# The Structure of Teuflin, a Diterpenoid from *Teucrium flavum*; *X*-Ray Crystallographic and Spectroscopic Determination

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Teuflin, isolated from *Teucrium flavum*, has been shown by *X*-ray analysis to be a C-10 epimer of teucvidin.

THE diterpenoids of *Teucrium* species (Labiatae) have been the subject of a number of investigations.[1-5] Previously we have described some clerodanes from *T. fruticans*.[6] In continuation of our work [7] on *T. flavum* (yellow germander) we have isolated a further nor-clerodane diterpenoid, teuflin, $C_{19}H_{20}O_5$ (1). The i.r. spectrum showed that this contained a γ-lactone, an $\alpha\beta$-unsaturated-γ-lactone, and a β-substituted furan ring. ^{1}H (220 MHz) N.m.r. spin decoupling studies, based on signals at δ 1.23, 5.38, and 5.75 established the presence of the following fragments:

$$\ce{>C.CH_2.CH(O.C=O).C=} \text{ and } \ce{>C.CH.CH_2.CHMe}$$
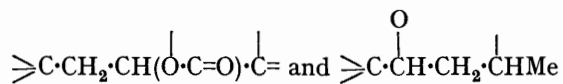
Whilst the salient features of the ^{1}H and ^{13}C n.m.r. spectra (see Table 1) were reminiscent of teuflidin (2)

TABLE 1

N.m.r. signals of teuflin (p.p.m. from Me$_4$Si; in CDCl$_3$)

Carbon no.	^{13}C Signals	^{1}H Signals
1	18.7	*c*
2	23.7 *a*	*c*
3	23.3 *a*	*c*
4	123.8	
5	166.5	
6	76.7	5.75
7	31.9	2.10 and 1.85
8	35.8	2.25
9	51.0	
10	43.1	2.75
11	42.8	2.68 and 2.40
12	71.6	5.38
13	124.3	
14	107.9	6.43
15	144.3	7.50
16	139.9	7.47
17	17.6	1.23
18	176.0 *b*	
20	173.7 *b*	

a,b These assignments may be interchanged. *c* Signal not assigned. Coupling constants (Hz): $J_{6,7}$ 5 and 13; $J_{8,17}$ 7; $J_{11,11'}$ 14; $J_{11,12}$ 7.5 and 10.

which had previously been obtained [7] from the same species, they were sufficiently different to suggest some skeletal difference. In particular the signal at δ 5.75 assigned to the 6-H appeared at much lower field ($\Delta\delta$ 0.72 p.p.m.) whilst there was a 4.5 p.p.m. shift in the ^{13}C signal assigned to C-10. Furthermore the compound differed from both teucvin (3) and teucvidin (4) which occur in *T. viscidum* [3] and with which it is isomeric. These differences could be explained if teuflin was a C-10 epimer of teucvidin. This would have the effect of bringing the 6-H close to the oxygen atom of the C-20

carbonyl group. However it is extremely rare for C-10 epimers of diterpenoids to co-occur and hence the molecule was subjected to *X*-ray analysis.

(1)
(3) (6β–H)
(2) R = OH
(4) R = H
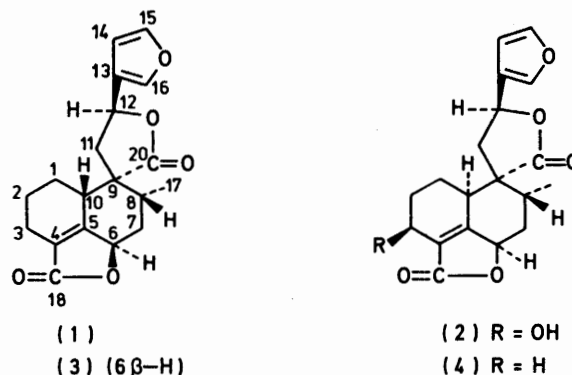
The structure and stereochemistry of teuflin are shown in Figure 1. Teuflin crystallized with a molecule of methanol of crystallization, which initially posed some problems in the structure determination. The methanol was attached through a hydrogen bond O(11)–H(111) · · · O(1) of length 2.08 Å. There were no particularly short intermolecular contacts as seen in the packing diagram (Figure 2). The majority of the bond distances and angles were normal. Ring A deviates from the preferred half-chair conformation of a cyclohexene ring whilst ring B is a distorted chair. The C(4)–C(5) double bond brings the 18 ⟶ 6 lactone ring into the plane of ring A, the angles between the lactone ring and rings A and B being 10.0 and 38.1° respectively.

The sign of the c.d. curve associated with the $\alpha\beta$-unsaturated lactone has been used [3,8] as evidence for the absolute stereochemistry of this series. Teuflin showed a strong negative Cotton effect at 218 nm suggesting that it possesses the same absolute stereochemistry at C-6 as teucvidin. In teuflin, there is a *trans–anti–trans* relationship between the 8-H, C-20, and 10-H which suggests that it is formed by rearrangement of an *ent*-labdane. Compounds of the teucvidin (10α-H) series may be formed from teuflin by a base-catalysed epimerization involving the $\alpha\beta$-unsaturated lactone in which the driving force is the relief of the 20-C=O:6-H interaction.

EXPERIMENTAL

General experimental details have been described previously.[9]

Isolation of Teuflin.—*Teucrium flavum* (collected in the Botanic Gardens, Palermo) was extracted as described previously. *Teuflin* (120 mg) was obtained from 1 kg of
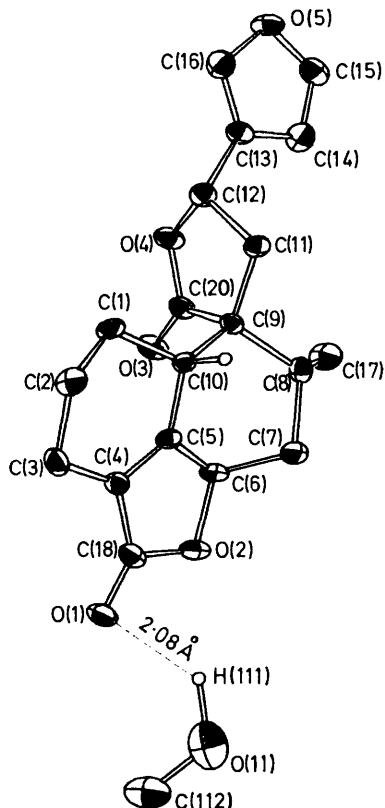

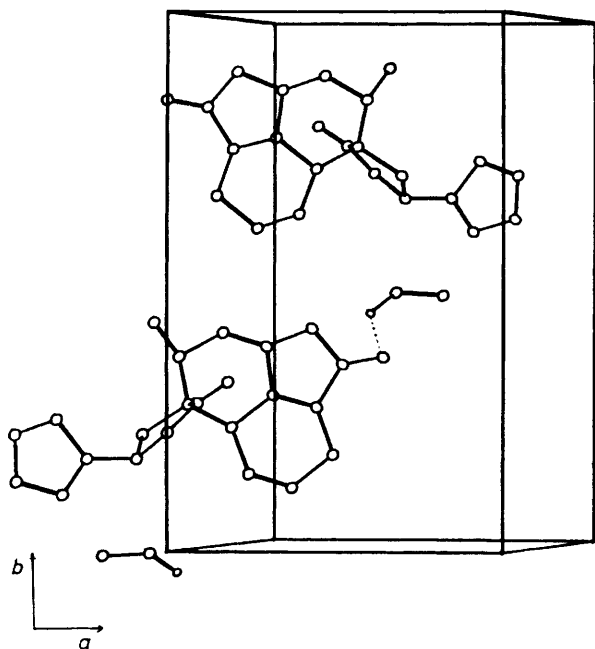FIGURE 1   Crystal structure and stereochemistry of teuflin (1)

FIGURE 2   Packing diagram of the molecular structure of teuflin (1)

dry plant. It crystallized as needles, m.p. 153 °C, from ethyl acetate–light petroleum, $[\alpha]_D$ +12° (c 0.2) (Found: C, 69.3; H, 5.95. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1%); $\nu_{max.}$ 1 760, 1 725, 1 690, and 875 cm⁻¹; c.d. (in dioxan) 280 (0), 246 (46 464), 235 (0), 218 −(134 110), and 200 (0) nm; m/e 328 (10), 283 (15), 233 (8), 95 (100), and 81 (30).

Crystal Data.—A sample of teuflin was crystallized from methanol for *X*-ray analysis. $C_{19}H_{20}O_5 \cdot CH_3OH$, $M = 360.4$, monoclinic, $a = 9.169$ (2), $b = 15.312$ (4), $c = 6.944$ (1) Å, $\beta = 113.67°$, $U = 892.89$ Å³, $Z = 2$, $D_c = 1.34$ g cm⁻³, $F(000)$ 384, Mo-K_α radiation, μ(Mo-K_α) 1.06

TABLE 2

Fractional atomic co-ordinates ($\times 10^4$) with estimated standard deviations in parentheses in the units of the last significant figure

(a) Non-hydrogen atoms

	x	y	z
C(1)	0 251(8)	1 334(4)	3 238(10)
C(2)	1 130(9)	1 049(5)	1 852(11)
C(3)	2 369(7)	1 681(6)	1 719(10)
C(4)	1 916(7)	2 596(5)	1 932(9)
C(5)	0 716(7)	2 828(4)	2 398(8)
C(6)	0 586(8)	3 768(5)	2 604(10)
C(7)	−1 126(8)	4 024(5)	1 462(12)
C(8)	−2 093(7)	3 571(5)	2 594(10)
C(9)	−1 483(7)	2 664(4)	3 617(9)
C(10)	−0 520(7)	2 211(4)	2 511(8)
C(11)	−2 883(7)	2 091(4)	3 575(9)
C(12)	−2 328(7)	1 660(5)	5 741(9)
C(13)	−3 545(7)	1 668(5)	6 676(9)
C(14)	−4 417(9)	2 410(5)	6 852(11)
C(15)	−5 361(9)	2 130(7)	7 792(12)
C(16)	−3 988(9)	1 002(6)	7 557(12)
C(17)	−2 360(10)	4 222(5)	4 073(14)
C(18)	2 610(7)	3 414(5)	1 563(10)
C(20)	−0 435(8)	2 711(5)	5 947(10)
O(1)	3 704(5)	3 550(4)	1 051(7)
O(2)	1 721(5)	4 107(3)	1 744(7)
O(3)	0 772(5)	3 110(4)	6 825(7)
O(4)	−0 954(5)	2 171(4)	7 078(6)
O(5)	−5 154(6)	1 258(4)	8 215(8)

(b) Proposed co-ordinates ($\times 10^4$) of the hydrogen atoms

	x	y	x	Bonded to
H(1)	1 031	1 207	4 872	C(1)
H(2)	−0 147	0 770	3 714	C(1)
H(3)	0 085	0 926	0 381	C(2)
H(4)	1 804	0 434	2 412	C(2)
H(5)	3 467	1 564	2 582	C(3)
H(6)	2 776	1 707	0 401	C(3)
H(7)	0 844	4 010	4 060	C(6)
H(8)	−1 084	4 689	1 273	C(7)
H(9)	−1 517	3 875	−0 046	C(7)
H(10)	−3 152	3 504	1 457	C(8)
H(11)	−1 487	2 105	1 018	C(10)
H(12)	−3 887	2 576	3 105	C(11)
H(13)	−3 065	1 624	2 526	C(11)
H(14)	−1 980	0 906	5 912	C(12)
H(15)	−4 832	2 966	6 125	C(14)
H(16)	−6 511	2 263	7 792	C(15)
H(17)	−4 116	0 152	7 506	C(16)
H(18)	−1 389	4 552	4 989	C(17)
H(19)	−2 698	4 796	3 612	C(17)
H(20)	−2 740	3 904	4 535	C(17)

(c) Co-ordinates ($\times 10^4$) of the atoms of the solvent molecule

	x	y	z	
O(11)	−3 005(10)	−0 210(6)	2 597(12)	
C(112)	−4 560(16)	−0 266(7)	2 339(18)	
H(111)	−2 537	−0 615	1 462	O(11)
H(112)	−5 217	0 022	0 564	C(112)
H(113)	−4 664	−0 963	2 915	C(112)
H(114)	−4 850	0 223	2 775	C(112)

cm^{-1}, space group $P2_1$ (no. 4) [10] from the systematic absences $0k0$ for k odd.

Crystallographic Measurement.—All data collection was made using a crystal of dimensions *ca.* 0.15 × 0.05 × 0.10 mm. Accurate cell dimensions were determined from a least-squares treatment of setting angles for 12 reflections measured on a Hilger and Watts Y290 four-circle diffractometer. Intensity data were collected by an ω/2θ step scan for the quadrant $hkl \longrightarrow h\bar{k}l$ in two consecutive shells θ = 2 − 22° and 22 − 25° with Mo-K_α radiation (graphite monochromator). Each reflection was measured in 50 steps of 2.0 s each and background counts of 50 s were made at the end of each scan. The intensities of three standard reflections, monitored every 100 reflections, showed no significant changes. The intensities were corrected for Lorentz and polarization effects. Of the 1 461 reflections measured, 1 242 having $I > 2\sigma (I)$ were used in the structure analysis.

Structure Determination and Refinement.—Normalized structure factor magnitudes, $|E|$, were calculated for all reflection data. Phases were derived by multiple start tangent formula procedures [11] using the 285 reflections with $|E| > 1.20$. *E*-maps were then computed with $|E| > 1.50$. The best *E*-map gave a partial structure with rough atom positions for 6 non-hydrogen atoms which were taken as carbon. The remaining non-hydrogen atoms were located in three cycles of tangent refinement of the partial structure.[12] The atom positions with anisotropic temperature factors were refined by large-block-matrix least-square procedures with unit weights. Temperature factors and bond lengths were used to differentiate between oxygen and carbon atoms. Two successive difference Fourier maps revealed the unexpected presence of a molecule of solvent of crystallization (methanol) and gave the positions of all the hydrogen atoms. Each hydrogen atom was given the iostropic temperature factor of the carbon or oxygen atom to which it is bonded. A few more cycles of least-squares refinement of all non-hydrogen atoms with anisotropic

temperature factors and a weighting scheme defined as ω = $1.04/[\sigma^2(F) + 0.001(F)^2]$ gave convergence at a residual $R_F = 0.07$ and $R_{\omega F} = 0.066$, when the shift to e.s.d. ratio for any non-hydrogen atom parameter was less than 0.11 and a final difference Fourier map was everywhere less than 0.27 eÅ^{-3}. Initial data processing and conversion of data into a format suitable for the SHELX programme of G. M. Sheldrick were done with local programmes. Scattering factors for C, O, H atoms were taken from ref. 13. Final atom co-ordinates are listed in Table 2. The final structure factors together with the torsion angles and thermal parameters are listed in Supplementary Publication No. SUP 22507 (11 pp.).*

* For details see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1978, Index issue.

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