2 (4) |
| C(1)—C(5)—C(6)—C(7) | 61·6 (2) | 61·6 (5) | 30·7 (4) |
| C(15)—C(6)—C(7)—C(8) | −40·3 (2) | −33·6 (5) | 47·5 (3) |
| C(6)—C(7)—C(8)—C(9) | 60·2 (3) | 51·4 (5) | −94·3 (3) |
| C(7)—C(8)—C(9)—C(10) | −79·2 (2) | −77·8 (5) | 68·4 (4) |
| C(8)—C(9)—C(10)—C(1) | 30·9 (2) | 35·5 (5) | −47·8 (4) |
| C(9)—C(10)—C(1)—C(5) | 50·9 (2) | 47·4 (5) | 72·6 (3) |
| C(10)—C(1)—C(5)—C(6) | −94·6 (2) | −96·4 (4) | −89·7 (3) |
| C(7)—C(8)—O(8)—C(12) | −32·2 (2) | −29·3 (4) | −13·2 (3) |
| C(8)—O(8)—C(12)—C(11) | 12·0 (3) | 13·2 (4) | 1·3 (4) |
| O(8)—C(12)—C(11)—C(7) | 14·0 (2) | 9·3 (4) | 11·4 (4) |
| C(12)—C(11)—C(7)—C(8) | −32·4 (2) | −26·1 (5) | −18·4 (3) |
| C(11)—C(7)—C(8)—O(8) | 38·3 (2) | 32·6 (4) | 19·0 (3) |
| C(1)—C(5)—C(6)—O(6) | −61·7 (2) | −58·9 (5) | 151·7 (2) |
| C(8)—C(7)—C(6)—O(6) | 80·6 (2) | 85·3 (5) | −76·5 (3) |
| C(5)—C(6)—C(7)—C(11) | 86·3 (2) | 94·2 (5) | 169·0 (3) |
| O(8)—C(8)—C(9)—C(10) | 169·9 (2) | 168·0 (5) | −174·9 (3) |
| O(6)—C(6)—C(7)—C(11) | −152·8 (2) | −146·9 (5) | 45·0 (4) |
| C(6)—C(7)—C(8)—O(8) | 173·3 (2) | 167·5 (5) | 147·7 (2) |

* Polymorph (Fronczek, Ober & Fischer, 1987).

hindered than in (1), both molecules form hydrogen bonds between O(6) and O(12) of an adjacent molecule (see Figs. 3 and 4). In compound (1) the hydrogen bond is characterized by O(6)—H(60) = 0·75 (3), H(60)···O(12) $(-x,\ 0{\cdot}5-y,\ 1-z)$ = 2·12 (3), O(6)···O(12) = 2·876 (3) Å with an angle at the H atom of 176 (2)°, while the hydrogen bond in (2) is characterized by O(6)—H(60) = 0·82 (3), H(60)···O(12) $(1+x,\ y-1,\ z)$ = 2·14 (3), O(6)···O(12) = 2·932 (3) Å with an angle at the H atom of 164 (2)°. The O(6)···O(12) distance in (1) is slightly shorter than in (2) and the angle at the H atom is more nearly linear which would imply a stronger H bond, a higher melting point and a lower solubility which is contrary to observation. The H bonding in (2) leads to an almost linear chain through the crystal while that in (1) forms a sharp zigzag chain through the solid.

The isolated molecules in the polymorph of (1) (Fronczek, Ober & Fischer, 1987) exhibit the same molecular conformation with equivalent distances and angles to those reported herein (see Tables 4 and 5); however, intermolecular hydrogen bonding occurs between the hydroxyl group and the keto O(4) atom rather than to the carbonyl O atom of the lactone. The structure is more loosely packed with a density of 1·271 g cm$^{-3}$ as compared with 1·348 g cm$^{-3}$ and should exhibit a lower melting point and dissolve more rapidly in $CDCl_3$. There are no structural reasons for (1) reported in the current work to differ significantly in melting point or solubility from that of (2). Our one unused crystal of (1) melted at 441–442 K; however, the crystal used for the X-ray determination appeared to undergo a phase transition at 433 K, partially melted at 438 K and sharply melted at 444 K. The two polymorphs cannot be distinguished microscopically; however, the majority of the material probably has the structure reported by Fronczek, Ober & Fischer (1987). The best looking crystal may often represent a minority of the sample.

Molecular mechanics calculations (Serena Software) indicate that the strain-energy difference between the isolated diastereoisomers is only 5·69 kJ mol$^{-1}$. If van der Waals radii are assigned to each atom, the surface area of the molecules can be calculated. The exposed surface area can be apportioned into polar and nonpolar regions. Compound (1) is calculated to have nonpolar and polar surface areas of 185 and 61 Å$^2$ with a total surface of 245 Å$^2$ while (2) is estimated to have nonpolar and polar surface areas of 198 and 64 Å$^2$ for a total of 261 Å$^2$. If the difference in solubility is to be attributed to differences in solvation energies, (1) must have a significantly larger interaction with chloroform. Compound (1) is calculated to have the smaller nonpolar and polar surface areas which is contrary to the observed solubilities. The differences in solubilities must be related to the solid-state structures and not the solvent interactions.

There are several bond lengths and bond angles in (1) and (2) which differ by more than 3$\sigma$. These differences are related primarily to the different stereochemistry at C(6) and C(8) and the subsequent differences in conformation. These differences are reproduced by molecular mechanics calculations (Serena Software). The current structures may be compared with helenalin oxide (McPhail & Onan, 1975) and bromohelenalin and mexicanin-E monobromide (Ul-Hague & Caughlan, 1967).

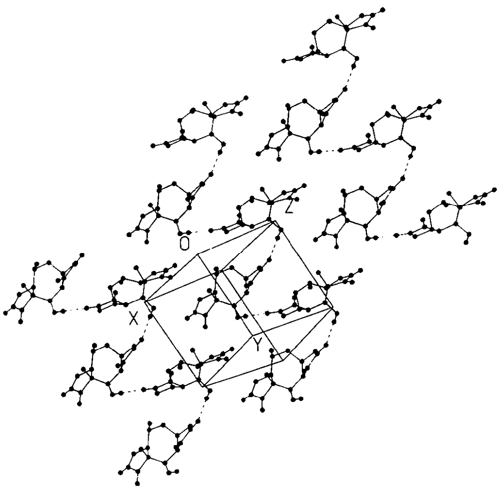

Fig. 3. Packing diagram of compound (1) with hydrogen bonds represented by dashed lines.

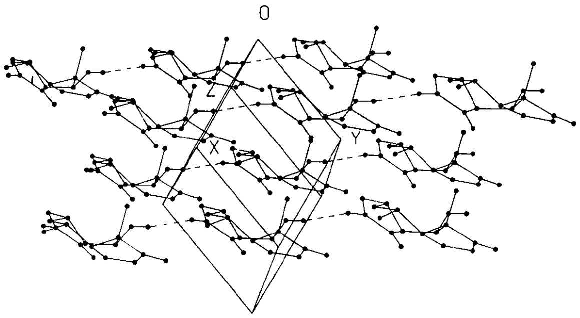

Fig. 4. Packing diagram of compound (2) with hydrogen bonds represented by dashed lines.

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# Neutron Structure of the Immunosuppressant Cyclosporin A

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**Abstract.** Cyclosporin A, $C_{62}H_{111}N_{11}O_{12}.H_2O$, $M_r = 1220{\cdot}6$, orthorhombic, $P2_12_12_1$, $a = 12{\cdot}674\,(1)$, $b = 15{\cdot}684\,(2)$, $c = 36{\cdot}304\,(30)$ Å, $V = 7216{\cdot}5$ Å$^3$, $Z = 4$, $D_x = 1{\cdot}107$ g cm$^{-3}$, $\lambda$(neutron) = 1·184 Å, $F(000) = 67{\cdot}39$, room temperature, final $R = 0{\cdot}074$ for 4121 observed reflections. There is one cyclosporin A molecule and one water molecule per asymmetric unit.

**Introduction.** Cyclosporin A is a neutral, cyclic undecapeptide of fungal origin. Seven of the eleven amino acids are *N*-methylated (Fig. 1). Cyclosporin A is an immunosuppressant drug with wide clinical application primarily for solid organ and bone marrow transplantation. The ability of this drug to inhibit the activation of subpopulations of immunocompetent cells is a fundamental innovation in immunology. In order to investigate details of the molecular interactions involved in the pharmacological function of cyclosporin A, a detailed knowledge of the structure is required. The structure of cyclosporin A and eighteen derivatives have been determined by X-ray diffraction (Petcher, Weber & Ruegger, 1976; Loosli, Kessler, Oschkinat, Weber, Petcher & Widmer, 1985; Weber, 1986; Walkinshaw & Boelsterli, 1988), and various features investigated by two-dimensional NMR techniques (Loosli *et al.*, 1985). The molecular backbone of cyclosporin A forms a rigid structure with four hydrogen bonds holding the backbone in its folded configuration. Three of the four hydrogen bonds are involved in the formation of a short segment of $\beta$-sheet. The high-resolution X-ray studies indicate flexibility in a number of the side chains. Studies investigating the relation between the chemical structure and the pharmacological function have concentrated attention on the region around amino-acid residues MeBmt-1 and Abu-2 (Wenger, 1981; Loosli *et al.*, 1985; Wenger, 1985; Rich, Dhaon, Dunlap & Miller, 1986). However, the structural differences that lead to the dramatic changes in observed pharmacological function have yet to be defined. Because of the fundamental importance of this drug, a neutron diffraction diffraction study was undertaken for two main reasons. The first reason was to locate all hydrogen atoms particularly those involved in the four intramolecular hydrogen bonds. The second reason was to locate solvent molecules alluded to in the X-ray studies.

**Experimental.** Cyclosporin A is an extremely hydrophobic molecule (water solubility < 0·04 mg ml$^{-1}$). It has been crystallized in different space groups ($P2_1$, $P4_1$, $P2_12_12_1$) depending primarily on the organic solvent(s) used (Petcher *et al.*, 1976; Loosli *et al.*, 1985; Weber, 1986). From the X-ray studies, only the $P2_12_12_1$ crystal form diffracted to 2·0 Å, and was therefore chosen for this study. A large crystal (approximate dimensions 2 × 2 × 5 mm) was crystallized from a mixture of oil, ethanol and a non-ionic surfactant (unpublished data), and supplied for this study by Dr Hans-Peter Weber (Sandoz, Switzerland). It is designated cyclosporin A mod III to distinguish it from the other crystal forms.

The neutron diffraction data were collected on the H3A Protein Crystallography Diffractometer located at the High Flux Beam Reactor, Brookhaven

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