

The Structure and Absolute Configuration of $\Delta 9(12)$ -Capnellene- $3\beta,8\beta,10\alpha$ -triol

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The sesquiterpene $\Delta 9(12)$ -capnellene- $3\beta,8\beta,10\alpha$ -triol, $C_{15}H_{24}O_3$, is extracted from the soft coral *Capnella imbricata*. It crystallizes in space group $P2_1$ with $a = 11.935$ (1), $b = 14.768$ (3), $c = 8.314$ (5) Å, $\gamma = 95.720$ (8)°. The asymmetric unit consists of two terpenes and one water molecule. The structure was determined from X-ray data by direct methods, which included tangent recycling in space group $P1$, and was refined to $R = 0.05$. Twenty enantiomer-sensitive Bijvoet differences were measured with Cu $K\alpha$ and Cr $K\alpha$ radiation to determine the absolute configuration. The structure solution and hydrogen-bond system are discussed.

Introduction

The X-ray diffraction analysis of the title compound (CAP) (Fig. 1) was undertaken because chemical and spectroscopic investigations (Tursch *et al.*, 1974) had not succeeded in elucidating the structure.

Experimental

The compound crystallized from ether as transparent plates. The density was measured by flotation in CCl_4 and cyclohexane. The space group and cell constants were found and all subsequent data collected with a Philips PW 1100 four-circle diffractometer equipped with a graphite monochromator. The cell constants were refined by least squares from the positions of 11 high-angle reflexions with an average 2θ value of 146° (Cu $K\alpha_1$).

Crystallographic data

$2(C_{15}H_{24}O_3) \cdot H_2O$, $M_r = 522.7$, m.p. $116^\circ C$; monoclinic space group $P2_1$, $a = 11.935$ (1), $b = 14.768$ (3),

$c = 8.314$ (5) Å, $\gamma = 95.720$ (8)°, $Z = 2$, $V = 1452$ Å³, $D_m = 1.19$, $D_x = 1.195$ g cm⁻³. A uniform crystal of diameter 0.5 mm was mounted in an arbitrary orientation on a glass fibre. Data with $\theta < 83^\circ$ were collected for half the reciprocal sphere ($l \geq 0$) with Cu $K\alpha$ radiation and the ω - 2θ scan. Equivalent reflexions were averaged to yield 3276 independent intensities to which Lp factors were applied.

Structure solution and refinement

The convergence method (Germain, Main & Woolfson, 1970) was applied with all phase relationships generated from 252 E values. E maps of the rather consistent solutions each showed only one large peak, nearly always corresponding to one of the large peaks in the Harker section. In one case the large peak [corresponding to the largest vector (0.26, 0.80, $\frac{1}{2}$), later shown to have multiplicity ten] and four weak neighbouring peaks formed a five-membered ring with acceptable geometry. Expansion of the partial structure

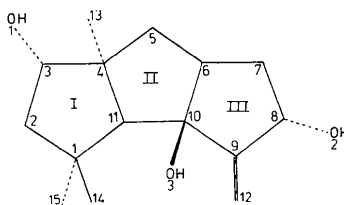


Fig. 1. Absolute configuration of CAP.

by the tangent recycling procedure (Karle, 1968) in space group $P1$ yielded an E map which displayed four more atoms, related to the input fragment by a twofold screw axis along \mathbf{c}^* . A correct choice of origin could thus be made. Further tangent recycling revealed two independent terpenes (A and B) and one water molecule.

The atoms C(11), C(4), C(5), C(6) and C(13) are related to C(7), C(8), C(9), C(10) and O(2) respectively in molecule A by an approximate twofold axis which intersects the centre of the C(6)–C(10) bond and is parallel to \mathbf{c}^* . This ten-atom fragment and its symmetry-related part are related by the above-mentioned tenfold non-Harker vector. A Fourier synthesis or a vector superposition in $P1$ based on one of

the rings must contain the tenfold vector as a pseudo-translation element. This gives rise to some of the strong 'false' peaks in the E map in $P1$.

Least-squares refinement with anisotropic C and O atoms followed by a difference Fourier synthesis clearly revealed 47 of the H atoms, but not H(O2) B , H(O3) B or H2(W). A final refinement, which included the 47 isotropic H atoms, reduced R to 0.05 for all reflexions given unit weights.* The average shift/e.s.d. ratio was 0.09. Atomic scattering factors were taken

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32200 (5 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 1. Positional ($\times 10^4$) and thermal ($\times 10^4$) parameters of the C and O atoms

$$T = \exp[-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl)].$$

Molecule A	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(1)	1618 (2)	-107 (2)	6944 (4)	65 (2)	41 (1)	115 (5)	-3 (3)	-32 (6)	-31 (5)
C(2)	1508 (3)	-1096 (2)	7615 (5)	110 (3)	37 (1)	155 (6)	-21 (3)	9 (8)	-43 (5)
C(3)	2648 (3)	-1193 (2)	8301 (5)	111 (3)	28 (1)	139 (6)	24 (3)	40 (7)	6 (5)
C(4)	2925 (2)	-316 (2)	9278 (4)	64 (2)	32 (1)	111 (5)	30 (3)	15 (5)	18 (4)
C(5)	4184 (3)	78 (2)	9209 (5)	62 (2)	49 (2)	187 (7)	46 (3)	-7 (7)	41 (6)
C(6)	4275 (2)	821 (2)	7948 (4)	46 (2)	36 (1)	123 (5)	17 (2)	26 (5)	-12 (4)
C(7)	5143 (3)	1623 (2)	8326 (5)	55 (2)	61 (2)	209 (8)	1 (3)	37 (7)	-35 (7)
C(8)	4550 (2)	2239 (2)	9457 (4)	60 (2)	42 (1)	130 (5)	-9 (3)	0 (6)	-14 (5)
C(9)	3321 (2)	1874 (2)	9457 (4)	55 (2)	26 (1)	116 (5)	14 (2)	1 (5)	-11 (4)
C(10)	3131 (2)	1203 (2)	8066 (4)	48 (2)	29 (1)	86 (4)	21 (2)	3 (4)	1 (4)
C(11)	2251 (2)	390 (2)	8383 (4)	47 (2)	28 (1)	90 (4)	12 (2)	-4 (4)	-8 (4)
C(12)	2555 (3)	2112 (2)	0491 (5)	76 (2)	47 (2)	181 (7)	13 (3)	47 (7)	-74 (6)
C(13)	2552 (3)	-453 (2)	11031 (4)	106 (3)	48 (2)	107 (5)	46 (4)	11 (7)	19 (5)
C(14)	2260 (3)	-89 (2)	5332 (4)	120 (3)	50 (2)	91 (5)	6 (4)	-18 (7)	-36 (5)
C(15)	472 (3)	242 (3)	6694 (5)	68 (2)	90 (3)	188 (8)	21 (4)	-97 (8)	-44 (8)
O(1)	2682 (2)	-2016 (1)	9259 (4)	163 (3)	30 (1)	189 (5)	31 (3)	46 (7)	24 (4)
O(2)	5016 (2)	2245 (2)	11030 (4)	84 (2)	125 (2)	152 (5)	-58 (4)	-35 (6)	-41 (6)
O(3)	2971 (2)	1722 (1)	6626 (3)	81 (2)	35 (1)	104 (3)	24 (2)	16 (4)	24 (3)
Molecule B									
C(1)	3283 (2)	5061 (2)	7116 (4)	69 (2)	35 (1)	122 (5)	19 (3)	-21 (6)	-3 (4)
C(2)	2942 (3)	4028 (2)	7105 (5)	83 (2)	34 (1)	154 (6)	21 (3)	-6 (7)	24 (5)
C(3)	1761 (2)	3949 (2)	6440 (4)	66 (2)	28 (1)	162 (6)	10 (2)	41 (6)	6 (4)
C(4)	1843 (2)	4584 (2)	4960 (4)	54 (2)	28 (1)	128 (5)	3 (2)	3 (5)	-17 (4)
C(5)	788 (2)	5104 (2)	4707 (4)	51 (2)	30 (1)	171 (6)	-4 (2)	-35 (6)	-7 (4)
C(6)	1037 (2)	6046 (2)	5482 (4)	40 (2)	34 (1)	123 (5)	5 (2)	3 (5)	-14 (4)
C(7)	508 (2)	6819 (2)	4583 (4)	51 (2)	37 (1)	155 (5)	18 (2)	-20 (6)	-24 (5)
C(8)	1405 (2)	7203 (2)	3343 (4)	61 (2)	32 (1)	153 (6)	8 (2)	-38 (6)	7 (4)
C(9)	2366 (2)	6618 (2)	3546 (4)	52 (2)	27 (1)	111 (4)	-4 (2)	-18 (5)	-13 (4)
C(10)	2315 (2)	6242 (2)	5230 (4)	40 (2)	28 (1)	102 (4)	4 (2)	5 (4)	-22 (4)
C(11)	2817 (2)	5333 (2)	5434 (4)	41 (2)	30 (1)	101 (4)	10 (2)	5 (4)	-8 (4)
C(12)	3102 (3)	6486 (2)	2400 (4)	86 (3)	46 (2)	121 (5)	5 (3)	26 (6)	0 (5)
C(13)	2113 (3)	4062 (2)	3440 (5)	101 (3)	41 (1)	145 (6)	-5 (3)	15 (7)	-44 (5)
C(14)	2757 (4)	5471 (2)	8600 (4)	134 (4)	52 (2)	104 (5)	43 (4)	-28 (8)	-4 (5)
C(15)	4565 (3)	5280 (2)	7169 (6)	76 (3)	58 (2)	224 (8)	16 (3)	-107 (8)	14 (7)
O(1)	1383 (2)	3014 (1)	6101 (4)	79 (2)	26 (1)	259 (5)	4 (2)	34 (5)	13 (4)
O(2)	936 (2)	7175 (2)	1747 (3)	84 (2)	68 (1)	169 (5)	7 (3)	-76 (5)	76 (4)
O(3)	2779 (1)	6970 (1)	6255 (3)	57 (1)	31 (1)	136 (3)	5 (2)	-21 (4)	-41 (3)
O(W)	5301 (2)	7748 (1)	-732 (4)	246 (2)	105 (2)	248 (5)	33 (3)	-259 (5)	-65 (5)

from *International Tables for X-ray Crystallography* (1968). Final parameters are given in Table 1 for the C and O atoms and in Table 2 for the H atoms.

Table 2. *Hydrogen positions ($\times 10^3$) and thermal parameters (\AA^2)*

The average e.s.d.'s are 0.003 for x , 0.002 for y and 0.005 for z .

Molecule A	x	y	z	B
H1(C2)	117	-147	662	7
H2(C2)	87	-113	858	3
H(C3)	328	-108	727	8
H1(C5)	458	-46	880	5
H2(C5)	419	29	1053	12
H(C6)	425	56	667	4
H1(C7)	563	201	740	10
H2(C7)	587	136	885	5
H(C8)	469	299	912	7
H(C11)	164	55	929	4
H1(C12)	273	253	1147	4
H2(C12)	160	185	1065	5
H1(C13)	162	-90	1114	3
H2(C13)	240	17	1150	5
H3(C13)	297	-98	1123	8
H1(C14)	315	-32	573	5
H2(C14)	228	57	493	8
H3(C14)	174	-46	459	3
H1(C15)	-12	-19	590	14
H2(C15)	56	90	619	7
H3(C15)	-6	10	782	5
H(O1)	179	-215	897	4
H(O2)	464	289	1106	11
H(O3)	241	194	716	6
Molecule B	x	y	z	B
H1(C2)	287	374	834	4
H2(C2)	348	370	628	3
H(C3)	120	426	730	3
H1(C5)	21	474	518	3
H2(C5)	68	522	350	4
H(C6)	94	607	671	2
H1(C7)	38	736	533	3
H2(C7)	-23	660	405	4
H(C8)	168	788	374	4
H(C11)	341	532	468	3
H1(C12)	368	611	266	3
H2(C12)	323	680	136	6
H1(C13)	299	370	367	5
H2(C13)	230	443	269	3
H3(C13)	156	355	328	3
H1(C14)	193	540	827	3
H2(C14)	315	624	872	11
H3(C14)	305	516	933	4
H1(C15)	466	511	814	2
H2(C15)	480	595	727	3
H3(C15)	493	483	610	4
H(O1)	57	299	631	10
H1(W)	588	808	0	15

Absolute configuration

The absolute configuration was determined by the method of Bijvoet, Peerdeman & van Bommel (1951) with Cu $K\alpha$ and Cr $K\alpha$ radiation. The same prismatic, uniform, crystal of centrosymmetric shape, not larger than 0.35 mm on an edge, used earlier for the determination of the cell constants was used for the measurements given in Table 3. The dispersion parameters were taken from Cromer & Liberman (1970). The strong reflexions 222, 111 and 011 have relatively large Bijvoet differences but low Bijvoet ratios $2(I_h - I_{\bar{h}})/(I_h + I_{\bar{h}})$, although these are measurable with Cr $K\alpha$ radiation.

Table 3. *Comparison of calculated (X_c) with observed (X_o) Bijvoet ratios ($\times 10^2$)*

Standard deviations based on counting statistics are in parentheses.
 $X_c(\text{Cr } K\alpha) = 2.3 X_c(\text{Cu } K\alpha)$.

h	k	l	$X_c(\text{Cu})$	$X_o(\text{Cu})$	$X_o(\text{Cr})$
6	-15	1	5.0	7.0 (20)	
3	-5	1	1.2	1.0 (7)	
2	-2	1	-1.2	-2.4 (4)	-3.2 (8)
3	0	1	1.2	1.9 (3)	4.0 (4)
6	0	1	0.8	-0.2 (4)	3.1 (6)
0	1	1	0.5	0.3 (1)	0.9 (3)
1	1	1	0.4		0.8 (2)
1	2	1	0.5	1.5 (3)	2.3 (3)
2	4	1	-0.9	-0.7 (3)	-1.4 (4)
3	4	1	1.0	1.6 (6)	2.8 (6)
4	-6	2	-1.0		-2.0 (9)
1	-5	2	-1.0	-1.4 (5)	-1.9 (6)
4	-4	2	1.2	0.4 (4)	3.7 (3)
0	2	2	-1.3	-1.4 (3)	-3.1 (6)
1	2	2	1.1	2.8 (4)	1.6 (7)
0	5	2	0.9	1.1 (3)	2.4 (5)
2	-2	3	-1.5	-1.3 (5)	-3.0 (7)
4	1	3	-0.9	-0.1 (4)	0.0 (7)
0	3	3	1.2	0.3 (6)	
2	2	2	0.3		1.2 (4)

Discussion

The three missing hydroxyl H atoms were tentatively located, and their interactions with neighbouring atoms investigated, by rotation of their possible positions about their C—O bonds, with H—O taken as 1.1 Å and H—O—C as 108°. Their positions were, however, not refined. H(O2)B and H(O3)B were identified in a difference map with a rather low positive electron density at (0.11, 0.65, 0.12) and (0.54, 0.51, 0.71) respectively. A possible position for H2(W) at (0.45, 0.74, -0.04), which is favourable for a H2(W)—O(1)A hydrogen bond, was assigned after rotation about the O(W)—H1(W) bond with H—O—H 105°. Any devia-

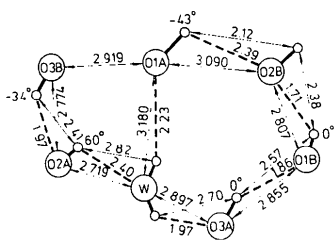


Fig. 2. The hydrogen bond scheme with H—O—C—O' torsion angles.

tion from this position will decrease H2(W)—H1(C5)A (2.35) or H2(W)—H1(C7)A (2.35 Å).

The molecules are connected by seven hydrogen bonds, as illustrated in Fig. 2, which shows the difficulties in hydrogen-bond formation as a result of repulsive forces between H atoms. Thus H(O2B) is prevented both by H(O1A) and H(O1B) from forming a hydrogen bond. However, H(O1A) and H(O2B) can be placed simultaneously in hydrogen-bonding positions to O(3)B and O(1)A respectively, without repulsive interactions with other neighbouring atoms. These two alternative positions for H(O1A) and H(O2B) were, indeed, weakly indicated in the difference map. H2(W) prevents H(O2A) from ap-

Table 4. *Interatomic distances (Å) for molecules A and B*

The average e.s.d. is 0.004 Å.

	A	B		A	B
C(1)—C(2)	1.558	1.540	C(5)—C(6)	1.514	1.535
C(1)—C(11)	1.560	1.572	C(6)—C(7)	1.527	1.550
C(1)—C(14)	1.543	1.536	C(6)—C(10)	1.533	1.539
C(1)—C(15)	1.524	1.533	C(7)—C(8)	1.531	1.553
C(2)—C(3)	1.496	1.509	C(8)—C(9)	1.511	1.513
C(3)—C(4)	1.536	1.545	C(8)—O(2)	1.421	1.439
C(3)—O(1)	1.457	1.436	C(9)—C(10)	1.525	1.505
C(4)—C(5)	1.558	1.553	C(9)—C(12)	1.328	1.325
C(4)—C(11)	1.569	1.572	C(10)—C(11)	1.537	1.534
C(4)—C(13)	1.532	1.532	C(10)—O(3)	1.444	1.439

proaching W, which in its turn prevents H(O3B) from getting closer to O(2)A. The torsion angles H—O—C—O' (with H...O' as a possible hydrogen bond) show how many degrees the H atoms must be rotated about their O—C axes to get closest to O'.

A stereoscopic view of CAP is given in Fig. 3. Bond distances (Table 4), bond angles (Table 5) and torsion angles (Fig. 4) show similar geometries for molecules A and B. The largest deviations lie in the C—C—O angles

Table 5. *Bond angles (°) for molecules A and B*

The average e.s.d. is 0.25°.

	A	B		A	B
2-1-11	99.2	100.5	5-6-10	102.7	102.2
2-1-14	108.8	108.5	7-6-10	105.1	105.3
2-1-15	111.8	111.6	6-7-8	105.6	105.8
11-1-14	116.2	116.5	7-8-9	106.2	104.6
11-1-15	110.7	110.1	7-8-O(2)	111.4	110.5
14-1-15	109.7	109.4	9-8-O(2)	111.5	113.7
1-2-3	103.5	103.3	8-9-10	107.9	108.0
2-3-4	104.0	104.1	8-9-12	125.1	123.8
2-3-O(1)	112.9	110.3	10-9-12	127.0	128.1
4-3-O(1)	113.1	114.9	6-10-9	102.0	101.5
3-4-5	114.5	113.7	6-10-11	106.7	106.7
3-4-11	103.2	103.0	6-10-O(3)	108.2	111.1
3-4-13	110.9	110.8	9-10-11	115.2	114.9
5-4-11	105.8	105.4	9-10-O(3)	107.7	106.1
5-4-13	109.9	111.0	11-10-O(3)	116.1	115.7
11-4-13	112.2	112.5	1-11-4	107.9	107.4
4-5-6	107.1	107.3	1-11-10	119.8	120.0
5-6-7	114.5	114.1	4-11-10	104.2	105.1

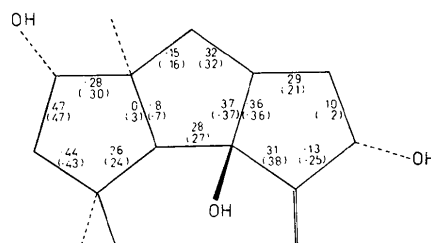


Fig. 4. Torsion angles of the two independent molecules; values for molecule B are in parentheses.

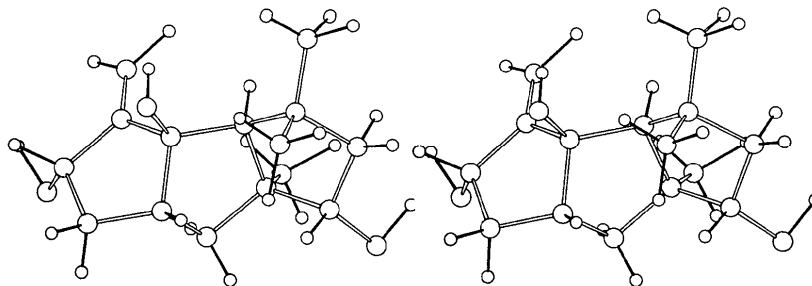


Fig. 3. A stereoscopic view of CAP: molecule A seen along c.

and in the conformation of the third ring (Fig. 1); this probably reflects the differences in hydrogen-bond geometry between the two molecules. The third ring has the twist form in molecule *A* and the envelope form in molecule *B*. Another natural product, hirsutic acid (Comer & Trotter, 1967), contains the same group of three five-membered rings but with the opposite stereochemistry at C(10) and C(11). The H—C and H—O bond lengths are in the range 0.85–1.17 Å.

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The X-ray Crystal Structures of Loxapine {2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[*b,f*][1,4]oxazepine} and Amoxapine {2-Chloro-11-(1-piperazinyl)dibenz[*b,f*][1,4]oxazepine}

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The X-ray crystal structures of the psychoactive agents loxapine {2-chloro-11-(4-methyl-1-piperazinyl)dibenz[*b,f*][1,4]oxazepine} and amoxapine {2-chloro-11-(1-piperazinyl)dibenz[*b,f*][1,4]oxazepine} have been determined. Loxapine, C₁₈H₁₈N₃OCl, is monoclinic, space group *P*2₁/*c*, *a* = 12.953 (3), *b* = 10.908 (4), *c* = 12.584 (4) Å, β = 109.53 (3)°; amoxapine, C₁₇H₁₆N₃OCl, is orthorhombic, space group *Pna*2₁, *a* = 11.765 (4), *b* = 9.743 (3), *c* = 12.990 (2) Å. Both structures were solved by the heavy-atom method and refined by standard least-squares methods to *R* = 0.054 for loxapine and *R* = 0.049 for amoxapine. There are no significant differences between bond lengths and angles in the two structures. The orientation of the piperazine ring with respect to the dibenzoxazepine system is approximately the same in the two molecules. Low-temperature NMR spectra for the two compounds indicate a preferred orientation for the piperazine ring that is consistent with the X-ray results.

Introduction

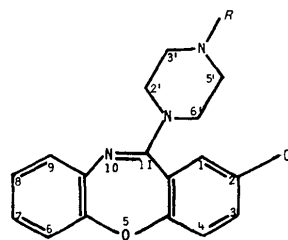
The chemistry and structure–activity relationships of the psychoactive agents loxapine {2-chloro-11-(4-methyl-1-piperazinyl)dibenz[*b,f*][1,4]oxazepine} and amoxapine {2-chloro-11-(1-piperazinyl)dibenz[*b,f*][1,4]oxazepine} have been reviewed by Schmutz (1975).^{*} Loxapine, C₁₈H₁₈N₃OCl (*R* = CH₃), differs structurally from amoxapine, C₁₇H₁₆N₃OCl, only by the presence of a methyl group at the 4 position of the

^{*} This article includes a preliminary note on an independent X-ray analysis of the loxapine structure. The data presented are in agreement with results reported here.

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piperazine ring. Physiologically, however, loxapine acts as a tranquilizing agent (Latimer, 1969) whereas amox-



R = CH₃, Loxapine
R = H, Amoxapine