

The Crystal and Molecular Structure at -165°C of the 1:1 Molecular Complex Formed by 8β -Hydroxy- Δ^9 -tetrahydrocannabinol and *N,N*-Dimethylformamide

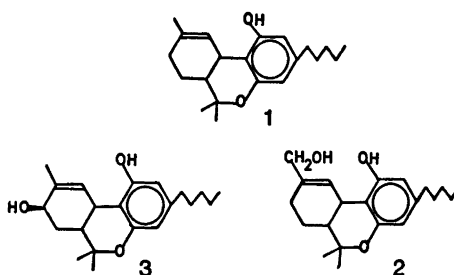
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The structure of the title compound $\text{C}_{21}\text{H}_{30}\text{O}_2 \cdot \text{C}_3\text{H}_7\text{NO}$ has been determined by X-ray methods using 2431 reflections collected by counter methods at -165°C . The complex crystallizes in the space group $P2_1$ with two formula units per unit cell. Cell dimensions at -165°C are: $a = 8.815(4) \text{ \AA}$; $b = 10.256(5) \text{ \AA}$; $c = 12.877(3) \text{ \AA}$; $\beta = 102.27(3)^{\circ}$. The structure model was refined to a conventional R of 0.047 and a weighted R_w of 0.045. The side chain shows a fully extended all-*anti* conformation and the cyclohexene and pyrane rings are in the half-chair conformation. The variations of the bond angles and deviations from planarity in the benzene ring, indicate strains in the aromatic system. The phenolic group is bent 0.126 \AA out of the plane of the benzene ring. The angle between this plane and a plane through the cyclohexene ring is 40.4° . Along the twofold axes run channels where the *N,N*-dimethylformamide molecules fit. The carbonylic group of the dimethylformamide molecules acts as acceptor for hydrogen bond [$2.733(3) \text{ \AA}$] from the 8β -hydroxylic group. The phenolic group acts as donor for another hydrogen bond [$2.701(3) \text{ \AA}$] along the a -axes to the 8β -hydroxylic group in a molecule one cell edge away.

The metabolism of Δ^9 -tetrahydrocannabinol (Δ^9 -THC) (1), the predominant active principle of marijuana, has been extensively investigated (for a review, see Mechoulam *et al.*)¹ The major pathway so far identified, is through hydroxylation of the C11 position to give 11-hydroxy- Δ^9 -THC (2). Another important metabolite, 8β -hydroxy- Δ^9 -THC (3) has been isolated

from incubation of Δ^9 -THC with rabbit liver homogenate.²



Both metabolites are biologically active in *Rhesus* monkeys and it has been suggested that these compounds are indeed the active forms of Δ^9 -THC on the molecular level.³

We have earlier studied the structure of the Δ^9 -THC skeleton in form of the psychotomically inactive Δ^9 -THC Acid B (THCAB).⁴ However, a fuller understanding of the activity of the cannabinoids requires more information than at the present is available. The effect of different environments on the conformation, and the mode of interaction between Δ^9 -THC and other molecules, are important topics to be investigated. Of particular interest would be a complex between a cannabinoid and a model molecule for the receptor. As 8β -hydroxy- Δ^9 -THC is an "active" molecule and also forms a stable 1:1 complex with *N,N*-dimethylformamide (DMF), we found this system well suited for a structural study.

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Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations. The anisotropic temperature factor is given by: $\exp\{-2\pi^2[u_{11}(a^*k)^2 + \dots + 2u_{23}(b^*c^*kl)]\}$.

Atom	x	y	z	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
O1	.5618(2)	.3397(0)	.7100(1)	.0144(10)	.0209(11)	.0177(10)	.0037(9)	.0022(8)	-.0016(9)
C2	.4275(3)	.4083(4)	.7103(2)	.0150(14)	.0186(15)	.0155(14)	.0020(13)	.0041(11)	.0029(13)
C3	.3021(2)	.3733(4)	.6298(2)	.0371(17)	.0289(17)	.0314(15)	-.0012(13)	.0099(13)	-.0013(13)
C4	.1597(3)	.4346(3)	.6233(2)	.0174(14)	.0201(16)	.0162(14)	-.0000(13)	.0035(11)	.0033(13)
C5	.1434(3)	.5270(4)	.6983(2)	.0139(14)	.0212(16)	.0171(14)	-.0021(12)	.0042(12)	.0019(12)
C6	.2691(3)	.5603(4)	.7788(2)	.0170(14)	.0189(16)	.0140(14)	-.0013(13)	.0067(11)	-.0010(12)
C7	.4176(3)	.5070(4)	.7836(2)	.0135(13)	.0186(16)	.0137(13)	-.0016(12)	.0046(11)	.0014(12)
C8	.5610(3)	.5466(4)	.8657(2)	.0119(13)	.0192(15)	.0142(13)	.0011(12)	.0026(11)	-.0004(12)
C9	.5826(3)	.6917(4)	.8851(2)	.0154(14)	.0235(16)	.0146(14)	.0037(13)	.0026(11)	-.0004(12)
C10	.7207(3)	.7491(4)	.9150(2)	.0183(15)	.0228(16)	.0190(15)	.0012(13)	.0040(11)	-.0019(13)
C11	.8716(3)	.6751(4)	.9285(2)	.0121(13)	.0279(19)	.0223(15)	.0012(13)	.0030(12)	-.0042(13)
C12	.8496(3)	.5274(4)	.9192(2)	.0143(14)	.0271(18)	.0192(15)	-.0021(13)	.0023(12)	-.0061(14)
C13	.7069(3)	.4921(4)	.8334(2)	.0114(13)	.0210(16)	.0136(13)	.0017(13)	-.0004(12)	-.0002(14)
C14	.6865(3)	.3484(4)	.8049(2)	.0172(14)	.0175(15)	.0169(14)	.0039(12)	.0034(11)	-.0005(12)
O15	.2840(2)	.6455(3)	.8574(2)	.0154(10)	.0257(12)	.0202(10)	.0050(12)	.0026(11)	.0024(13)
C16	.7356(4)	.8932(4)	.9386(3)	.0147(9)	.0275(19)	.0550(24)	.0011(9)	.0050(6)	-.0087(9)
O17	.9603(2)	.7234(3)	.8540(2)	.0172(16)	.0295(13)	.0233(11)	-.0029(15)	.0073(16)	-.0157(18)
C18	.6449(4)	.2636(4)	.8923(3)	.0340(18)	.0234(18)	.0245(17)	-.0002(10)	.0086(9)	-.0039(10)
C19	.8259(4)	.2914(4)	.7683(3)	.0214(16)	.0235(18)	.0283(17)	.0006(15)	.0053(15)	.0066(14)
C20	.0266(3)	.4039(4)	.5304(2)	.0168(14)	.0214(16)	.0204(16)	.0076(14)	.0060(14)	.0019(14)
C21	.0231(3)	.4942(4)	.4345(2)	.0184(14)	.0223(16)	.0204(16)	-.0044(13)	.0024(12)	-.0010(14)
C22	-.1174(3)	.4664(4)	.3455(2)	.0143(14)	.0233(16)	.0176(14)	-.0008(13)	.0021(12)	-.0001(13)
C23	-.1340(3)	.5585(4)	.2511(2)	.0219(15)	.0301(18)	.0202(15)	-.0012(13)	.0010(12)	.0020(13)
C24	-.2925(4)	.5423(5)	.1757(3)	.0259(18)	.0608(27)	.0205(16)	-.0009(15)	.0010(12)	.0017(15)
O25	.7377(2)	.7266(3)	.6508(2)	.0249(12)	.0847(18)	.0314(13)	.0024(19)	-.0003(14)	.0053(18)
C26	.6485(4)	.7543(4)	.6343(3)	.0344(19)	.0285(19)	.0253(18)	.0008(13)	.0067(10)	.0163(13)
N27	.5383(3)	.6918(3)	.5655(2)	.0241(14)	.0226(14)	.0236(13)	-.0019(12)	.0093(15)	.0105(16)
C28	.5746(5)	.5807(4)	.5058(3)	.0578(24)	.0238(19)	.0383(20)	.0010(18)	.0100(11)	.0050(12)
C29	.3761(4)	.7302(4)	.5508(3)	.0259(17)	.0341(21)	.0373(19)	-.0010(16)	.0075(15)	-.0033(17)
									.0074(17)

EXPERIMENTAL AND STRUCTURE DETERMINATION

Synthetic ⁵ 8 β -hydroxy- Δ^9 -THC was kindly supplied by Professor R. Mechoulam, Hebrew University, Jerusalem. Colourless prismatic crystals of the complex were formed by slow evaporation of a saturated solution of the compound in *N,N*-dimethylformamide.

Oscillation and Weissenberg diagrams indicated monoclinic symmetry. Systematic extinctions of the *0k0* reflections for *k* odd uniquely determined the space group to *P2*₁ for the optically active compound. A computer-controlled Syntex P1 four-circle diffractometer with graphite-monochromatized MoK α radiation and equipped with a modified Enraf-Nonius liquid nitrogen cooling device was utilized for preliminary experiments and for the measurement of diffraction intensities. The work was carried out using a crystal of dimensions 0.3 \times 0.3 \times 0.1 mm.

Unit cell parameters were determined by a least-squares treatment of the angular coordinates of 15 symmetry independent reflections with 2θ -values from 22 to 45°. The temperature at the crystal site was -165 °C.

Three-dimensional intensity data were recorded using the ω - 2θ -scanning mode, with scan speed variable from 2-12° min⁻¹, depending on the peak intensity of the reflections. Background counting time was equal to 0.35 \times scan time on each side of the scan area. Reflections with 2θ -values larger than 45° which had integrated counts of less than 5 cps, determined in a 2 s scan over the reflections, were not measured.

The variations in the intensities of three standard reflections which were remeasured after every sixty reflections were random. Accordingly no corrections were applied to the intensity data for these variations.

The estimated standard deviations were taken as the square root of the total counts with a 2% addition for experimental uncertainties. Of the 2793 symmetry-independent reflections measured ($2\theta_{\max} = 60^\circ$), 2431 had intensities larger than twice their standard deviations. These were regarded as "observed" reflections, and the remaining were excluded from further calculations. The intensities were corrected for Lorentz and polarization effects. The computer programs utilized in all calculations are part of a local assembly of programs for CYBER-74 described in Ref. 6.

Atomic form factors used were those of Doyle and Turner⁷ for oxygen, carbon and nitrogen and those of Stewart *et al.*⁸ for hydrogen.

The phase problem was solved by the MULTAN⁹ program assembly. The structure model was refined with isotropic thermal parameters to a conventional *R* of 0.11. Introduction of anisotropic thermal parameters and least-squares refinement yielded an *R* of

Atom	x	y	z	B	Atom	x	y	z	B
H31	.312(6)	.289(6)	.567(4)	4.4(14)	H51	.034(5)	.563(5)	.700(4)	2.7(12)
H81	.562(5)	.501(5)	.941(3)	1.2(9)	H91	.488(6)	.743(6)	.878(4)	3.6(13)
H111	.939(5)	.700(5)	1.003(4)	2.4(12)	H121	.953(5)	.490(5)	.901(4)	2.2(11)
H122	.843(6)	.485(6)	.992(4)	4.0(14)	H131	.721(5)	.540(5)	.764(4)	2.2(11)
H151	.144(7)	.661(7)	.847(5)	6.7(16)	H161	.631(6)	.954(6)	.918(4)	3.4(14)
H162	.807(5)	.926(5)	.893(3)	1.9(11)	H163	.785(7)	.928(7)	1.019(5)	6.6(16)
H171	.898(7)	.758(7)	.793(5)	9.0(18)	H181	.536(8)	.280(7)	.915(5)	7.1(17)
H182	.643(6)	.165(5)	.871(3)	1.4(10)	H183	.737(6)	.271(5)	.954(4)	3.7(13)
H191	.802(5)	.193(6)	.730(4)	3.0(12)	H192	.922(7)	.281(6)	.824(5)	4.3(15)
H193	.857(5)	.348(5)	.716(4)	1.7(11)	H201	—	.407(5)	.554(3)	1.1(10)
H202	.036(6)	.301(5)	.515(4)	2.8(12)	H211	.205(6)	.596(5)	.462(4)	2.6(13)
H212	.125(5)	.477(5)	.404(4)	2.8(11)	H221	—	.478(5)	.382(4)	2.0(11)
H222	.113(6)	.372(6)	.323(4)	4.5(14)	H231	—	.657(5)	.282(4)	2.8(12)
H232	—	.044(5)	.209(4)	3.2(12)	H241	—	.446(7)	.146(5)	6.4(16)
H242	—	.308(7)	.605(7)	6.4(15)	H243	—	.562(6)	.217(5)	5.5(16)
H261	.601(6)	.832(6)	.674(4)	4.2(13)	H281	—	.725(7)	.521(5)	5.8(17)
H282	.521(6)	.593(6)	.424(4)	3.5(12)	H283	—	.521(7)	.520(6)	7.1(18)
H291	.336(7)	.757(7)	.463(5)	6.9(17)	H292	—	.311(7)	.556(5)	7.5(16)
H293	.375(6)	.814(6)	.599(4)	2.7(13)					

0.08. At this point a difference Fourier map was calculated and all the 37 hydrogen atoms were found in the map. These were included in the calculations. Full-matrix least-squares refinement of all positional and anisotropic thermal parameters for the non-hydrogen atoms and isotropic thermal parameters for the hydrogen atoms, resulted in a conventional R of 0.047 and a weighted R_w of 0.045.

Atomic parameters are listed in Table 1. 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.

CRYSTAL DATA

1:1 8β -Hydroxy- Δ^9 -tetrahydrocannabinol N,N -dimethylformamide $C_{24}H_{37}NO_4$, $M = 403.5$ amu, space group: $P2_1$, cell dimensions at -165°C : $a = 8.815(4)$ Å, $b = 10.256(5)$ Å, $c = 12.877(3)$ Å, $\beta = 102.27(3)^\circ$, $V = 1137.5(8)$ Å³, $Z = 2$, $D_{\text{calc}} = 1.178$ gcm⁻³, $F(000) = 440$.

DISCUSSION

The observed molecular geometries and intramolecular distances and angles are shown in Fig. 1, together with the atomic labels used in this study. Selected dihedral angles are presented in Table 2. Compared to the structure determination of THCAB,⁴ the standard deviations of the present study are improved by a factor of approximately three.

With the exception of the side chain, the bond angles, distances and conformation are close to the corresponding values in THCAB, and may all be regarded as normal values.

The influence on the conformation of the cyclohexene ring from the hydroxyl-substituent seems to be small, but significant. The dihedral angle C9-C10-C11-C12 has changed from -11.3 (15) $^\circ$ in THCAB to -7.6 (4) $^\circ$ in this structure, which gives a more distorted half-chair conformation, with C12 0.14 Å below and C13 0.61 Å above plane C (Table 3). The corresponding values in THCAB are 0.21 and 0.59 Å. The conformation of the pyran ring is also half-chair, with C13 0.41 Å above and C14 0.38 Å below a least-squares plane through O1, C2, C7, C8 (plane B, Table 3). The main

Table 2. Selected dihedral angles ($^\circ$) with estimated standard deviations. The angles are positive in a righthand screw.

Angle	($^\circ$)
C7-C2-O1-C14	15.4(4)
C2-C7-C8-C9	138.2(3)
C2-C7-C8-C13	15.1(4)
C7-C8-C9-C10	-150.3(3)
C13-C8-C9-C10	-26.7(4)
C7-C8-C13-C12	-177.5(2)
C7-C8-C13-C14	-48.6(3)
C9-C8-C13-C12	55.3(3)
C9-C10-C11-C12	-7.6(4)
C10-C11-C12-C13	37.7(4)
C11-C12-C13-C8	-63.0(3)
C11-C12-C13-C14	171.0(2)
C8-C13-C14-O1	65.0(3)
C12-C13-C14-O1	-170.0(2)
C2-O1-C14-C13	-47.8(3)
C8-C7-C6-O15	-4.5(4)
C3-C4-C20-C21	-90.0(3)
C4-C20-C21-C22	-176.7(2)
C20-C21-C22-C23	176.0(3)
C21-C22-C23-C24	-168.9(3)
C16-C10-C11-O17	-63.1(3)
O25-C26-N27-C28	1.9(5)
O25-C26-N27-C29	179.7(3)

Table 3. Deviations from least-squares planes ($\text{Å} \times 10^3$). The deviations for those atoms used to define the plane are marked with an asterisk.*

Atom	Plane A	Plane B	Plane C
O1	69	4*	-1667
C2	22*	-9*	
C3	9*	-75	
C4	-25*		
C5	5*		
C6	28*	103	
C7	-40*	9*	-697
C8	-109	-4*	4*
C9	-1071	-898	-10*
C10	-1697		10*
C11	-1547		-4*
C12	-478		143
C13	-474	-415	-613
C14	397	381	-718
O15	126		
C16			64
O17			-1202
C18	1896		
C19	34	-30	
C20	-138		

* Angle between: A and C, 40.4 $^\circ$; A and B, 3.3 $^\circ$; B and C, 37.1 $^\circ$.

differences in geometry between the pyran rings in the two structures, are the opening of the C7–C2–O1 angle from 118.7 (7)° in THCAB to 123.2 (3)° in this structure and the closing of the C2–O1–C14 angle from 122.3 (7)° in THCAB to 117.4 (3)° in this structure. The dihedral angle C8–C13–C14–O1, which was calculated (Westheimer calculations) by Archer *et al.*¹⁰ to be 56° in Δ^8 -THC, is here 65.0(3) and in THCAB 60.8 (10)°. The differences may be explained by the effects of the intramolecular hydrogen bond to the pyran oxygen in THCAB. As in THCAB, the variations of the bond angles and the deviation from planarity in the benzene ring (Plane A), indicate strains in the aromatic system. The phenolic group (O15) is bent 0.126 Å out of the plane of the benzene ring and away from the C9 proton, which is situated only 2.25 Å away from O15. The dihedral angle C8–C7–C6–O15 is –4.5°, and the C9–H91···O15 angle is 121°.

In this low temperature determination the atomic positions in the pentyl side chain are fixed with low thermal vibrations and normal C(*sp*³)–C(*sp*³) single bond distances and angles. From the crystal structures of the cannabinoids hitherto studied: THCAB,⁴ cannabicyclol,¹¹ cannabinol,¹² cannabidiol,¹³ we do not find any preferred side chain conformation. In this structure there is a fully extended all-*anti* conformation. Compared to THCAB there is a rotation of 180° around the C4–C20 bond, and the side chain is on the same side of plane A as the cyclohexene ring (see Fig. 1). Structure activity relationship studies have shown that changes in the side chain are of importance for the psychotomimetic activity. For example, cannabinoids with a dimethylheptyl side chain are considerably more active than those with a pentyl side chain.¹⁴ There is therefore good evidence for the assumption that the side chain is involved in a stereospecific interaction with a hydrophobic part of the receptor. Exactly in what way the 8β -OH- Δ^8 -THC molecule will interact with a receptor is not possible to predict, but if we imagine the DMF-molecule as a part of the binding site, we suggest that this complex may represent the mutual orientation of the molecules also in a cell membrane.

As seen from Fig. 1 and the packing diagram

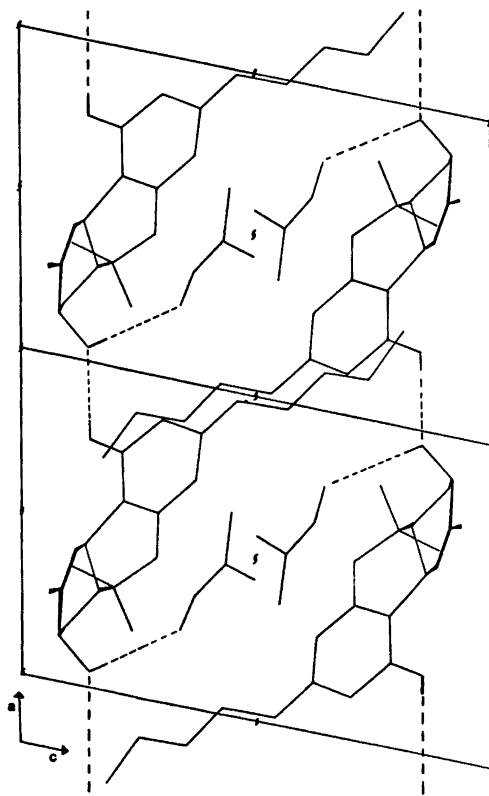


Fig. 2. The crystal structure of the complex as viewed along the *b*-axis.

in Fig. 2, the 8β -OH- Δ^8 -THC and the DMF molecules are kept together by hydrogen bonds from the β -hydroxylic group to the carbonylic oxygen in DMF. The O17···O25 distance is 2.733(3) Å and the O17–H171···O25 angle is 146.9°.

The 8β -OH- Δ^8 -THC molecules are also linked together by hydrogen bonds along the *a*-axis with the phenolic group in one molecule as hydrogen donor and the 8β -hydroxylic oxygen in another as acceptor. The O15···O17 distance is 2.701(3) Å and the angle O15–H151···O17 is 163.7°.

Between the columns of 8β -OH- Δ^8 -THC molecules are channels running along the two-fold axis, into which the DMF molecules fit. These are very nearly planar with no atoms more than 0.01 Å out of the least-squares plane through the heavy atoms. Bond angles and distances agree well with the values observed

in a nitramin.DMF complex studied by Cobble-dick and Small.¹⁵

There are only van der Waals contacts between the DMF molecules.

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