

The Crystal and Molecular Structure of Δ^9 -Tetrahydrocannabinolic Acid B

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The crystal and molecular structure of the title compound $C_{22}H_{30}O_4$, has been determined by X-ray methods using 1106 reflections above background level collected by counter methods. The crystals are orthorhombic, space group $P2_12_12_1$, with cell dimensions $a=16.514(2)$ Å; $b=14.324(2)$ Å; $c=8.744(1)$ Å; there are four molecules per unit cell. The structure was refined to an R of 0.084 (weighted $R_w=0.068$).

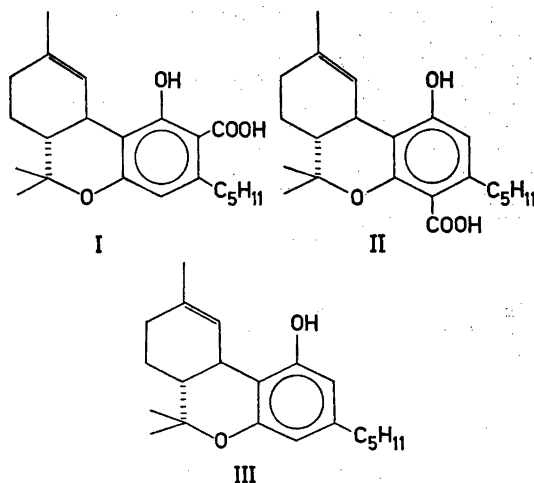
The cyclohexene and the pyran part of the molecule occurs in the half-chair conformation. The bond distances and angles, and a slight twist of the benzene ring, indicate considerable strains in the aromatic system. Both the phenolic and carboxylic group are significantly out of the plane through the aromatic ring. The angle between this plane and a plane through the cyclohexene ring is 37.7° . The pentyl side-chain occurs in an extended *gauche* conformation, and the thermal parameters of this part of the molecule are very high.

The molecules are held together by van der Waals forces in the c -directions, and hydrogen bonds (2.688 Å) from phenolic to carboxylic groups in the a - b plane. There is a short *intra*-molecular hydrogen bond (2.490 Å) from the carboxylic group to the pyran oxygen.

It is now well established that the major psychotomimetic constituent in hashish is *l*- Δ^9 -tetrahydrocannabinol (Δ^9 -TCH).¹ Although a great deal of information about the structure-activity relationship has been collected over the years, and empirical correlation of these data have been inferred,² the mode and site of action of Δ^9 -THC still remains obscure.

While most cannabinoids are oily liquids or very low melting compounds, Mechoulam *et al.*³ have isolated in some samples of hashish a crystalline isomer of Δ^9 -THC acid. In order to

distinguish between the two isomers, they call them, respectively, Δ^9 -THC acid A (I) (the more common component of hashish) and Δ^9 -TCH acid B (II). Neither of these are hallucinogenic *per se*, but are decarboxylated upon heating (smoking) to form the active Δ^9 -THC (III).



To get a basis for further studies of the interrelationship between the molecular structure and pharmacological activity of cannabinoids, a structure determination would be of interest. A crystal structure investigation of Δ^9 -THC acid B was therefore carried out.

EXPERIMENTAL

The product obtained from R. Mechoulam was recrystallized by slow evaporation of a chloroform solution. Colourless, prismatic crystals were formed. A crystal of dimensions $0.45 \times 0.30 \times 0.12$ mm was selected for the crystallographic work.

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Oscillation and Weissenberg diagrams indicated orthorhombic symmetry with systematic extinctions corresponding to the space group $P2_12_12_1$. Unit cell parameters were determined from diffractometer measurements of 15 general reflections. A Picker manual diffractometer was applied using $\text{CuK}\beta$ radiation ($\lambda = 1.3922 \text{ \AA}$) and a take-off angle of 1° . The computer program utilized in the least-squares calculations of cell parameters, as well as programs used in all subsequent calculations, are part of a local assembly of programs for a CYBER-74 computer which is described in Ref. 4.

Three-dimensional intensity data were recorded on an automatic Picker four-circle diffractometer with graphite monochromated $\text{MoK}\alpha$ radiation using the $\omega - 2\theta$ scanning mode with a 2θ scan speed of 1° min^{-1} . Background counting time was 40 s at each end of the scan range. The temperature was kept constant within 1° at 18°C . The variations in the intensities of three standard reflections which were remeasured after every fifty reflections were random and less than three times their standard deviations. Accordingly no corrections were applied for these variations.

The estimated standard deviations were taken as the square root of the total count with a 2 % addition for experimental uncertainties. Of the 1854 symmetry-independent reflections measured ($2\theta_{\text{max}} = 50^\circ$), 1109 had intensities larger than twice their standard deviations. These were regarded as "observed" reflections, and the remaining reflections were excluded from further calculations. The intensities were corrected for Lorentz and polarization effects.

The atomic scattering factors used were those

of Doyle and Turner⁵ for carbon and oxygen, and of Stewart *et al.*⁶ for hydrogen.

CRYSTAL DATA

Δ^8 -Tetrahydrocannabinolic acid B, $\text{C}_{22}\text{H}_{30}\text{O}_4$, orthorhombic. Cell dimensions: $a = 16.514(2) \text{ \AA}$; $b = 14.324(2) \text{ \AA}$; $c = 8.744(1) \text{ \AA}$. Figures in parentheses are estimated standard deviations. $V = 2068.5 \text{ \AA}^3$, $M = 358.5 \text{ amu}$; $D_{\text{obs}} = 1.12 \text{ g/cm}^3$; $Z = 4$; $D_{\text{calc.}} = 1.151 \text{ g/cm}^3$; $F(000) = 776$. Absent reflections: ($h00$) for h odd; ($0k0$) for k odd; ($00l$) for l odd; space group $P2_12_12_1$.

STRUCTURE DETERMINATION

The phase problem was solved by a computer procedure⁷ based on direct methods utilizing tangent refinement.

The structure model was refined to a conventional R of 0.19. Introduction of anisotropic thermal parameters for all nonhydrogen atoms and least-squares refinement yielded an R of 0.14. At this point the hydrogen atoms were placed in calculated positions (C-H: 1.0 \AA , O-H: 0.95 \AA) and included in the structure factor calculations. Three reflections [(13 4 1), (0 1 4), (3 0 7)] which were obviously mismeasured, (due to diffractometer errors), were removed from the data set (leaving 1106 F_o 's).

Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations ($\times 10^4$) for non-hydrogen atoms. The temperature factor is given by $\exp -(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hl + B_{13}kl + B_{23}kl)$.

Atom	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
O1	2099(3)	1829(4)	2856(8)	51(3)	61(4)	336(14)	-17(6)	-13(12)	-45(13)
C2	1847(5)	1081(6)	2785(10)	44(4)	50(5)	193(16)	-22(8)	-29(16)	55(18)
C3	741(5)	1297(6)	3127(11)	40(4)	48(5)	285(20)	3(8)	-11(16)	-1(19)
C4	184(5)	573(7)	3041(12)	32(4)	59(7)	323(23)	-18(9)	11(16)	22(22)
C5	450(5)	-287(6)	2432(11)	51(5)	46(5)	281(20)	-12(8)	39(17)	-17(19)
C6	1228(5)	-453(6)	2005(10)	47(4)	49(5)	169(16)	1(8)	34(14)	-49(17)
C7	1832(5)	226(6)	2154(9)	44(4)	48(5)	201(16)	-4(8)	-19(15)	-33(17)
C8	2738(4)	94(6)	1746(9)	39(4)	71(6)	183(18)	9(9)	41(14)	20(18)
C9	3062(5)	-829(6)	2198(12)	45(4)	82(7)	267(21)	5(9)	29(18)	-74(21)
C10	3846(5)	-941(6)	2544(12)	54(5)	101(8)	299(22)	27(11)	57(20)	-73(24)
C11	4439(5)	-162(8)	2879(14)	48(4)	112(9)	394(27)	-21(11)	10(20)	-114(30)
C12	4111(6)	725(7)	1904(12)	57(5)	103(8)	366(27)	-58(11)	49(21)	13(26)
C13	3235(5)	862(5)	2435(10)	38(4)	74(6)	221(19)	-32(8)	21(14)	-48(21)
C14	2896(5)	1819(7)	2131(10)	53(5)	89(8)	184(19)	-38(10)	20(18)	-15(23)
O15	1429(3)	-1277(4)	1397(7)	53(3)	56(3)	263(11)	-21(5)	45(9)	-92(12)
C16	439(7)	2263(7)	3570(15)	61(6)	75(8)	355(27)	-24(12)	-1(25)	30(25)
O17	-234(4)	2456(4)	3837(11)	59(4)	68(4)	620(26)	49(7)	76(18)	22(18)
O18	1809(4)	2919(4)	3679(12)	72(4)	66(4)	794(30)	16(7)	-4(19)	-159(20)
C19	4186(5)	-1926(8)	3021(16)	81(6)	111(8)	557(39)	72(13)	75(29)	-98(32)
C20	3344(6)	2598(6)	2975(14)	80(6)	75(6)	336(26)	-59(10)	-91(23)	-22(22)
C21	2022(7)	2036(7)	492(15)	133(9)	111(8)	279(23)	-22(15)	23(25)	39(26)
C22	-702(5)	629(7)	3587(14)	66(6)	82(7)	353(25)	34(10)	-44(22)	-1(25)
C23	-1181(7)	930(8)	2315(17)	65(6)	133(10)	464(35)	-18(13)	-22(27)	-42(36)
C24	-2122(12)	989(12)	2663(25)	117(13)	198(17)	696(58)	-51(22)	-164(53)	154(51)
C25	-2506(12)	344(15)	3010(27)	113(11)	303(20)	813(58)	-97(27)	267(43)	24(72)
C26	-3453(7)	470(11)	3067(17)	63(5)	251(14)	549(39)	-65(16)	59(26)	-71(44)

Table 2. Fractional atomic coordinates (calculated) ($\times 10^3$) and isotropic thermal parameters used for hydrogen atoms. A hydrogen atom is bonded to the atom given in parentheses. (For the identities of these see Fig. 1.)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>
H27 (O15)	101	-171	129	6.0
H28 (O18)	157	275	351	10.0
H29 (C5)	5	-80	235	6.0
H30 (C8)	271	11	55	6.0
H31 (C9)	269	-137	219	8.0
H32 (C11)	493	-36	200	8.0
H33 (C11)	460	-1	365	8.0
H34 (C12)	410	65	69	8.0
H35 (C12)	445	127	210	8.0
H36 (C13)	322	79	360	6.0
H37 (C19)	478	-181	330	11.0
H38 (C19)	414	-233	214	11.0
H39 (C19)	389	-215	393	11.0
H40 (C20)	391	266	255	11.0
H41 (C20)	337	244	408	11.0
H42 (C20)	305	320	283	11.0
H43 (C21)	334	203	-3	11.0
H44 (C21)	254	265	35	11.0
H45 (C21)	245	154	0	11.0
H46 (C22)	-75	108	440	11.0
H47 (C22)	-89	0	385	11.0
H48 (C23)	-109	52	144	11.0
H49 (C23)	-100	159	205	11.0
H50 (C24)	-237	118	161	14.0
H51 (C24)	-221	151	336	14.0
H52 (C25)	-231	26	413	14.0
H53 (C25)	-231	-18	242	14.0
H54 (C26)	-365	-21	346	15.0
H55 (C26)	-364	47	197	15.0
H56 (C26)	-364	91	369	15.0

Full-matrix least-squares refinement of all positional and anisotropic thermal parameters for all non-hydrogen atoms resulted in a conventional *R* of 0.084 and a weighted *R_w* of 0.068.

Atomic parameters for non-hydrogen atoms are listed in Table 1, and parameters used for hydrogen atoms are given in Table 2. A listing of observed and calculated structure factors is available from the authors upon request. (May also be obtained from: Department of Chemistry, University of Oslo, Oslo 3, Norway).

Standard deviations in molecular parameters were calculated from the correlation matrix ignoring standard deviations in cell parameters.

DISCUSSION

Description of the structure. The molecular parameters and the numbering of the atoms

are presented in Fig. 1. A sketch of the molecular conformation is given in Fig. 2. The absolute configuration at the chiral centers is *R,R*, as determined by Mechoulam.⁸

The variation of the bond angles in the benzene ring [$126.6^\circ(7) - 113.8^\circ(7)$], indicates a considerable strain in the aromatic system. This is also implied by the differences in bond lengths and the deviations from planarity (see Plane A, Table 4), which indicates a slightly twisted conformation of the benzene ring. This strain is probably due to the pyran ring. However, the short intramolecular O1-O18 contact may also affect the conformation of the aromatic system to some extent. The phenolic oxygen is bent 0.096 Å out of the plane, and away from the C9 proton (H31). The distance between this proton and O15 is only 2.20 Å (assuming normal C-H bond length and angle). From Westheimer calculations and NMR studies on Δ^9 -THC, Archer *et al.*⁹ report this distance to be 2.30 Å. Their calculations also show that the phenolic group is bent out of the plane, and a slight opening of the O15-C6-C7 angle. The last effect is not observed here. The C6-O15 distance, 1.337(8) Å is somewhat shorter than the normal phenolic C-O bond of 1.36-1.38 Å.

The carboxylic groups is also significantly out of plane A, and at the same side as the phenolic group. From spectroscopic data (carboxylic absorptions: Acid A: $\nu_{\max} = 1615 \text{ cm}^{-1}$; Acid B: $\nu_{\max} = 1710 \text{ cm}^{-1}$), Mechoulam⁸ concludes that the plane of the carboxylic group is twisted with respect to the aromatic ring in Δ^9 -THC Acid B. We do not observe this; the dihedral angle (C4-C3)-(C16-O17) is only $-1.4^\circ(2.0)$. This gives a short O18...O1 distance [2.490(8) Å]. Although the hydrogen atom was not located, we believe that this indicates the presence of an intramolecular hydrogen bond of the same type as in *o*-ethoxybenzoic acid.¹⁰ There are no short contacts to other hydrogen bond acceptors from O18. We believe that in both isomers the COOH group is near coplanar with the aromatic ring, but that there are different types of intramolecular hydrogen bonds in the two compounds. In Δ^9 -THC Acid B, the COOH is donor and the pyran oxygen acceptor, while in Acid A the phenolic group is probably donor and the carboxylic group acceptor, as in salicylic acid.¹¹ This will also explain the spectroscopic results.

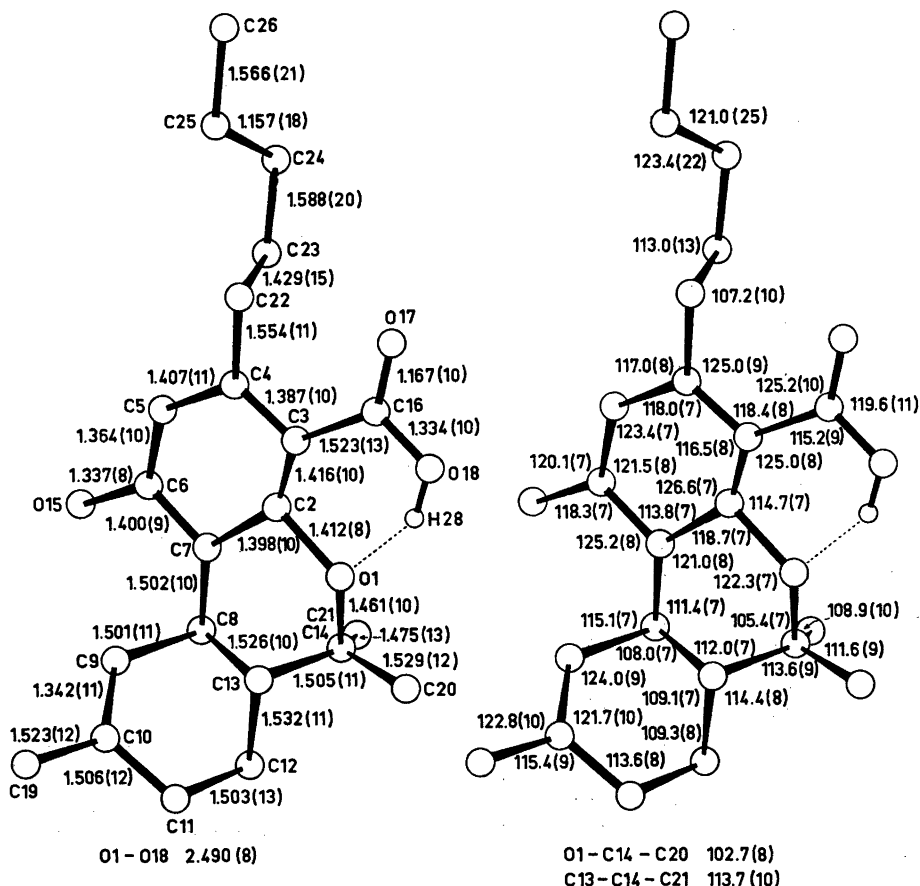


Fig. 1. Bond lengths (Å) and bond angles (°). Estimated standard deviations in the last digit listed for the corresponding parameter are given in parentheses.

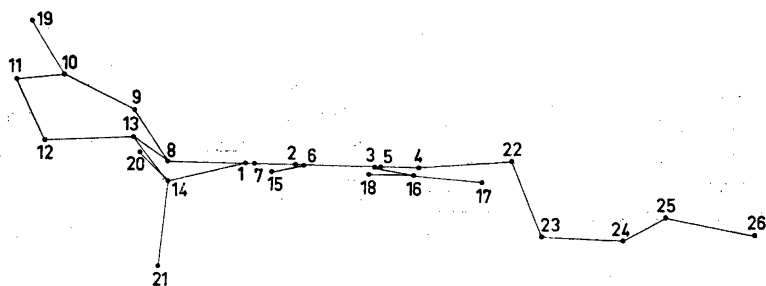


Fig. 2. A view along the plane of the benzene ring, showing the conformation of the molecule.

A least-squares plane through O1, C2, C7, C8 (Plane B, Table 4) shows a half-chair conformation of the pyran ring, with C13 0.422 Å above and C14 0.332 Å below the plane. This gives a staggered conformation around the C13-C14 bond [the dihedral angle (C8-C13)-(C14-O1)

is 60.8°], with the C21 methyl group in an axial and the C20 in an equatorial position. This conformation agrees well with the observations of Archer *et al.*⁹ from NMR spectroscopy of Δ^9 -THC in solution. The angle between plane A and plane B is only 1.0°.

The cyclohexene ring also occurs in the half-chair conformation. Archer *et al.*⁹ have calculated this conformer of Δ^9 -THC to be 18.8 KJ/mol more stable than the half-boat form. The bond distances and angles agree very well with the electron diffraction results for cyclohexene,¹³ although the true two-fold axis through the centers of the C9–C10 and the C12–C13 bonds is distorted, with C12 0.206 Å below and C13 0.591 Å above plane C (Table 4).

The conformation of the pentyl side chain (See Fig. 2 and Table 3) is extended and gauche with respect to the C23–C24 bond. The thermal vibrations in this part of the molecule are very high and anisotropic, and the accuracy in the positions low. The thermal libration cause an apparent shortening of the C22–C23 and C24–C25 bond lengths. The plane through C4–C22–C23 is perpendicular to the aromatic ring (90.1°).

Crystal packing. The low density and high thermal parameters indicate weak intermolecular forces and an open packing of the molecules in the crystal. A packing diagram of the crystal structure is given in Fig. 3. This shows that the molecules are stacked in layers perpendicular to the *c*-axis. There are only van

Table 3. Selected dihedral angles (°) with estimated standard deviations. The angles are positive in a righthand screw.

Angle	(°)
C7–C2–O1–C14	14.9 (12)
C2–C7–C8–C9	140.1 (9)
C2–C7–C8–C13	16.6 (12)
C7–C8–C9–C10	–150.8 (10)
C13–C8–C9–C10	–25.6 (13)
C7–C8–C13–C12	–176.6 (8)
C7–C8–C13–C14	–48.9 (10)
C9–C8–C13–C12	56.0 (9)
C9–C10–C11–C12	–11.3 (15)
C10–C11–C12–C13	42.0 (12)
C11–C12–C13–C8	–66.4 (10)
C11–C12–C13–C14	167.2 (9)
C8–C13–C14–O1	60.8 (10)
C12–C13–C14–O1	–174.4 (7)
C2–O1–C14–C13	–44.9 (11)
C2–C3–C16–O18	–5.3 (17)
C4–C3–C16–O17	–1.4 (20)
C3–C4–C22–C23	90.1 (12)
C4–C22–C23–C24	177.5 (10)
C22–C23–C24–C25	–62.4 (30)
C23–C24–C25–C26	–168.8 (14)

Table 4. Deviations from least-squares planes (Å × 10³). The deviations for those atoms used to define the plane are given in italicized figures. Plane equations:

$$\begin{aligned} \text{A, } & (-0.0127x + 0.0208y - 0.1065z)R + 2.274 = 0 \\ \text{C, } & (0.0132x - 0.0129y - 0.1096z)R + 0.511 = 0 \\ \text{B, } & (-0.0119x + 0.0201y - 0.1082z)R + 2.272 = 0 \end{aligned}$$

Atom	Plane A	Plane B	Plane C
O1	<i>–1</i>	<i>–1</i>	1609
C2	<i>4</i>	<i>4</i>	
C3	<i>–24</i>	<i>2</i>	
C4	<i>22</i>		
C5	<i>2</i>		
C6	<i>–22</i>	<i>–42</i>	
C7	<i>18</i>	<i>–4</i>	693
C8	<i>46</i>	<i>2</i>	<i>1</i>
C9		868	<i>7</i>
C10		1460	<i>–20</i>
C11		1352	<i>6</i>
C12		326	<i>–206</i>
C13	<i>463</i>	<i>422</i>	591
C14	<i>–311</i>	<i>–332</i>	711
O15	<i>–96</i>		
C16	<i>–174</i>		
O17	<i>–278</i>		
O18	<i>–173</i>		
C19			<i>7</i>
C22	132		

Angle between: A and C, 37.7°; A and B, 1.0°; B and C, 36.7°.

der Waals forces between the layers, which are separated by *c*/2. As seen from the diagram, the side chain is located in a very open cave in the crystal. What apparently holds the molecules together, and is the reason for Δ^9 -THC Acid B to crystallize, is the intermolecular hydrogen bond network, going from the phenolic group in one molecule to the carboxylic group in the neighbour molecule [O15...O17 2.688(8) Å].

MOLECULAR STRUCTURE AND BIOLOGICAL ACTIVITY

As mentioned in the introduction the mode and site of action of Δ^9 -THC is still completely unknown. Several investigators have attempted to correlate the structure and hallucinogenic activity of compounds like Δ^9 -THC, LSD, and psilocybin, and drawn attention to the structural similarities of the molecules (see, *e.g.*,

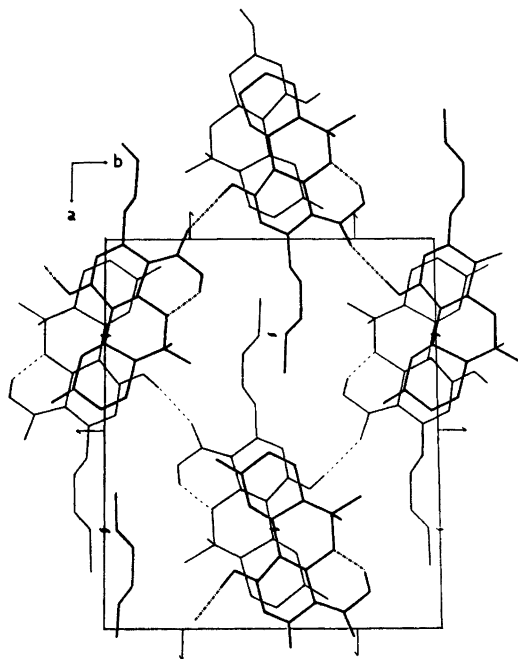


Fig. 3. Crystal packing in the unit cell, as seen along the *c*-axis.

Petrzilka^{13a} or Razdan and Pars^{13b}). However, the solubility properties of these drugs are quite different. While Δ^9 -THC is a hydrophobic molecule, the others are easily soluble in water. This will give a different distribution and adsorption to membranes and enzyme systems in the central nervous system. Also the entire pattern of effects of Δ^9 -THC is different from that of any other drugs, so another view¹⁴ is that cannabis should be regarded as unique.

If Δ^9 -THC is fixed by hydrogen bonds to a receptor there are only two possible sites for bond formation; the phenolic group and the pyran oxygen, and the distance between these is 4.76 Å. Other types of fixation might be π - π interaction with the C9-C10 double bond or the phenyl ring, or van der Waals forces.

As this work represents the first and only direct structure determination of the Δ^9 -THC skeleton, and the molecule is substituted and psychotomimetic inactive, it is not possible to draw any absolute conclusions on what is the active conformation for Δ^9 -THC. However, we want to point out that the effect of the carboxylic group on the rest of the molecule

is probably small. We believe therefore that this structure may also describe the Δ^9 -THC molecule well, and that the conformation of Δ^9 -THC Acid B in the crystal (maybe with exception of the side chain) is that relevant to the hallucinogenic activity of Δ^9 -THC.

Added in proof. Del Castillo *et al.* [*Nature (London)* 253 (1975) 365], draw attention to the similarities between Δ^9 -THC and thujone, the active principle of *Artemisia absinthium* and the liqueur absinthe. They propose that both drugs exert their psychotomimetic effects by interacting with a common receptor in the central nervous system.

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