The Crystal and Molecular Structure of Cannabidiol

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The structure of cannabidiol, $C_{21}H_{30}O_2$, has been determined by X-ray methods using 2046 reflections collected by counter methods. The compound crystallizes in the space group $P2_1$ with two molecules in the asymmetric unit. Cell dimensions are: $a = 10.644(5)$ Å, $b = 10.667(2)$ Å, $c = 17.323(5)$ Å, $\beta = 95.42(3)°$. The structure model was refined to a conventional R of 0.073. The cyclohexene ring is in the half-chair conformation. The aryl and the isopropenyl substituents are quasi-equatorial and the conformation around the pivot bonds are syn-periplanar relative to the quasi-axial protons. The main difference between the two molecules in the asymmetric unit is in the conformation of the pentyl side-chain. The molecules are kept together mainly by van der Waals forces. There is only one hydrogen bond [2.861(8) Å] which connects the phenolic groups in the two molecules in the asymmetric unit.

Cannabidiol (CBD, *1*) is the biogenetic precursor of $(-)\Delta^9$-tetrahydrocannabinol (Δ^9-THC, *2*), which is the major psychotomimetic constituent in hashish. Cannabidiolic acid (CBDA) was the first cannabinoid to be studied [1] and is the predominant cannabinoid in nature.[2,3] CBD is psychotomimetically inactive, but it is reported [4] that it will interfere with some of the actions of Δ^9-THC when given in combination. It is also known that CBD potentiates

barbiturates [5] and is antibiotic to Gram-positive bacteria *in vitro*.[6]

We have earlier studied the three-dimensional structures of cannabinoids with a pyran ring (Δ^9-THC Acid B,[7] 8-β-hydroxy-Δ^9-THC[8] and cannabinol [9]), and in view of the increasing interest in and importance of cannabinoids which do not possess a pyran ring, we found it of importance to undertake this investigation (see note on p. 811).

EXPERIMENTAL AND STRUCTURE DETERMINATION

A crystal of extreme dimensions $0.24 \times 0.38 \times 0.44$ mm was selected for the crystallographic work. A computer-controlled Syntex PĪ four-circle diffractometer with graphite-monochromatized MoKα radiation was utilized in the preliminary experiments and the collection of intensity data. The axial solutions (computer program written by R. Sparks, part of the diffractometer program library) from the angular coordinates of fifteen reflections implied a monoclinic system. The systematic absences found in a fast low-angle data collection indicated the space group $P2_1$ or $P2_1/m$ with four molecules in the unit cell. For the optically active compound this uniquely determines the space group to be $P2_1$ with two molecules per asymmetric unit, which will be denoted A and B, respectively. Unit cell dimensions and their standard deviations were determined by a least-squares treatment of the

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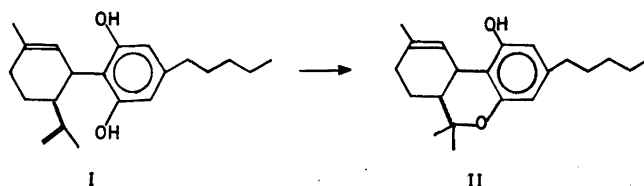
angular coordinates of fifteen reflections with 2θ-values between 4 and 16°.

Three-dimensional intensity data were recorded using the $\omega - 2\theta$ scanning mode with scan speed variable from 3 to 12° min^{-1} depending on the intensity of the reflection, and a scan area from 2θ (α_1) $-0.7°$ to $2\theta(\alpha_2)$ $+0.8°$. Background counting time was equal to $0.35 \times$ (scan time) on each side of the scan area. The temperature was kept constant within 2° at 23 °C. The variations in the intensities of three check reflections which were remeasured after every hundred reflections, were random.

The estimated standard deviations were taken as the square root of the total counts with a 2 % addition of the net intensity for experimental uncertainties. Of the 2754 symmetry-independent reflections measured $(2\theta_{max} = 45°)$, 2046 had intensities larger than twice their standard deviations. These were regarded as observed reflections, whereas the remaining were excluded from further calculations. The intensities were corrected for Lorentz and polarization effects.[10]

The phase problem could not be solved by the standard MULTAN[11] program assembly. Starting phases were, therefore, generated by the use of magic integers.[12] In the resulting E-map from the statistically best solution from the run with starting phases generated by the use of the four integers 2, 3, 7 and 13, 34 of the 46 nonhydrogen atoms could be located. The other nonhydrogen atoms were found by successive Fourier-refinements. The program used as well as programs subsequently employed, is part of a local (Oslo) assembly of computer programs which is described in Ref. 13. Atomic scattering factors used were those of Doyle and Turner[14] for oxygen and carbon, and those of Stewart et al.[15] for hydrogen.

The structure model was refined to a conventional R of 0.13. The introduction of anisotropic temperature factors for all nonhydrogen atoms in the least-squares refinement lowered R to 0.092. Due to the large number of parameters each molecule (A and B, respectively) was refined successively by "full-matrix" refinement. At this point the hydrogen atoms were placed in calculated positions and included in the structure factor calculation with estimated isotropic thermal parameters. The least-squares refinement of all nonhydrogen atomic parameters converged to a weighted R_w of 0.074 and an R of 0.073. The weights used in the refinement were $1/\sigma^2$ (F_{obs}). A final difference Fourier synthesis showed only spurious peaks of maximum height 0.4 e $Å^{-3}$.

Atomic parameters for nonhydrogen atoms are given in Table 1. A list of observed and calculated structure factors is available upon request from: Department of Chemistry, University of Oslo, Oslo 3, Norway, as is a list of the parameters used for hydrogen atoms.

CRYSTAL DATA

Cannabidiol, $C_{21}H_{30}O_2$, $M = 314.47$ amu, space group $P2_1$, $a = 10.644(5)$ Å, $b = 10.667(2)$ Å, $c = 17.323(5)$ Å, $\beta = 95.42°(3)$, $V = 1958.2(11)$ $Å^3$, $Z = 4$, $D_{calc} = 1.067$ g cm^{-3}, $F(000) = 688$.

DISCUSSION

The molecular structure and the atomic numbering of the two CBD molecules in the asymmetric unit are shown in Fig. 1, together with a view along the plane of the aromatic ring showing the conformation. Selected dihedral angles are given in Table 2. The absolute configuration was arbitrarily chosen $(S,S$ shown). By chemical synthesis[16] the absolute configuration of the naturally occuring $(-)$-CBD has been shown to be R,R. A list of bond lengths and bond angles is available from the authors upon request. The estimated standard deviations in bond lengths and bond angles are 0.01 Å and $0.7 - 1.0°$, respectively, except for the side-chains where the e.s.d.'s are $0.02 - 0.03$ Å and $2 - 3°$. Except for some abnormal
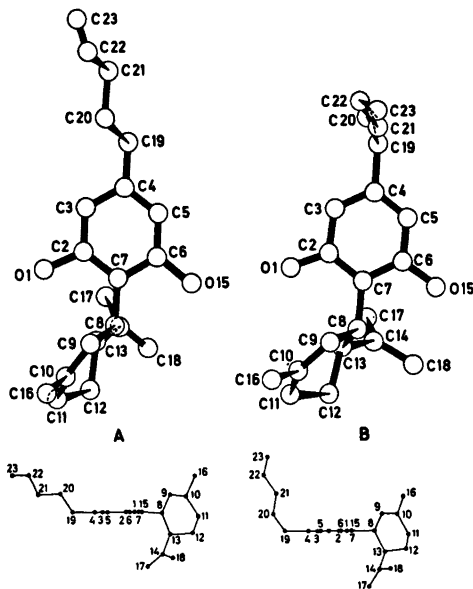

Fig. 1. The molecular structure and the atomic numbering of the two molecules in the asymmetric unit. The upper part of the figure is a view down on the plane of the phenyl ring and the lower part along the plane.

Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations for nonhydrogen atoms. The temperature factor is given by $\exp\{-2\pi^2[U_{11}(a^*h)^2 + U_{22}(b^*k)^2 + U_{33}(c^*l)^2 + 2U_{12}(a^*b^*hk) + 2U_{13}(a^*c^*hl) + 2U_{23}(b^*c^*kl)]\}$.

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O1A	1.0370(4)	.5666(—)	.8153(3)	.046(3)	.087(4)	.105(4)	−.016(3)	.016(3)	−.028(4)
C2A	.9353(7)	.4824(8)	.8001(4)	.057(5)	.064(6)	.058(5)	−.001(5)	.004(4)	−.008(5)
C3A	.9572(8)	.3771(10)	.7547(5)	.064(6)	.083(7)	.065(6)	.007(6)	.012(4)	−.006(6)
C4A	.8629(8)	.2896(9)	.7403(4)	.054(5)	.074(7)	.055(5)	−.010(5)	−.011(4)	−.004(5)
C5A	.7529(8)	.3075(9)	.7713(5)	.058(6)	.066(7)	.088(6)	−.015(5)	−.024(5)	−.004(6)
C6A	.7272(8)	.4153(10)	.8130(5)	.066(6)	.074(7)	.069(6)	−.003(6)	−.011(5)	.006(5)
C7A	.8211(7)	.5091(8)	.8278(4)	.044(5)	.069(6)	.046(5)	−.001(5)	.004(4)	−.002(4)
C8A	.7938(7)	.6291(9)	.8675(4)	.068(5)	.077(7)	.053(5)	−.005(5)	.012(4)	−.017(5)
C9A	.8868(7)	.6452(10)	.9417(5)	.062(6)	.095(8)	.067(6)	.005(6)	.000(5)	−.017(6)
C10A	.9310(8)	.7542(13)	.9667(5)	.081(7)	.103(9)	.066(6)	−.008(7)	.012(5)	−.035(7)
C11A	.8998(10)	.8727(11)	.9252(7)	.103(8)	.086(9)	.121(9)	−.004(7)	.025(7)	−.033(8)
C12A	.7833(10)	.8623(9)	.8666(6)	.125(9)	.055(6)	.119(8)	−.001(6)	.008(7)	−.004(7)
C13A	.7959(7)	.7467(9)	.8157(5)	.074(6)	.068(7)	.080(6)	−.003(5)	.003(5)	−.007(6)
C14A	.6999(10)	.7384(10)	.7455(7)	.1116(8)	.076(7)	.108(9)	.000(7)	−.001(7)	.011(7)
O15A	.6119(5)	.4381(6)	.8404(3)	.052(3)	.103(5)	.107(4)	−.023(4)	.034(3)	−.008(4)
C16A	1.0178(9)	.7587(12)	1.0425(6)	.108(8)	.141(11)	.116(9)	−.005(6)	.000(7)	−.055(8)
C17A	.7342(10)	.7184(13)	.6768(7)	.115(8)	.136(11)	.106(8)	−.030(8)	.000(7)	.003(9)
C18A	.5599(9)	.7500(14)	.7603(8)	.062(7)	.175(13)	.243(14)	.030(8)	.021(7)	.019(12)
C19A	.8849(8)	.1737(10)	.6966(5)	.091(7)	.083(8)	.071(6)	.001(6)	−.017(5)	−.003(6)
C20A	.9998(11)	.0963(10)	.7251(6)	.145(10)	.078(8)	.103(8)	.010(7)	.007(7)	−.019(7)
C21A	1.0212(12)	−.0162(12)	.6781(8)	.143(11)	.092(10)	.180(11)	.034(9)	.017(8)	.008(10)
C22A	1.1315(21)	−.0953(18)	.7178(13)	.215(21)	.162(16)	.262(24)	.043(15)	.041(17)	−.068(15)
C23A	1.1811(23)	−.1557(5)	.6821(16)	.222(22)	.795(91)	.286(28)	.244(37)	.070(19)	.041(38)
O1B	.5046(5)	.1922(—)	.6452(3)	.088(4)	.072(4)	.108(5)	.021(3)	.035(4)	−.009(4)
C2B	.4363(7)	.2446(10)	.6990(5)	.058(5)	.079(7)	.073(6)	.000(5)	.008(4)	.003(6)
C3B	.4152(8)	.1715(8)	.7642(5)	.082(6)	.063(7)	.085(6)	−.002(5)	.008(5)	.001(6)
C4B	.3447(8)	.2186(11)	.8214(5)	.067(6)	.093(9)	.071(6)	−.015(6)	.019(5)	.014(6)
C5B	.2973(7)	.3350(10)	.8136(5)	.062(5)	.086(8)	.056(5)	.003(5)	.004(4)	−.006(6)
C6B	.3135(6)	.4076(10)	.7497(5)	.041(4)	.089(8)	.058(5)	−.008(5)	.002(4)	−.005(6)
C7B	.3847(7)	.3624(9)	.6893(4)	.050(4)	.057(6)	.065(5)	−.008(5)	.004(4)	.005(5)
C8B	.4050(6)	.4437(8)	.6196(4)	.048(4)	.084(6)	.057(5)	−.002(5)	.003(4)	.006(5)
C9B	.5422(7)	.4542(8)	.6084(4)	.072(5)	.068(6)	.075(6)	−.012(5)	−.004(4)	.010(5)
C10B	.5971(8)	.4409(9)	.5406(5)	.080(6)	.090(7)	.017(6)	−.004(6)	.031(5)	.007(6)
C11B	.5148(8)	.4233(10)	.4661(4)	.093(6)	.117(9)	.063(5)	.002(7)	.005(6)	.001(6)
C12B	.3751(8)	.4646(9)	.4746(4)	.090(6)	.091(7)	.065(5)	−.002(6)	.004(5)	.009(6)
C13B	.3289(7)	.3974(8)	.5447(4)	.074(5)	.081(7)	.066(5)	.009(5)	.009(11)	.002(5)
C14B	.1849(8)	.4122(12)	.5486(5)	.055(6)	.119(10)	.089(6)	−.010(7)	−.012(5)	.014(7)
O15B	.2647(5)	.5255(6)	.7433(3)	.073(4)	.077(4)	.089(6)	.008(4)	.020(3)	.018(4)
C16B	.7322(8)	.4440(11)	.5381(5)	.076(6)	.152(10)	.099(7)	−.025(7)	.026(5)	.015(7)
C17B	.1122(10)	.3163(14)	.5477(7)	.080(7)	.181(13)	.145(10)	−.020(8)	.002(7)	.007(9)
C18B	.1343(9)	.5412(14)	.5530(7)	.081(8)	.155(12)	.163(11)	.034(8)	.012(7)	−.016(10)
C19B	.3264(10)	.1345(11)	.8903(7)	.109(8)	.130(10)	.104(8)	−.019(8)	−.009(7)	.027(8)
C20B	.4289(18)	.1036(16)	.9471(8)	.171(14)	.218(48)	.112(10)	−.038(13)	−.005(10)	.060(12)
C21B	.5129(18)	.1874(23)	.9792(9)	.177(14)	.355(27)	.121(13)	−.108(17)	−.058(11)	.102(15)
C22B	.6275(24)	.1438(23)	1.0316(12)	.307(30)	.278(29)	.159(16)	−.150(24)	−.022(17)	.020(16)
C23B	.6909(18)	.2397(28)	1.0661(14)	.159(15)	.312(30)	.278(26)	.029(19)	.012(15)	.121(24)

Table 2. Dihedral angles (°). The angles are positive in a right-hand screw.

Angles (°)	A	B	Angles (°)	A	B
C2−C7−C8−C9	−60.1(9)	−51.4(10)	C2−C7−C8−C13	64.6(9)	73.5(9)
C7−C8−C9−C10	145.2(8)	133.4(9)	C13−C8−C9−C10	18.1(11)	7.5(12)
C8−C9−C10−C11	−2.0(13)	5.1(14)	C9−C10−C11−C12	17.6(13)	17.9(12)
C10−C11−C12−C13	−49.2(11)	−52.6(10)	C11−C12−C13−C8	65.3(9)	65.9(8)
C11−C12−C13−C14	−168.9(9)	−169.1(8)	C12−C13−C8−C9	−48.4(8)	−42.6(9)
C12−C13−C8−C7	−172.9(8)	−167.7(7)	C8−C13−C14−C17	−106.7(12)	−115.4(11)
C12−C13−C14−C17	129.3(12)	120.9(11)	C3−C4−C19−C20	52.2(11)	69.4(15)
C4−C19−C20−C21	−177.8(9)	45.4(22)	C19−C20−C21−C22	−173.6(12)	−172.7(15)
C20−C21−C22−C23	−155.9(35)	−171.8(20)	C8−C13−C14−C18	71.2(11)	64.9(12)
			C12−C13−C14−C18	−52.6(12)	−58.6(13)

Table 3. Deviations from least-squares planes ($\text{Å} \times 10^3$). The deviations for those atoms used to define the plane are given in italicized figures.[a]

Atom	A1	B1	Atom	A2	B2	Atom	A3	B3
O1	91	0	C7	−806	−1016	C7	−2520	−2518
C2	*32*	*13*	C8	*16*	*−29*	C8	−1373	−1295
C3	*−11*	*−5*	C9	*−20*	*39*	C9	−1318	−1152
C4	*−20*	*−8*	C10	*−7*	*6*	C10	−200	−18
C5	*27*	*12*	C11	*−2*	*6*	C11	1130	1286
C6	*−6*	*−3*	C12	415	493	C12	1080	1215
C7	*−23*	*−10*	C13	−385	−334	C13	*−4*	*1*
C8	−151	5	C14	−270	−116	C14	*11*	*−2*
O15	−47	20	C16	*13*	*−21*	C17	*−4*	*1*
C19	16	−23				C18	*−4*	*1*

[a] Angle between planes A1 and A2: 80.3°. Angle between planes B1 and B2: 73.4°.

short bonds in the side-chains [C22A−C23A: 1.07(3) Å, and C22B−C23B: 1.34(3) Å] caused by the large thermal vibration, the mean values of bond angles and lengths are normal within their e.s.d.'s, although there are some large differences between molecule A and B.

As seen from Fig. 1, the main difference in conformation between molecule A and molecule B is found in the side-chain. In molecule A the chain is fully extended and all-*anti* while in B the conformation is *gauche* around the C19−C20 bond, with a dihedral angle C4−C19−C20−C21 of 45.4(2.2)°. The mean value of the dihedral angle C3−C4−C19−C20 is 60.9°. The corresponding angle was approximately 90° in both the two Δ^9-THC structures studied.[7,8] The present structure shows that there is no preferred side chain conformation

in the cannabinoids but that this will be determined by the packing in a crystal.

The aromatic ring is planar within 0.03 Å in both molecules, but the deviations from the plane for the atoms directly attached to the ring are considerably greater in molecule A than in B (see Table 3, plane A1 and B1).

A comparison of the cyclohexene conformation in CBD and in Δ^9-THC clearly demonstrates the effect of the pyran ring formation. In the present structure the conformation is closer to a true C_2 symmetric half-chair, as observed in cyclohexene,[17] than it was in Δ^9-THC. The mean dihedral angle C10−C11−C12−C13 in CBD is 50.9°, while the value observed in 8β-hydroxy-Δ^9-THC was 37.7°. The deviation from the plane through C8−C9−C10−C11 (plane A2 and B2, Table 4) is +0.41 Å and
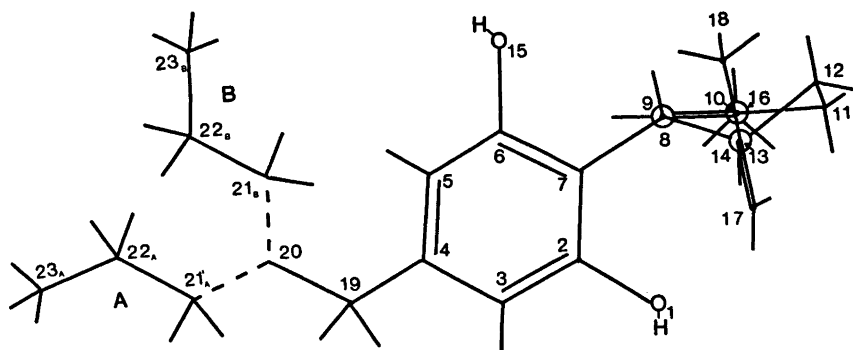
−0.39 Å for C12 and C13 in molecule A, respectively, and +0.49 Å and −0.33 Å in molecule B. The corresponding values in 8β-hydroxy-Δ^9-THC were +0.12 and −0.61 Å.

Both the aryl and the isopropenyl groups are quasi-equatorial substituents on the cyclohexene ring, and the conformation around the pivot bonds C7−C8 and C13−C14 are *syn*-clinal. The torsion angle C2−C7−C8−C13 is 64.9(9)° in molecule A and 73.5(9)° in B. The torsion angle C8−C13−C14−C18 is 71.2(9)°. in mole-cule A and 64.9(10)° in B. This means that the C6−C7 and C14−C17 bonds are *syn*-periplanar relative to the quasi-axial protons on C8 and C13, respectively. This conformation leads to a short contact between the phenolic oxygen O15 and the proton on C8. In molecule A this distance is 2.28 Å and in B 2.34 Å (assuming normal C−H bond distance and angle.)

A packing diagram of the crystal is shown in Fig. 2. The molecules are kept together mainly by van der Waals forces. Although there are four free phenolic groups in the asymmetric unit, only one hydrogen bond is formed. This is from the phenolic group O1 in molecule A to the phenolic oxygen O15 in molecule B in the neighbour cell. The O1A···O15B distance is 2.861(8) Å. There are no other *inter*-molecular contacts between nonhydrogen atoms shorter than 3.5 Å.

Note added in proof. An independent X-ray crystallographic structure determination of cannabidiol has been published: Jones, P. G., Falvello, L., Kennard, O., Sheldrick, G. M. and Mechoulam, R. *Acta Crystallogr. B 33* (1977) 3211. The results do not differ signifi-cantly.

Fig. 2. The molecular packing in the unit cell, as seen down the *b*-axis.

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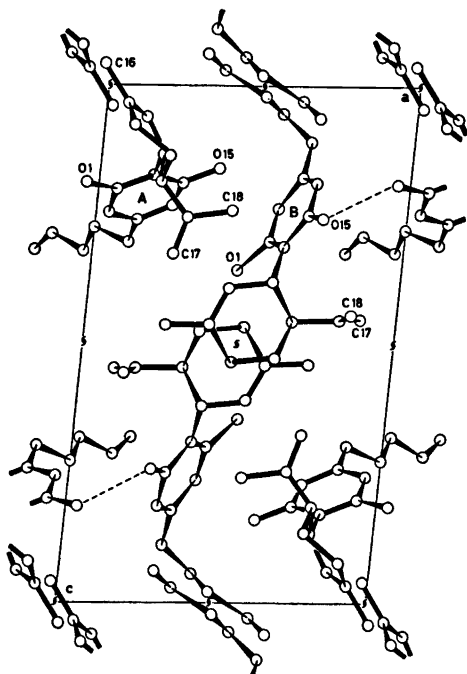6. Kabelik, J., Krejči, Z. and Šantarý, F. *Bull. Narc. 12(3)* (1960) 5.

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