

Cannabidiol

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Abstract. $C_{21}H_{30}O_2$, $M_r = 314.47$, monoclinic, $P2_1$, $a = 10.617$ (4), $b = 10.649$ (5), $c = 17.266$ (6) Å, $\beta = 95.30$ (4)°, $U = 1943$ Å³, $Z = 4$, $D_x = 1.074$ g cm⁻³, $\mu(\text{Cu } K\alpha) = 4.5$ cm⁻¹, m.p. 66–67°C. There are two independent molecules in the asymmetric unit, differing mainly in the *n*-pentyl side-chain conformation. The side chains exhibit thermal disorder. The structure was refined to $R = 0.068$ for 2270 independent reflexions.

Introduction. Cannabidiol (Fig. 1) is one of the major components of hashish. Its chemical structure and absolute configuration have been determined (Mechoulam & Shvo, 1963; Mechoulam & Gaoni, 1967). It is a potent anti-epileptic in rats (Izquierdo, Orsingher & Berardi, 1973; Carlini, Leite, Tannhauser & Berardi, 1973). The X-ray structure determination was undertaken to investigate possible structural correlations with other anticonvulsant drugs. These, together with potential-energy calculations, will be discussed elsewhere (Falvello, Jones, Kennard, Mechoulam, Meyer & Tamir, 1977).

Cannabidiol crystallized from pentane as well shaped colourless crystals. Intensities were determined on an automated Syntex $P2_1$ four-circle diffractometer with Cu $K\alpha$ radiation and a graphite monochromator, for a crystal $0.6 \times 0.2 \times 0.15$ mm. Cell dimensions were obtained by least squares from 15 strong reflexions. 2986 reflexions were measured in the range $0 < 2\theta < 115^\circ$; averaging equivalent reflexions gave 2279 unique reflexions with $F > 4\sigma(F)$. Systematic absences were $0k0$, k odd, implying space group $P2_1$.

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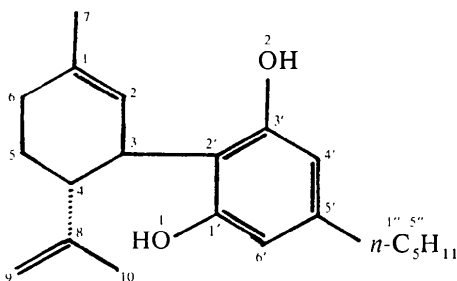


Fig. 1. Cannabidiol, showing the numbering scheme.

The structure was solved with *XCSD*, which incorporates a pseudo-tangent refinement to select the starting set (Roberts, Pettersen, Sheldrick, Isaacs & Kennard, 1973) and the negative quartet test *NQEST* (De Titta, Edmonds, Langs & Hauptman, 1975). The best *E* map established positions for 37 heavy atoms; only 5 small peaks in the top 42 were false. Two atoms of the cyclohexene ring were missing from one molecule; all other missing atoms were the terminal portions of the *n*-pentyl side chains. Figures of merit were *NQEST* -0.208 , R_A (a point-atom *R* factor based on observed peaks) 0.362 , $R\alpha$ (Roberts *et al.*, 1973) 0.142 . The second *E* map (*NQEST* -0.188 , R_A 0.357 , $R\alpha$ 0.124) was almost identical. A difference map based on the *E*-map peaks showed all the missing atoms except two terminal side-chain atoms of one molecule and one of the other. Isotropic least-squares refinement, followed by a difference map, showed the remaining heavy atoms; when these were included, the isotropic *R* for all heavy atoms was 0.13 . Anisotropic

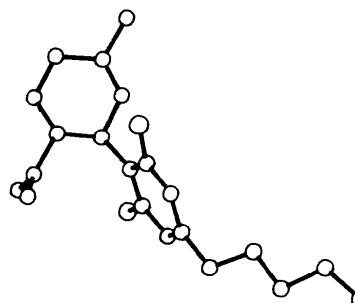
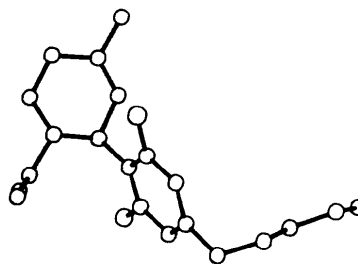


Fig. 2. Perspective views of molecules 1 (top) and 2, omitting H atoms.

Table 1. *Atom coordinates* ($\times 10^4$)

Molecule 1	x	y	z	Molecule 2	x	y	z
C(1)	-943 (6)	2337 (7)	4583 (4)	C(1)	5706 (7)	-785 (8)	328 (4)
C(2)	-439 (5)	2208 (6)	3906 (3)	C(2)	6181 (6)	279 (7)	591 (3)
C(3)	954 (5)	2290 (6)	3797 (3)	C(3)	7062 (5)	450 (6)	1311 (3)
C(4)	1721 (5)	2766 (7)	4556 (3)	C(4)	7053 (6)	-729 (6)	1844 (3)
C(5)	1237 (6)	2124 (8)	5258 (3)	C(5)	7158 (8)	-1876 (8)	1337 (5)
C(6)	-142 (7)	2493 (9)	5330 (3)	C(6)	6045 (8)	-2010 (9)	737 (5)
C(7)	-2362 (6)	2299 (10)	4619 (4)	C(7)	4814 (8)	-859 (10)	-430 (4)
C(8)	3128 (6)	2614 (9)	4533 (4)	C(8)	7993 (6)	-643 (7)	2543 (5)
C(9)	3897 (9)	3622 (12)	4556 (6)	C(9)	7599 (9)	-449 (9)	3265 (5)
C(10)	3651 (8)	1312 (11)	4498 (5)	C(10)	9417 (8)	-770 (13)	2385 (7)
C(1')	1860 (5)	2661 (6)	2508 (3)	C(1')	7707 (5)	2573 (6)	1880 (3)
C(2')	1155 (5)	3100 (6)	3096 (3)	C(2')	6796 (5)	1656 (5)	1732 (3)
C(3')	659 (5)	4289 (6)	3001 (3)	C(3')	5637 (5)	1906 (6)	2008 (3)
C(4')	832 (6)	5038 (7)	2359 (3)	C(4')	5423 (5)	2929 (6)	2437 (3)
C(5')	1568 (6)	4585 (7)	1788 (3)	C(5')	6354 (5)	3842 (5)	2592 (3)
C(6')	2044 (5)	3395 (7)	1864 (3)	C(6')	7484 (6)	3660 (6)	2289 (4)
C(1'')	1793 (7)	5380 (9)	1087 (4)	C(1'')	6123 (6)	5009 (6)	3061 (4)
C(2'')	667 (10)	5760 (12)	555 (5)	C(2'')	4989 (8)	5760 (7)	2748 (5)
C(3'')	-196 (12)	4797 (14)	180 (9)	C(3'')	4783 (10)	6903 (8)	3237 (6)
C(4'')	-1344 (12)	5301 (14)	-326 (7)	C(4'')	3572 (14)	7554 (15)	2876 (11)
C(5'')	-1974 (12)	4205 (17)	-755 (9)	C(5'')	3202 (19)	8719 (21)	3262 (11)
O(1)	2351 (4)	1483 (5)	2581 (2)	O(1)	8879 (4)	2370 (5)	1603 (3)
O(2)	-57 (4)	4821 (5)	3550 (2)	O(2)	4621 (3)	1087 (4)	1844 (2)
H(1)	403	5957	2302	H(1)	4516	3043	2664
H(2)	2574	3017	1413	H(2)	8212	4369	2369
H(3)	1573	3765	4605	H(3)	6171	-798	2106
H(4)	1298	1119	5189	H(4)	7212	-2700	1703
H(5)	1810	2408	5778	H(5)	8009	-1800	1043
H(6)	-172	3464	5507	H(6)	6274	-2694	310
H(7)	-514	1907	5766	H(7)	5239	-2333	1020
H(9)	-1081	2031	3395	H(9)	5913	1112	259
H(11)	1306	1363	3684	H(11)	8011	541	1140
H(12)	2417	4859	746	H(12)	6949	5602	3069
H(13)	2258	6231	1301	H(13)	5985	4725	3648
H(14)	1020	6296	90	H(14)	5128	6063	2165
H(15)	98	6359	888	H(15)	4160	5170	2733

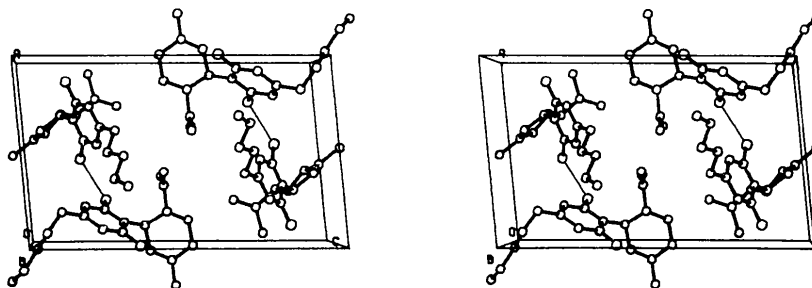


Fig. 3. Stereo packing diagram of the unit-cell contents, omitting H atoms.

refinement reduced R to 0.09, but the dimensions of the side chains were not chemically reasonable and the temperature factors of the terminal C atoms were high. The refinement was continued (blocked full-matrix methods with each molecule as one block) with all bond lengths of the side chains constrained to be equal within an e.s.d. of 0.01 Å. No H atoms could be discerned on the consequent difference map and the temperature factors of side-chain C atoms remained high. In the

final stages of refinement 26 H atoms were included on well defined C atoms at geometrically calculated positions (C-H 1.08 Å, H-C-H 109.5°). An overall isotropic temperature factor for H refined to 0.125 (7) Å²; the constrained side-chain bond length refined to 1.508 Å. Nine reflexions showing pronounced extinction were omitted. The final $R' = \sum w^{1/2} \Delta / \sum w^{1/2} |F_o|$ was 0.0752, with a corresponding R of 0.0682; the weighting scheme was $w = 1/[\sigma^2(F) +$

$0.002F^2$], which gave mean values of $w\Delta^2$ varying only slightly with $\sin \theta$ or $|F_o|$. A final difference map showed no peaks $>0.21 \text{ e } \text{Å}^{-3}$.

Table 2. Bond lengths (Å)

	Molecule 1	Molecule 2
C(2)–C(1)	1.336 (9)	1.304 (12)
C(7)–C(1)	1.514 (11)	1.546 (12)
C(2)–C(3)	1.510 (10)	1.496 (9)
C(4)–C(3)	1.562 (9)	1.556 (11)
C(5)–C(4)	1.521 (11)	1.512 (12)
C(8)–C(4)	1.507 (11)	1.497 (10)
C(6)–C(5)	1.531 (12)	1.505 (13)
C(1)–C(6)	1.487 (9)	1.511 (14)
C(9)–C(8)	1.347 (15)	1.367 (13)
C(10)–C(8)	1.497 (15)	1.566 (13)
O(1)–C(1')	1.360 (9)	1.391 (8)
C(3')–C(2')	1.376 (10)	1.386 (8)
C(3)–C(2')	1.518 (10)	1.515 (10)
C(1')–C(2')	1.396 (9)	1.382 (9)
C(4')–C(3')	1.392 (10)	1.348 (9)
O(2)–C(3')	1.389 (8)	1.396 (8)
C(5')–C(4')	1.400 (10)	1.394 (9)
C(1'')–C(5')	1.513	1.516
C(6')–C(5')	1.365 (11)	1.367 (9)
C(1')–C(6')	1.388 (10)	1.387 (10)
C(2'')–C(1'')	1.496	1.503
C(3'')–C(2'')	1.483	1.510
C(4'')–C(3'')	1.529	1.542
C(5'')–C(4'')	1.506	1.479

Table 3. Bond angles (°)

	Molecule 1	Molecule 2
C(7)–C(1)–C(2)	120.9 (7)	121.7 (8)
C(1)–C(2)–C(3)	125.3 (6)	125.9 (7)
C(5)–C(4)–C(3)	109.5 (6)	107.7 (6)
C(8)–C(4)–C(3)	112.7 (6)	112.8 (6)
C(2)–C(3)–C(4)	110.8 (5)	110.8 (6)
C(6)–C(5)–C(4)	110.2 (6)	112.3 (8)
C(9)–C(8)–C(4)	120.9 (9)	120.5 (8)
C(10)–C(8)–C(4)	118.2 (8)	115.9 (8)
C(8)–C(4)–C(5)	112.5 (6)	115.9 (7)
C(1)–C(6)–C(5)	112.1 (6)	112.1 (8)
C(2)–C(1)–C(6)	121.8 (7)	121.4 (7)
C(7)–C(1)–C(6)	117.3 (7)	116.9 (8)
C(9)–C(8)–C(10)	120.9 (8)	123.6 (9)
C(3)–C(2')–C(1')	121.0 (6)	122.0 (6)
C(4')–C(3')–C(2')	123.0 (7)	123.0 (6)
C(2)–C(3)–C(2')	110.1 (5)	111.8 (6)
C(4)–C(3)–C(2')	112.6 (6)	112.9 (6)
C(6')–C(1')–C(2')	121.3 (7)	122.4 (6)
O(2)–C(3')–C(2')	121.4 (6)	120.2 (6)
O(1)–C(1')–C(2')	117.9 (6)	117.3 (6)
C(3)–C(2')–C(3')	122.5 (6)	122.6 (6)
C(1')–C(2')–C(3')	116.6 (6)	115.3 (6)
C(5')–C(4')–C(3')	119.1 (7)	121.1 (6)
C(6')–C(5')–C(4')	118.5 (7)	117.3 (6)
C(1'')–C(5')–C(4')	120.6 (8)	121.8 (6)
O(2)–C(3')–C(4')	115.5 (7)	116.7 (6)
C(1')–C(6')–C(5')	121.4 (7)	120.7 (7)
C(1'')–C(5')–C(6')	120.8 (7)	120.8 (6)
O(1)–C(1')–C(6')	120.9 (6)	120.3 (6)
C(2'')–C(1'')–C(5')	117.8 (8)	114.0 (6)
C(3'')–C(2'')–C(1'')	120.5 (11)	112.3 (8)
C(4'')–C(3'')–C(2'')	115.7 (13)	107.1 (10)
C(5'')–C(4'')–C(3'')	107.7 (13)	116.1 (15)

Final atomic coordinates are given in Table 1,* and bond distances and angles in Tables 2 and 3. Diagrams of the structure are given in Figs. 2 and 3.

Discussion. The relative configuration at the asymmetric C atoms is consistent with the absolute configuration established by chemical means (Mechoulam & Gaoni, 1967). The two independent molecules are substantially similar. Significant bond-length differences ($>0.025 \text{ Å}$) occur for C(3')–C(4'), O(1)–C(1'), C(6)–C(5) and C(8)–C(10); significant bond-angle differences ($>2.0^\circ$) for C(8)–C(4)–C(5) and C(6)–C(5)–C(4). Differences in side-chain bond lengths and angles are not significant; the high temperature factors, particularly towards the ends of the chains, indicate thermal disorder (the melting point is $66\text{--}67^\circ\text{C}$) and the atom positions and derived parameters, therefore, cannot be reliable.

The major torsion-angle difference is for C(5')–C(1'')–C(2'')–C(3''), which is -57.2 and 179.2° in molecules 1 and 2 respectively. The differing side-chain conformation is clearly seen in Fig. 2. Potential-energy calculations (Falvello *et al.*, 1977) confirm that both these represent minimum-energy conformations.

The benzene ring in molecule 1 is planar and all substituents are coplanar within experimental error. In molecule 2 the aromatic ring is twisted slightly with a torsion angle of $-4.1 (1.5)^\circ$ for C(1')–C(2')–C(3')–C(4') and with O(1) bent out of the plane of the ring by 0.11 Å . A similar distortion was observed in Δ^9 -tetrahydrocannabinolic acid *B* (Rosenqvist & Ottersen, 1975) where, however, the strain could be attributed to the fused tricyclic ring system. The cyclohexene rings in both molecules are in the half-chair conformation; C(4) is 0.32 and 0.44 Å above, and C(5) 0.46 and 0.33 Å below, the plane of the remaining four atoms in molecules 1 and 2 respectively.

The two molecules are linked by hydrogen bonding between O(1) of molecule 1 and O(2) of molecule 2; the O–O distance is 2.86 Å . Apart from this the crystal packing is very open, as indicated by the low density and melting point and the high thermal parameters for the side chains.

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* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32796 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

References

- CARLINI, E. A., LEITE, J. R., TANNHAUSER, M. & BERARDI, A. C. (1973). *J. Pharm. Pharmacol.* **25**, 664–667.
- DE TITTA, G. T., EDMONDS, J. W., LANGS, D. A. & HAUPTMAN, H. (1975). *Acta Cryst.* **A31**, 472–479.
- FALVELLO, L., JONES, P. G., KENNARD, O., MECHOULAM, R., MEYER, A. Y. & TAMIR, I. (1977). To be published.
- IZQUIERDO, I., ORSINGER, O. A. & BERARDI, A. C. (1973). *Psychopharmacology*, **28**, 95–99.
- MECHOULAM, R. & GAONI, Y. (1967). *Tetrahedron Lett.* pp. 1109–1111.
- MECHOULAM, R. & SHVO, Y. (1963). *Tetrahedron*, **19**, 2073–2078.
- ROBERTS, P. J., PETERSEN, R. C., SHELDRIK, G. M., ISAACS, N. W. & KENNARD, O. (1973). *J. Chem. Soc. Perkin II*, pp. 1978–1984.
- ROSENQVIST, E. & OTTERSEN, T. (1975). *Acta Chem. Scand.* **B29**, 379–384.

Acta Cryst. (1977). **B33**, 3214–3215

(Triethylphosphine)(diethylethylidene phosphine)-
[2-methyl-1,2-dicarbadodecaboranyl(10)]platinum(II)

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Abstract. $\text{PtP}_2\text{B}_{10}\text{C}_{15}\text{H}_{42}$, $M_r = 587.6$, triclinic, $P\bar{1}$ (from structure determination), $a = 16.39$ (8), $b = 11.20$ (6), $c = 7.98$ (5) Å, $\alpha = 103.2$ (1), $\beta = 107.4$ (1), $\gamma = 90.5$ (1)°, $U = 1357.1$ Å³, $D_c = 1.44$, $Z = 2$, $D_m = 1.46$ g cm⁻³ (by flotation), $\mu(\text{Mo } K\alpha) = 55.6$ cm⁻¹. The structure was solved by Patterson and Fourier methods and refined to $R = 9.5\%$ for 2961 independent reflexions. The 2-methyl-1,2-carboranyl group is σ -bonded to Pt through its 1C atom. One phosphine is coordinated to the metal atom through its P atom, the other through its P atom and the first C atom of one ethyl side group.

Introduction. Single crystals were obtained by slow evaporation of a dichloromethane solution. Intensities were collected on a Siemens diffractometer by the θ - 2θ scan technique with Mo $K\alpha$ radiation for a maximum 2θ angle of 54°. All reflexions with $I < 3\sigma(I)$ were rejected, the remainder being corrected for Lorentz and polarization effects. 2961 independent reflexions were used in the subsequent calculations. No correction for absorption was applied, because of the small size of the crystal used (approximately a cylinder with a diameter of ca 0.2 mm). During data collection a strong decrease of the standard reflexion intensity was observed suggesting a significant disordering of the crystal, due to X-ray exposure, which greatly affects the accuracy of the structure analysis. This was partly avoided by correcting the intensities, which decreased by about 50% during the overall recording time with a nearly linear trend. The structure was determined by conventional Patterson and Fourier methods and refined by

the block-diagonal least-squares method. After isotropic refinement, $R = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$ was 0.152. The final anisotropic refinement reduced R to

Table 1. Fractional coordinates ($\times 10^4$) with estimated standard deviations in parentheses

	<i>x</i>	<i>y</i>	<i>z</i>
Pt	2363 (1)	1299 (1)	897 (1)
P(1)	3651 (4)	2067 (6)	834 (11)
P(2)	1547 (4)	2811 (6)	1260 (10)
B(1)	1540 (17)	-1520 (29)	4 (49)
B(2)	2329 (21)	-1402 (28)	2077 (53)
B(3)	3337 (20)	-1331 (28)	1644 (60)
B(4)	3129 (17)	-1394 (26)	-736 (59)
B(5)	1585 (23)	-2883 (31)	-1626 (59)
B(6)	1794 (21)	-2826 (27)	771 (62)
B(7)	2915 (25)	-2785 (30)	1803 (73)
B(8)	3405 (22)	-2703 (33)	58 (68)
B(9)	2529 (25)	-2787 (36)	-2095 (70)
B(10)	2399 (25)	-3621 (36)	-692 (60)
C(1)	3816 (16)	3605 (36)	1884 (52)
C(2)	4675 (25)	4402 (33)	2104 (75)
C(3)	4638 (16)	1483 (26)	2005 (50)
C(4)	4754 (23)	1706 (36)	4019 (58)
C(5)	3813 (20)	1844 (37)	-1533 (46)
C(6)	3178 (31)	2554 (51)	-2705 (50)
C(7)	1719 (21)	4041 (33)	3290 (54)
C(8)	937 (24)	4476 (40)	3684 (60)
C(9)	865 (20)	3443 (37)	-618 (49)
C(10)	548 (24)	2510 (38)	-2358 (49)
C(11)	1114 (13)	1421 (21)	1368 (34)
C(12)	999 (16)	1115 (31)	3007 (39)
C(13)	2482 (13)	-593 (19)	498 (32)
C(14)	2036 (17)	-1545 (28)	-1599 (46)
C(15)	1608 (28)	-811 (41)	-3182 (51)