Structural Studies of Cannabinoids. A Theoretical and Proton Magnetic Resonance Analysis

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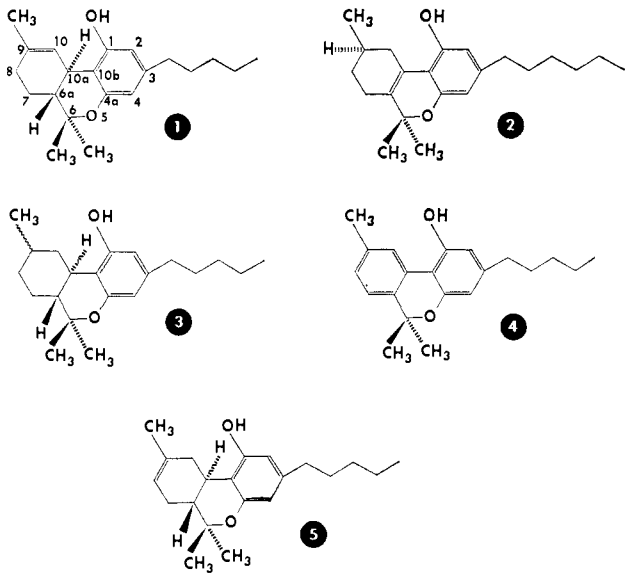
Abstract: A conformational analysis of the major active constituent of marijuana and its analogs is described. From Westheimer and extended Hückel molecular orbital calculations, structures and energies are obtained for *l*-Δ^9-tetrahydrocannabinol (THC) (**1**), $\Delta^{6a(10a)}$-THC (**2**), hexahydrocannabinol (HHC) (**3**), and cannabinol (**4**). Conclusions reached on the basis of these studies, concerning the conformation of the pyran ring, the preferred orientation of the phenolic O–H bond, and ring C conformational preferences in **1**, **2**, **3**, and Δ^8-THC (**5**), are in substantial agreement with pmr observations resulting from nuclear Overhauser effect and solvent effect studies.

The natural products of *Cannabis sativa* L.[2] have been the subject of chemical, pharmacological, and clinical investigations for many years. However, the major psychotomimetic[3] principle has been isolated only recently and further investigations have elucidated its structure as *l*-Δ^9-tetrahydrocannabinol (Δ^9-THC).[4] These advances have been partially responsible for an increased interest in the chemistry and pharmacology of cannabinoids. Nevertheless, despite many pharmacological and biochemical investigations, the mode and site of action of the cannabinoids remain obscure. This is not to say that attention has not been given to these very problems. Indeed, with regard to the psychotomimetic activity of cannabinoids, a great deal of structure–activity information has been collected[5] over the years, and empirical correlations from these data have been inferred. However, a fuller understanding of the activity of cannabinoids requires more information than is presently available. In many instances, a precise knowledge of the electronic and conformational features of a molecule can provide an insight into its biological mode of action. Since this type of data had not been collected for this important class of compounds, we decided to turn our attention to some of the more prominent members of the cannabinoids with the ultimate hope of obtaining structural information which would, in future studies, lead to a better understanding of the activity of these compounds.

Specifically, *l*-Δ^9-THC (**1**), $\Delta^{6a(10a)}$-THC (**2**), hexahydrocannabinol (HHC) (**3**), cannabinol (**4**), and Δ^8-THC (**5**) were chosen as representing varying structural types for this study.[6] As a first approach, detailed



information on the nuclear geometries (bond lengths and angles) for **1**–**4** were determined by classical Westheimer calculations.[7] The electronic structures followed from extended Hückel molecular orbital calculations[8–10] on the optimized geometries. The utility of these two types of calculation for elucidating structural and conformational problems has been established.[9,11–14] As a second approach, a proton magnetic resonance (pmr) study of compounds **1**, **2**, **3**, and **5** was undertaken, extensive use being made of nuclear Overhauser effect[15] (NOE) and pyridine solvent shift[16]

(1) (a) The Lilly Research Laboratories; (b) University of Georgia; (c) authors to whom correspondence should be addressed.

(2) For a recent review of the chemistry of the natural products of marijuana (hashish), see R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Org. Naturst.*, **25**, 175 (1967).

(3) For a definition of psychotomimetic and a discussion of drugs with this property, including the cannabinoids, see A. Hofmann in "Drugs Affecting the Central Nervous System," Vol. 2, A. Burger, Ed., Marcel Dekker, Inc., New York, N. Y., 1968, p 169.

(4) (a) Y. Gaoni and R. Mechoulam, *J. Amer. Chem. Soc.*, **86**, 1646 (1964); (b) R. Mechoulam and Y. Gaoni, *Tetrahedron Lett.*, 1109 (1967); (c) Y. Gaoni and R. Mechoulam, *Tetrahedron*, **22**, 1481 (1966).

(5) For a recent compilation of structure–activity relationships, see H. Isbell, Proceedings of the Meeting of the Committee on the Problems of Drug Dependence, National Academy of Sciences–National Research Council, Washington, D. C., 1968, Addendum 1.

(6) The numbering system used is that of dibenzo[*b*,*d*]pyran. α and β faces are designated by dotted and solid lines, respectively. Ring A corresponds to the phenolic ring, ring B to the pyran ring, and ring C to the remaining ring.

(7) F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 523.

(8) R. Hoffmann and W. N. Lipscomb, *J. Chem. Phys.*, **36**, 2179, 3489 (1962).

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(10) D. B. Boyd and W. N. Lipscomb, *J. Theor. Biol.*, **25**, 403 (1969).

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(12) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *ibid.*, **90**, 5773 (1968).

(13) N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van-Catledge, *ibid.*, **90**, 1199 (1968).

(14) N. L. Allinger, M. A. Miller, F. A. Van-Catledge, and J. A. Hirsch, *ibid.*, **89**, 4345 (1967).

(15) F. A. L. Anet and A. J. Bourn, *ibid*, **87**, 5250 (1965).

(16) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *ibid.*, **90**, 548 (1968).

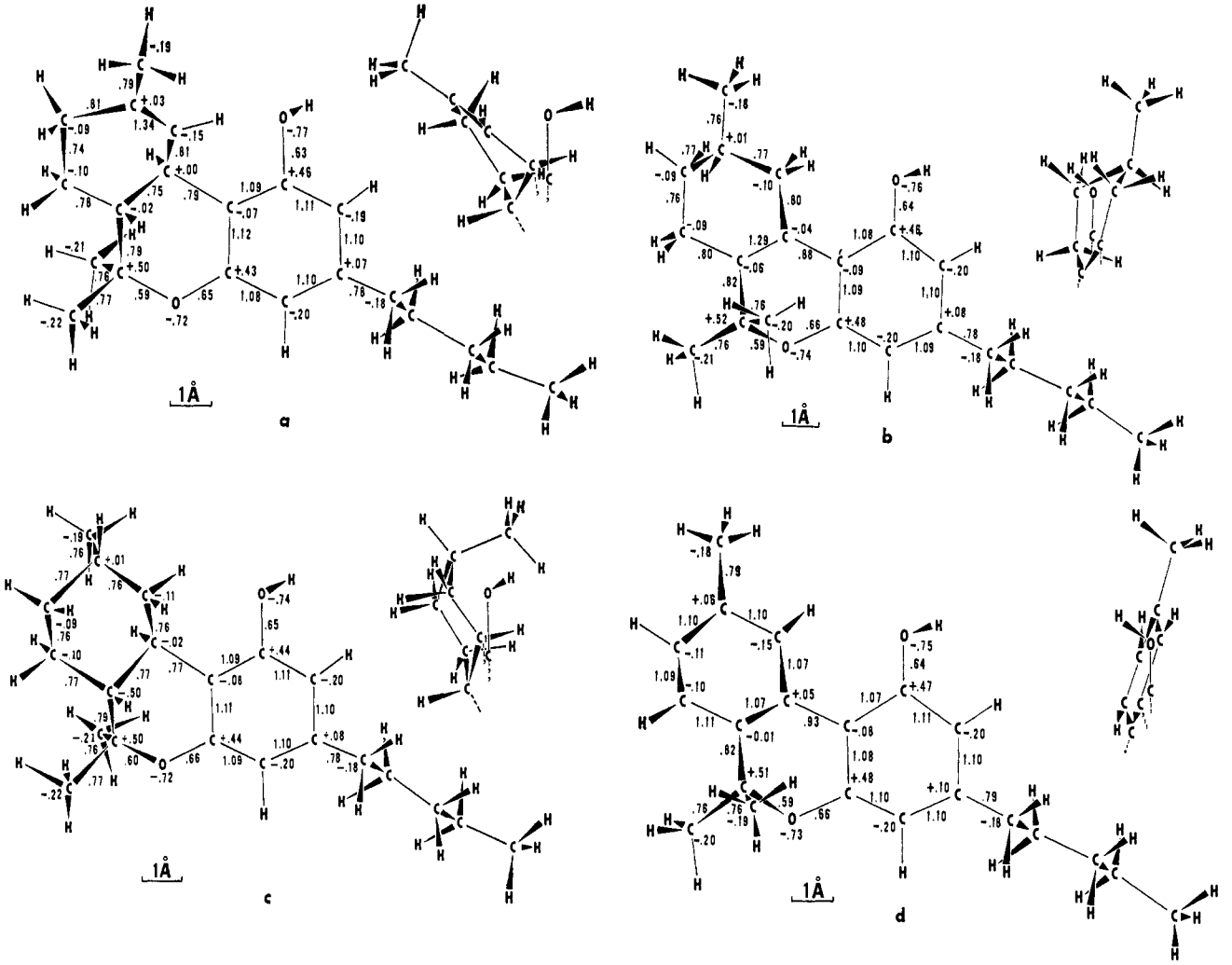

Figure 1. Conformations and charge distributions of (a) Δ^9-THC, (b) $\Delta^{6a(10a)}$-THC, (c) HHC, and (d) cannabinol. The complete structures show the atoms as viewed normal to the plane through C_2, C_3, C_4. The perspectives of the C rings are viewed in the direction parallel to the vector from C_2 to C_{10b}. Net atomic charges are given as signed numbers and overlap populations between atoms as unsigned numbers.

techniques, in order to obtain experimental evidence in support of conformational proposals made on the basis of the theoretical studies described below.

Calculational Methods and Results

Westheimer calculations on Δ^9-THC, $\Delta^{6a(10a)}$-THC, HHC, and cannabinol entails minimizing the steric energy in each of these molecules as expressed by a sum of bending, torsion, stretching, and van der Waals energies. Starting geometries were based on standard[17] bond lengths and angles using conformations which appeared to be most stable on the basis of molecular models. Subsequent pmr studies, which are discussed in the next section, verified these conformational assumptions.

The necessary parameters and details of the Westheimer method have been discussed previously.[11-14] The only important modification introduced in the present work is the inclusion of the effects of the lone pair electrons on the heteroatoms, in this case, oxygen. van der Waals properties, which will be published in detail later, had to be assigned to the lone pairs on these atoms in order to fit experimental data available on heterocyclic systems.[18,19] Since the cannabinoids are large molecules and much computer time is involved in the optimization of their geometries, the calculations were terminated when the rate of improvement in the energies became very small. It is estimated that the resultant bond lengths are accurate to within 0.02 Å, and the bond angles to within 2°.

Using optimized geometries from the Westheimer calculations, charge distributions in Δ^9-THC, $\Delta^{6a(10a)}$-THC, HHC, and cannabinol were obtained by extended Hückel molecular orbital calculations, employing previously described parameters.[10,20,21] The conformation of these molecules is depicted in Figure 1, where the atoms are located at their final, optimized positions. Also shown are the results of the molecular orbital calculations. The Mulliken population analysis results are given only for the nonhydrogenic atoms[20] and were computed for the 3-methyl derivatives, rather

(17) "Tables of Interatomic Distances and Configuration in Molecules and Ions," Special Publication No. 11, The Chemical Society, London, 1958; Special Publication No. 18, 1965.

(18) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, 90, 3444 (1968).

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(21) R. Hoffmann, D. B. Boyd, and S. Z. Goldberg, *ibid.*, 92, 3929 (1970).

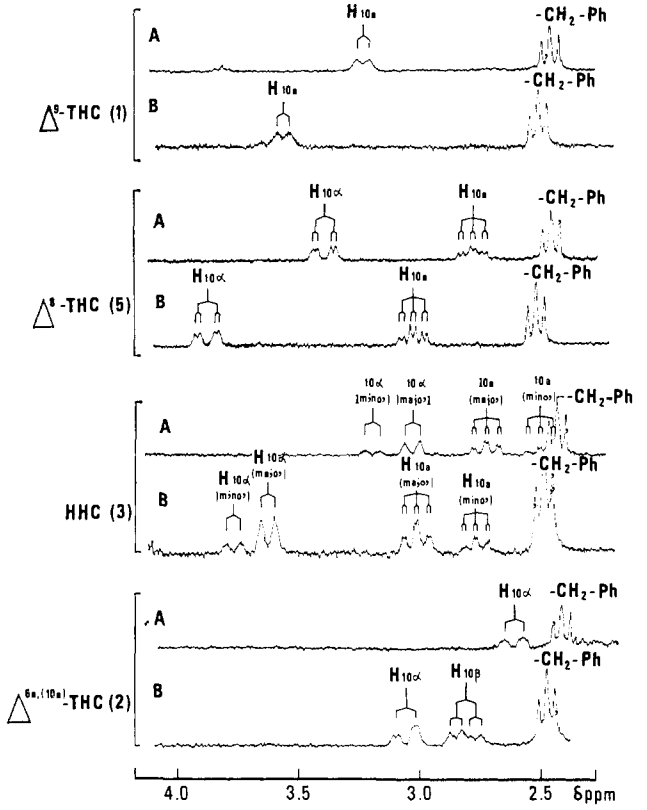

Figure 2. Partial 220-MHz spectra (δ 2.5–4.0 region) of **1**, **2**, **3**, and **5** in $CDCl_3$ (A) and C_5D_5N (B) solvents.

than the 3-*n*-amyl analogs as depicted, in order to conserve computer time. On the other hand, in the Westheimer calculations, the *n*-amyl side chain was included in an extended, all-staggered conformation[14] as shown in Figure 1.

We next discuss specific conformational features of each of the molecules. In Δ^9-THC and HHC, ring B conformation is determined by the interaction between the C_6 methyl groups and H_{6a}. Thus, ring B is assumed to adopt a conformation in which the axial C_6 methyl group is on the same side of the molecule (α side) as H_{10a}, so that the substituents on C_6 and C_{6a} are staggered with respect to each other (optimized C_{10a}–C_{6a}–C_6–O_5 dihedral angle is 56° in Δ^9-THC). This configuration puts one C_6 methyl group in much closer proximity to H_{10a} than the other, as seen in Figure 1. On the other hand, in $\Delta^{6a(10a)}$-THC there are no protons at C_{6a} and C_{10a}, and here ring B conformation would appear to be determined by the steric interaction between the C_{10} protons and the phenolic hydroxyl group. This interaction is reduced (on the basis of Dreiding models) if ring B assumes the other possible conformation, *i.e.*, with the C_6 β-methyl axial. If ring B of $\Delta^{6a(10a)}$-THC were to have the same conformation as in Δ^9-THC, HHC (and presumably Δ^8-THC), then $H_{10\alpha}$ would be much closer to the hydroxyl function than $H_{10\beta}$. In fact, pmr results suggest that both protons are approximately equidistant from the OH group as would be the case if ring B conformation is as described above.[22] The ring B conformation of $\Delta^{6a(10a)}$-THC was also employed in the computations on cannabinol, although here the almost planar nature of ring C makes the choice arbitrary, and, no doubt, both conformers would be present to an equal extent in solution.

The cyclohexene ring (ring C) of the tetrahydrocannabinols is expected to exist predominantly in a half-chair conformation.[12,23,24] In Δ^9-THC, Westheimer calculations indicate that the half-chair conformation is about 4.5 kcal/mol more stable than the boat form. This figure is consistent with the steric energy difference of 4.3 kcal/mol for the two forms of unsubstituted cyclohexene.[12] The difference in the sum (over all electrons) of the eigenvalues from extended Hückel calculations on Δ^9-THC also yields a comparable value of 3.3 kcal/mol.

The number of conformational possibilities in HHC is quite large. However, the cyclohexene ring was assumed to be in a chair form as subsequently confirmed by the pmr results. Although a methyl group on a cyclohexane ring is expected to be about 2 kcal/mol more stable in an equatorial *vs.* axial position,[12,14] the synthetic route to HHC gives predominantly the axial isomer, as deduced from pmr results. Consequently, only the calculations on this form of HHC are reported. In $\Delta^{6a(10a)}$-THC, the C_9 methyl was assumed to be equatorial for the calculations, and this assumption was also verified by the pmr data.

In all four cannabinoids studied by the calculational techniques, the C_1 hydroxyl group is subject to steric interaction with the C_{10} proton(s). This interaction causes the O_1–C_1–C_{10b} bond angle to open slightly (122–124°), the hydroxyl oxygen to bend out of the plane of the benzene ring (0.04–0.13 Å), and the C_{10} proton(s) to be similarly distorted. The shortest resulting O_1–H_{10} distances are about 2.3 Å. Also, in all four cannabinoids the hydroxyl proton optimizes at a position away from ring C with C_2–C_1–O_1–H dihedral angles in the range 30–50°.

Having discussed geometries which appear to be most stable on the basis of calculations on the unsolvated molecules and are consistent with the solution phase pmr data, we conclude this section by mentioning other structural and energetic features of the cannabinoids. All optimized bond lengths are within 0.02 Å of the following values: C_{sp^2}–C_{sp^2} (aromatic) 1.40 Å; C_{sp^2}–C_{sp^2} (olefinic) 1.33; C_{sp^2}–C_{sp^3} 1.51; C_{sp^3}–C_{sp^3} 1.53; C_{sp^2}–O 1.39; C_{sp^3}–O 1.41; C_{sp^2}–H 1.09; C_{sp^3}–H 1.10; and O–H 0.95. The only exception to these average values is the C_{10a}–C_{10b} bond in $\Delta^{6a(10a)}$-THC which is 1.47 Å. This distance is quite similar to that found between the rings in gas phase diphenyl (1.48 Å).[25] The C_{4a}–C_{10b}–C_{10a}–C_{6a} dihedral angle is 19° in $\Delta^{6a(10a)}$-THC. The corresponding dihedral angle is also 19° in Δ^9-THC, but is 13° in cannabinol. Delocalization over the C_{10b}–C_{10a} bond in cannabinol (where this bond distance is 1.41 Å), and to a lesser extent in $\Delta^{6a(10a)}$-THC, is reflected in the overlap populations for this bond (Figure 1). Based on the Westheimer calcula-

(22) These statements pertain to the enantiomorph as depicted in Figure 1b. The other enantiomorph can have a ring B conformation as in Δ^9-THC and still have the C_{10} protons equidistant from the phenolic OH group. The choice of the enantiomorph to use in the Westheimer calculations was arbitrary because both would have the same energy, and the sample of $\Delta^{6a(10a)}$-THC used in our pmr studies was racemic.

(23) F. R. Jensen and C. H. Bushweller, *J. Amer. Chem. Soc.*, **91**, 5774 (1969).

(24) J. F. Chiang and S. H. Bauer, *ibid.*, **91**, 1898 (1969).

(25) O. Bastiansen, *Acta Chem. Scand.*, **3**, 408 (1949); see also T. Nakamura, S. Kwun, and H. Eyring in "Molecular Orbitals in Chemistry, Physics and Biology," P.-O. Löwdin and B. Pullman, Ed., Academic Press, New York, N. Y., 1964, p 421.

Table I. Pmr Data[a] for Cannabinoids **1**, **2**, **3** and **5**

Resonance		Δ⁹-THC (1)	Δ⁸-THC (5)	HHC (3)	Δ⁶ᵃ⁽¹⁰ᵃ⁾-THC (2)
OH	δ[b]	(4.87) s	(4.81) s		(4.85) s
		[4.85] br s	[4.90] br s		[4.88] br s
H_2	δ	(6.15) [6.69] d	(6.11) [6.69] d	(6.09) [6.66] d	(6.12) [6.74] d
	J[c]	1.8	1.8	1.8	1.8
	Δ[d]	−0.54	−0.58	−0.57	−0.62
H_4	δ	(6.29) [6.57] d	(6.30) [6.57] d	(6.26) [6.57] d	(6.31) [6.62] d
	J	1.8	1.8	1.8	1.8
	Δ	−0.28	−0.27	−0.31	−0.31
6β-CH_3	δ	(1.41) [1.43] s	(1.37) [1.41] s	(1.35) [1.41] s	(1.40) [1.52] s
	Δ	−0.02	−0.04	−0.06	−0.12
6α-CH_3	δ	(1.09) [1.11] s	(1.09) [1.13] s	(1.08) [1.15 s]	(1.20) [1.36] s
	Δ	−0.02	−0.04	−0.07	−0.16
H_8	δ		(5.45) [5.45] br s		
	Δ		0.00		
9-CH_3	δ	(1.69) [1.69] br s	(1.70) [1.69] br s	(1.12) [1.16] d	(1.00) [0.98] d
	J			7.4	6.7
	Δ	0.00	+0.01	−0.04	+0.02
H_{10}	δ	(6.33) [7.06] t			
	J	1.7			
	Δ	−0.73			
$H_{10\beta}$	δ				(2.44) [2.79] dd
	J				17.5, 9.2
	Δ				−0.35
$H_{10\alpha}$	δ		(3.22) [3.83] d d	(2.89) [3.60] d t	(2.67) [3.11] d d
	J		17.0, 4.0	13.5, 3.5, 3.5	17.5, 4.0
	Δ		−0.61	−0.71	−0.44
H_{10a}	δ	(3.22) [3.55] br d	(2.70) [2.99] t d	(2.56) [2.99] t d	
	J	10.9	10.5, 10.5, 5.0	10.5, 10.5, 3.5	
	Δ	−0.33	−0.29	−0.43	
$PhCH_2$–	δ	(2.46) [2.50] t	(2.45) [2.50] t	(2.43) [2.48] t	(2.42) [2.48] t
	J	7.8	7.8	7.8	7.8
	Δ	−0.04	−0.05	−0.05	−0.06
$Ph(CH_2)_nCH_3$	δ	(0.89) [0.76] t	(0.87) [0.77] t	(0.87) [0.75] t	(0.85) [0.79] t
	J	6.0	6.0	6.0	6.0
	Δ	+0.13	+0.10	+0.12	+0.06

[a] Abbreviations used are as follows: s = singlet; d = doublet; t = triplet; q = quartet; d d = doublet of doublets; d t = doublet of triplets; br = broad. [b] Chemical shift values (δ) recorded in parentheses and brackets correspond to shifts measured in $CDCl_3$ and C_5D_5N solutions, respectively. All shifts were obtained at 220 MHz and were measured relative to TMS as internal reference. Sample concentrations were maintained at 5 ± 1% w/v in all cases. [c] Coupling constants are in hertz. [d] $\Delta = \delta_{CDCl_3} - \delta_{C_5D_5N}$.

tions, the five-carbon side chain attached to ring A of the cannabinoids has no significant distorting effect on ring A. In cannabinol, both aromatic rings have very similar geometries, suggesting two possible modes for this molecule to bind to a hydrophobic and electrophilic biological surface. One final observation is that $\Delta^{6a(10a)}$-THC is more stable than Δ^9-THC as computed by both the Westheimer (17.6 kcal/mol) and extended Hückel (25.2 kcal/mol) methods. Although $\Delta^{6a(10a)}$-THC does not exist naturally, these relative stabilities are consistent with limited experimental data on these two isomers.[4c]

Pmr Study. Table I summarizes the recorded pmr data and Figure 2 the partial 220-MHz spectra of compounds **1**, **2**, **3**, and **5**. Signal assignments for different protons in these systems, initially made on the basis of recorded signal multiplicities at 220 MHz, were confirmed by spin–decoupling and nuclear Overhauser experiments at 100 MHz. Comparison of spectral regions δ 2.3–4.0 in the deuteriochloroform and pyridine-d_5 spectra reveals considerable differences which allow ready characterization of these compounds.

The partial spectrum of Δ^9-THC (**1**) (Figure 2) reveals the presence of only a one-proton broad doublet which, because of its coupling (J = 10.9 Hz) and chemical shift position (δ_{CDCl_3} 3.22 and $\delta_{C_5D_5N}$ 3.55), is assigned to H_{10a}. The large 10.9-Hz splitting in this signal, which originates from *trans*-diaxial coupling to H_{6a}, is confirmed by observing the collapse of this signal, to a broad singlet, upon application of a secondary radio-frequency field at δ 1.62, the approximate resonance position of H_{6a}. Smaller unresolved splittings, which cause broadening of the C_{10a} doublet, originate from homoallylic coupling[26] to both the C_8 methylene and C_9 methyl protons.

In the partial spectra of Δ^8-THC (**5**), two proton signals are observed: a triplet of doublets (J = 10.9 and 5.0 Hz) centered at δ 2.70 and 3.02 and a doublet of doublets (J = 17.0 and 4.5 Hz) centered at 3.22 and 3.83 in their deuteriochloroform and pyridine-d_5 spectra, respectively. The former signal is assigned to H_{10a} since this proton is located *trans* diaxial to two protons, namely H_{6a} and $H_{10\beta}$ axial (and is therefore expected to give rise to a triplet with coupling in the order of 9–11 Hz[27]), and axial–equatorial to $H_{10\alpha}$ equatorial (and is therefore expected to give rise to further small splitting (2–5 Hz[27]) of each of the triplet lines). The latter doublet of doublet signal, formerly misassigned[4c,28,29] to H_{10a}, is herein correctly assigned to $H_{10\alpha}$ equatorial

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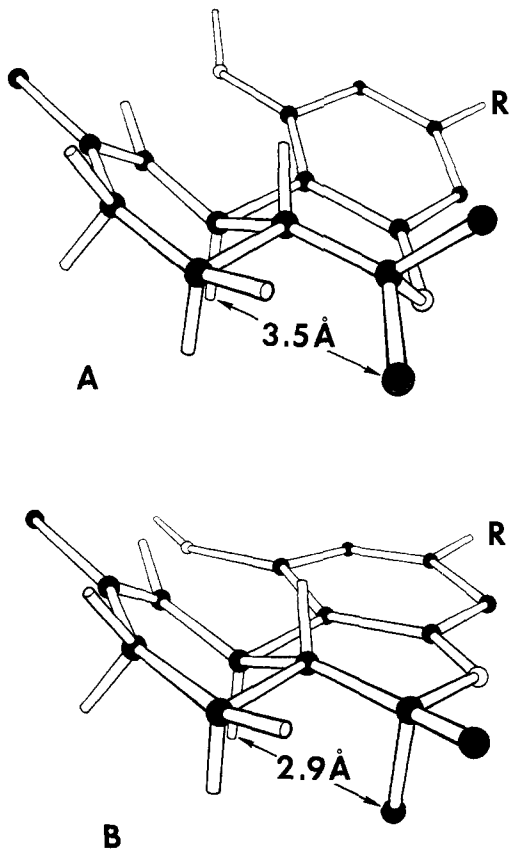

Figure 3. Possible conformations for ring B in Δ^9-THC. The internuclear distance between the 6α-methyl and H_{10a} in conformation A was obtained from measurement on Dreiding models; the corresponding distance in conformation B was derived from Westheimer calculations.

since this signal displays the requisite coupling to only only *two* protons (in contrast to three couplings necessary for H_{10a}), one of geminal (J = 17.0 Hz) and the other of vicinal magnitude (J = 4.5 Hz). The fact that saturation of the signal attributed to H_{10a} results in the collapse, to a sharp doublet (J = 17.0 Hz), of the double doublet assigned to $H_{10\alpha}$ equatorial, while reverse saturation results in the collapse of H_{10a} to a simple triplet (J = 10.9 Hz), further confirms these assignments.

The partial spectrum of HHC (**3**) clearly indicates that it is a mixture of C_9 axial and equatorial methyl isomers in the approximate ratio of 3:1. As in the previous example (**5**), the triplet of doublet signals are assigned to the tertiary C_{10a} proton. Since protons oriented 1,3-diaxial to methyl groups are deshielded[30] relative to protons in an environment where such interactions are absent, the lower field triplet of doublets signal of the major isomer in both deuteriochloroform (δ 2.56) and pyridine-d_5 (δ 2.99) solvents is accordingly assigned to the axial methyl isomer. Further evidence for this conclusion comes from nuclear Overhauser effect results which are discussed later in this section. The remaining broad low-field doublet signals, which exhibit couplings of geminal magnitude (J = 13.5 Hz), are accordingly assigned to $H_{10\alpha}$ equatorial of the major and minor components. Further vicinal coupling of $H_{10\alpha}$ to both H_{10a} and H_9 (2–4 Hz for protons subtending dihedral angles of approximately 60° to each other[27]) as well as long-range coupling to H_8 (1–2 Hz), which is favorably oriented in a W arrangement[31] to $H_{10\alpha}$, account for the observed doublet broadening.

The partial spectra of $\Delta^{6a(10a)}$-THC (**2**) exhibits broad doublets (J = 17.0 Hz) centered at δ 2.67 and 3.11 in both deuteriochloroform and pyridine-d_5, respectively, while in the latter solvent an additional signal, a broad double doublet (J = 17.0 and 9.2 Hz) centered at δ 2.79, is also present. Since H_{10a} is absent in **2**, these signals can arise only from the C_{10} methylene protons. Thus, the broad doublet signals arising at low field in both solvents are assigned to $H_{10\alpha}$ equatorial, whereas $H_{10\beta}$ axial, which must be oriented *trans* diaxial to the C_9 proton since J_{trans} = 9.8 Hz (the C_9 methyl in **2** is thus equatorial), is assigned to the broad quartet signal in pyridine-d_5. The considerable broadening inherent in these signals is caused by homoallylic coupling to the C_7 methylene protons. This is confirmed by saturation of the C_7 methylene hump (δ 2.1) which causes both the $C_{10\alpha}$ and $C_{10\beta}$ protons to reduce to sharp doublet of doublet signals with couplings of 17.0 and 4.0 Hz and 17.0 and 9.8 Hz, respectively. It is casually observed at this point that the magnitude of geminal coupling between the C_{10} protons is smaller in **3** (J_{gem} = 13.5 Hz) than in **5** and **2** (J_{gem} = 17.0 Hz). This is consistent with the accepted structures for **2**, **3**, and **5** since it is well established that π bonds adjacent to methylene protons cause J_{gem} to become more negative.[32]

Previous pmr investigations of cannabinoids have been mainly concerned with signal assignment as a means of structural elucidation with little emphasis directed to the use of this technique as a means of defining the three-dimensional identities of these systems. The nuclear Overhauser effect[15] (NOE) is a well-substantiated method for investigating conformational and configurational uncertainties in molecular entities as well as for confirming signal assignments for protons indistinguishable on the basis of their signal multiplicity. The pmr spectra of **1**, **3**, and **5** exhibit a number of NOE's which define unequivocally ring B conformation as well as provide unambiguous assignments for the C_6 geminal methyl and the aromatic protons (H_2 and H_4). The results of NOE experiments carried out on compounds **1**, **2**, **3**, and **5** are summarized in Table II. From these results, it is observed that irradiation at the high-field methyl singlet in the spectra of **1**, **3**, and **5** results in integrated intensity increases for H_{10a} of approximately 17 ± 1% in the case of **1** and **5** and approximately 25 ± 1% in the case of **3**. Alternatively, saturation of the low-field methyl singlet in the spectra of **1**, **3**, and **5** results in negligible integrated area increases for this proton. These results require that H_{10a} be spatially proximal to the high-field methyl group (which is accordingly assigned the α configuration) and spatially remote from the low-field methyl group (which is accordingly assigned β configuration). Of the two possible ring B conformations for compounds **1**, **3**, and **5**, *i.e.*, A or B as shown in Figure 3, only conformation B can reasonably account for the occurrence of an NOE between H_{10a} and the 6α methyl group since, in this con-

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(32) M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, **85**, 1899 (1963).

Table II. Nuclear Overhauser Effects in Cannabinoids **1**, **2**, **3**, and **5**

Compd	Proton(s) irradiated δ, ppm[a]	Proton obsd δ, ppm	% area increase[b] $CDCl_3$	% area increase[b] C_5D_5N	Internuclear distance,[c] Å
Δ^9-THC (**1**)	High-field methyl (1.09) [1.11]	H_{10a} (3.22) [3.55]	18	17	2.89
	Low-field methyl (1.41) [1.43]	H_{10a} (3.22) [3.55]	Nil	Nil	4.28
	OH (4.87) [4.85]	H_2 (6.15) [6.69]	13	9	2.45
	OH (4.87) [4.85]	H_4 (6.29) [6.57]	Nil	Nil	5.51
	H_{10} (6.33)	OH (4.87)	Nil		3.25
Δ^8-THC (**5**)	High-field methyl [1.13]	H_{10a} [2.99]		17	2.6
	Low-field methyl [1.41]	H_{10a} [2.99]		Nil	4.2
	OH (4.81) [4.90]	H_2 (6.11) [6.69]	13	12	2.4
	$H_{10\alpha}$ (3.22)	OH (4.81)	Nil		3.0
HHC (**3**)	High-field methyl [1.15]	H_{10a} [2.99]		25	2.83
	Low-field methyl [1.41]	H_{10a} [2.99]		Nil	4.28
	OH	H_2 (6.09) [6.66]	13	13	2.33
	OH	H_4 (6.26) [6.57]	Nil	Nil	5.63
	$10_{10\alpha}$ (eq) (2.89)	OH	Nil	Nil	3.18
$\Delta^{8a(10a)}$-THC (**2**)	OH (4.85) [4.88]	H_2 (6.12) [6.74]	12	12	2.36
	OH (4.85) [4.88]	H_4 (6.31) [6.62]	Nil	Nil	5.59

[a] Values in parentheses and brackets indicate resonance positions in $CDCl_3$ and C_5D_5N solutions, respectively. [b] See Experimental Section. [c] These values were obtained from the Westheimer calculations, except for the distances in Δ^8-THC, which were obtained from measurements on Dreiding models; distances involving methyl groups are to the methyl carbon, and all other distances are between protons.

formation, these protons are oriented 1,3 diaxial to each other and are thus in spatial proximity (r = 2.89 Å).[33] In conformation A, however, the distance between H_{10a} and 6α methyl is too large for an intramolecular relaxation process to exist between these protons.

The substantially large NOE recorded between 6α-CH_3 and H_{10a} in **3**, relative to **1** and **5**, is rationalized on the following basis. Since the chemical shifts of the C_9 and 6α methyl groups of **3** are identical in pyridine-d_5 solution (see Table I), irradiation of 6α methyl will also saturate C_9 methyl. Thus, if the C_9 methyl is oriented α, *i.e.*, 1,3-diaxial to H_{10a}, it will contribute, in addition to 6α methyl protons, to the intramolecular relaxation of H_{10a} and thus give rise to a larger NOE than in **1** and **5**. That this is indeed observed to be the case further confirms our previous stereochemical assignment for the C_9 methyl of the major isomer made on the basis of chemical shift information.

Additional NOE's are recorded between the phenolic OH and aromatic ring protons. When the OH proton in the spectra of **1**, **2**, **3**, and **5** is saturated, intensity increases of approximately 12–13% are observed for the high- and low-field aromatic doublets in their deuteriochloroform and pyridine-d_5 spectra, respectively. These signals are accordingly assigned to H_2 since this proton is proximally located with respect to the phenolic OH function, while the remaining unaffected doublet signals are assigned to H_4. It is important to note at this point that, irrespective of its *ortho* location to H_2, the phenolic OH proton cannot contribute to the intramolecular relaxation of H_2 unless it is oriented *syn* to this proton as indicated in Figure 3. The fact that an NOE does exist between these two protons in addition to the conspicuous absence of NOE's between the phenolic OH proton and H_{10} in **1** and $H_{10\alpha}$ in **3** and **5** (see Table II), confirm that the conformational preference of the OH bond is *syn* to H_2. This is in agreement with conclusions formulated on the basis of Westheimer calculations.

Pyridine solvent shifts[16] provide further information regarding conformational uncertainties in these systems. Since NOE confirmed assignments of the aromatic signals establish that crossover of these signals occur upon passing from deuteriochloroform to pyridine-d_5, substantial solvent Δ values are recorded for H_2 (see Table I) in these systems (Δ ranges from −0.54 to −0.62 ppm). In an earlier study, it was demonstrated that protons situated *ortho* to a hydroxyl function in phenolic systems experience deshielding effects in C_5D_5N relative to $CDCl_3$ of approximately 0.40–0.45 ppm. The substantially larger Δ value recorded for H_2 in these compounds therefore provides further indications of the rotational restriction imposed upon the phenolic O–H bond occasioned by steric interactions with C_{10} proton(s). In the predominant *syn* conformation, H_2 is situated considerably closer to the OH proton than when it is oriented *anti* to it and will, as a result, ex-

(33) Distances obtained from the Westheimer calculations (See Table II) on Δ^9-THC.

perience greater deshielding effects from proximal anisotropic pyridine molecules coordinated to the OH proton.

Subtle conformational differences in ring C between compound **2** and compounds **3** and **5** are indicated from the solvent shift results recorded for the C_{10} methylene protons (see Table I). Thus, in **2**, relative to **3** and **5**, both the C_{10} protons resonate to low enough field (in C_5D_5N) to be readily identifiable and, in addition, both $H_{10\beta}$ axial and $H_{10\alpha}$ equatorial experience smaller (but similar) solvent deshielding effects ($\Delta = -0.44$ and -0.35 ppm, respectively) than corresponding protons in **3** and **5**. Since the magnitude of pyridine solvent shifts is distance dependent,[16] these results are in corroboration with the conclusions of the previous section in that, in **2**, ring B assumes the other possible conformation such that the C_{10} methylene protons are almost equidistant from the phenolic oxygen. This is in contrast to the conformation of ring B of compounds **3** and **5** where $H_{10\alpha}$ equatorial is considerably closer to the phenolic OH (and hence the large solvent shift) than $H_{10\beta}$ axial. These conclusions are in good accord with the internuclear distance, r, between the phenolic oxygen and C_{10} protons obtained from the Westheimer method. Thus, in **1** ($r_{H_{10}-O_1} = 2.30$ Å) and **3** ($r_{H_{10\alpha}-O_1} = 2.34$ Å and $r_{10\beta-O_1} = 3.46$ Å), H_{10} and $H_{10\alpha}$ are in close proximity to the phenolic oxygen, whereas in **2** ($r_{H_{10\alpha}-O_1} = 2.65$ Å and $r_{H_{10\beta}-O_1} = 2.48$ Å), $H_{10\alpha}$ and $H_{10\beta}$ are located at nearly equal but intermediate distances from the phenolic oxygen.

Experimental Section

l-Δ^9-THC (**1**) and *l*-Δ^8-THC (**5**) were obtained from R. Mechoulam, Laboratory of Natural Products, School of Pharmacy, The Hebrew University, Jerusalem, Israel. Gas–liquid partition chromatography (glpc)[34] indicated that the purity of these samples was about 95%. The 3-*n*-hexyl analog of $\Delta^{6a(10a)}$-THC (**2**) ("synhexyl") was obtained from Abbott Laboratories. Glpc indicated that the sample was at least 90% pure. *l-trans*-Hexahydrocannabinol (**3**)[4c] was prepared by taking a 313-mg sample of Δ^8-THC (**5**) in 35 ml of ethanol and hydrogenating over 50 mg of PtO_2 for 4 hr at 45 psi pressure. Evaporation of the solvent after removal of the catalyst by suction filtration gave 300 mg of a light tan resin. Glpc and tlc investigation indicated that the product was a mixture of two isomers. The molecular weight of HHC (**3**) was confirmed by high-resolution mass spectrometry.

Nmr spectra were recorded using a Varian HR-220 spectrometer. Decoupling and NOE studies were carried out on a Varian HA-100 spectrometer in the frequency sweep mode. NOE effects were measured on nitrogen-sparged solutions (sample concentrations were approximately 8% w/v) with TMS as internal lock and reference. The irradiating audiooscillator was a Hewlett-Packard 200 ABR, and power requirements for NOE studies were determined by slowly increasing millivolt output until area increases were optimized. Each peak indicating increases in signal height was integrated at least ten times with and without optimum power and NOE's calculated from the average values.

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(34) An F&M 810 instrument was used with H_2 flame detector isothermally at 230°. The column was a 6 ft × 0.25 in. SS packed with 3% silicone gum XE-60 on 100–120 Chromosorb WAW DMCS. Tlc employed silica gel plates (Merck) using 1:4 Et_2O–hexene with 1% vanillin–H_2SO_4 spray for development.

The Stereochemistry of Aminophosphines[1]

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Abstract: The proton magnetic resonance (pmr) spectra of a series of aminophosphines, R_2NPXY, have been examined over the temperature range 40 to −150°. In the majority of these compounds the nitrogen substituents, R, became diastereotopic at low temperatures. Using the technique of matching the observed and computer simulated line shapes, it was possible to calculate the rates of, and activation parameters for, the implied stereochemical changes. The observed steric deceleration with increasing steric bulk of the nitrogen substituents, together with the inability to observe a barrier in 2,2-dimethyl-1-diphenylphosphinoaziridine, provide evidence that the observed barriers in the acyclic aminophosphines relate to torsion around the phosphorus–nitrogen bond rather than to pyramidal nitrogen inversion. The origins of these barriers are discussed from the standpoints of steric effects, lone pair–lone pair repulsions, and $p\pi$–$d\pi$ bonding. In contrast to an earlier report it is found that the symmetrical aminophosphines, R_2NPX_2, are still undergoing rapid P–N bond rotation on the nmr time scale at −80°. The observation of diastereotopic R groups below −120°, together with steric considerations, suggests that the *gauche*-type conformation is adopted at low temperatures. The pmr spectra of $C_6H_5As(Cl)N(CH_3)_2$ have also been recorded over a wide range of temperatures, leading to the measurement of the first arsenic–nitrogen rotational barrier.

There is considerable current interest in the use of nuclear magnetic resonance (nmr) to investigate the stereochemistry of trivalent nitrogen attached to group V and group VI heteroatoms. This area encompasses hydrazines,[4] aminophosphines,[5–8] hydroxyl-

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