Structural Studies of Cannabinoids. A Theoretical and Parallel 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 $\Delta^9$-tetrahydrocannabinol (THC) (1), $\Delta^{10\text{a}}$-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 $\Delta^9$-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. have been the subject of chemical, pharmacological, and clinical investigations for many years. However, the major psychotomimetic principle has been isolated only recently and further investigations have elucidated its structure as $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC). 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 problems. Indeed, with regard to the psychotomimetic activity of cannabinoids, a great deal of structure–activity information has been collected 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, $\Delta^9$-THC (1), $\Delta^{10\text{a}}$-THC (2), hexahydrocannabinol (HHC) (3), cannabinol (4), and $\Delta^9$-THC (5) were chosen as representing varying structural types for this study. As a first approach, detailed

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(3) For a definition of psychotomimetic and a discussion of drugs with this property, including the cannabinoids, see A. Hofmann in "Drugs and Dependence, National Academy of Sciences-National Research Council, Washington, D. C., 1968, Addendum 1.


(6) The numbering system used is that of dibenzopyran. $\alpha$ and $\beta$ 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.


(9) R. Hoffmann, ibid., 39, 1397 (1963).


(16) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, ibid., 90, 548 (1968).
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 Δ⁹-THC, Δ⁶a(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 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. 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. 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 Δ⁹-THC, Δ⁶a(10a)-THC, HHC, and cannabinol were obtained by extended Hückel molecular orbital calculations, employing previously described parameters. 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 and were computed for the 3-methyl derivatives, rather than the unsubstituted cannabinoids.

Figure 1. Conformations and charge distributions of (a) Δ⁹-THC, (b) Δ⁶a(10a)-THC, (c) HHC, and (d) cannabinol. The complete structures show the atoms as viewed normal to the plane through C₂, C₆, C₄. The perspectives of the C rings are viewed in the direction parallel to the vector from C₁ to C₁₅. Net atomic charges are given as signed numbers and overlap populations between atoms as unsigned numbers.

A"-THC were to have the same conformation as in 6a(10a) /3-methyl axial. If ring B of A"-THC, i.e.,
This interaction is reduced (on the basis of Dreiding models) if ring B assumes the other possible conformation puts one C SP3 methyl group in much closer proximity to H 16a than the other, as seen in Figure 1. On the other hand, in 6a(10a)-THC there are no protons at C 16a and C 18a, 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 SP2 b-methyl axial. If ring B of 6a(10a)-THC were to have the same conformation as in 6a-THC, HHC (and presumably 6a-THC), then H 16a would be much closer to the hydroxyl function than H 16g. In fact, pnm 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 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 6a-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 6a-THC also yields a comparable value of 3.5 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 pnm results. Although a methyl group on a cyclohexene 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 pnm results. Consequently, only the calculations on this form of HHC are reported. In 6a(lla)-THC, the C 9 methyl was assumed to be equatorial for the calculations, and this assumption was also verified by the pnm 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 7-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 pnm 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 SP3-C SP3 (aromatic) 1.40 Å; C SP2-C SP2 (olefinic) 1.33; C SP2-C SP1 1.51; C SP2-C SP3 1.53; C SP2-O 1.39; C SP2-O 1.41; C SP2-H 1.09; C SP1-H 1.10; and O-H 0.95. The only exception to these average values is the C 10a-C 10b bond in 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 6a(10a)-THC. The corresponding dihedral angle is also 19° in 6a-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 6a(10a)-THC, is reflected in the overlap populations for this bond (Figure 1). Based on the Westheimer calculations was arbitrary because both would have the same energy, and the sample of 6a(10a)-THC used in our pnm studies was racemic.

(22) These statements pertain to the enantiomorph as depicted in Figure 1b. The other enantiomorph can have a ring B conformation as in 6a-THC and still have the C 6 protons equidistant from the phenolic OH group. The choice of the enantiomorph to use in the Westheimer
Table I. Pmr Data* for Cannabinoids 1, 2, 3 and 5

<table>
<thead>
<tr>
<th>Resonance</th>
<th>δ&lt;sup&gt;8&lt;/sup&gt;-THC (1)</th>
<th>δ&lt;sup&gt;8&lt;/sup&gt;-THC (5)</th>
<th>HHC (3)</th>
<th>δ&lt;sup&gt;4&lt;/sup&gt;-10a-THC (2)</th>
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</thead>
<tbody>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
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<tr>
<td>H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1.8</td>
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<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>0.94 [1.11] s</td>
<td>1.08 [1.15] s</td>
<td>1.20 [1.36] s</td>
<td>1.20 [1.36] s</td>
</tr>
<tr>
<td>6β-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.41 [1.43] s</td>
<td>1.37 [1.41] s</td>
<td>1.35 [1.41] s</td>
<td>1.40 [1.52] s</td>
</tr>
<tr>
<td>6α-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0.04 [0.05] s</td>
<td>0.04 [0.05] s</td>
<td>0.04 [0.05] s</td>
<td>0.04 [0.05] s</td>
</tr>
<tr>
<td>H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>0.00 [0.01] t</td>
<td>+0.01</td>
<td>-0.04</td>
<td>+0.02</td>
</tr>
<tr>
<td>H&lt;sub&gt;10&lt;/sub&gt;</td>
<td>0.33 [0.06] t</td>
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<td>6.7</td>
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<td>H&lt;sub&gt;10α&lt;/sub&gt;</td>
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<tr>
<td>H&lt;sub&gt;10α&lt;/sub&gt;</td>
<td>0.22 [0.32] d</td>
<td>0.29 [0.27] d</td>
<td>0.35 [0.32] d</td>
<td>0.35 [0.32] d</td>
</tr>
<tr>
<td>H&lt;sub&gt;10β&lt;/sub&gt;</td>
<td>0.51 [0.59] br d</td>
<td>0.61 [0.69] br d</td>
<td>0.44 [0.42] br d</td>
<td>0.44 [0.42] br d</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>10.9 [10.5] t</td>
<td>10.5, 5.0, 5.0</td>
<td>10.5, 5.0, 5.0</td>
<td>10.5, 5.0, 5.0</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-0.33</td>
<td>-0.28</td>
<td>-0.43</td>
<td>-0.44</td>
</tr>
<tr>
<td>H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0.24 [0.20] t</td>
<td>0.43</td>
<td>0.43</td>
<td>0.43</td>
</tr>
<tr>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>0.78</td>
<td>0.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.49 [0.70] t</td>
<td>0.87 [0.77] t</td>
<td>0.85 [0.79] t</td>
<td>0.85 [0.79] t</td>
</tr>
<tr>
<td>J</td>
<td>+0.13</td>
<td>+0.10</td>
<td>+0.12</td>
<td>+0.06</td>
</tr>
</tbody>
</table>

* Abbreviations used are as follows: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad. b Chemical shift values (δ) recorded in parentheses and brackets correspond to shifts measured in CDCl<sub>3</sub> and CD<sub>3</sub>OD 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 Δ = δ<sub>C-DCl<sub>3</sub></sub> - δ<sub>C-D<sub>3</sub>N<sub>2</sub></sub>.

In the partial spectra of δ<sup>8</sup>-THC (1), 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<sub>5</sub> spectra. Although δ<sup>4</sup>-10<sup>α</sup>-THC does not exist naturally, these relative stabilities are consistent with limited experimental data on these two isomers. e

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<sub>5</sub> spectra reveals considerable differences which allow ready characterization of these compounds.

The partial spectrum of δ<sup>8</sup>-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<sub>C-DCl<sub>3</sub></sub> 3.22 and δ<sub>C-D<sub>3</sub>N<sub>2</sub></sub> 3.55), is assigned to H<sub>10α</sub>. The large 10.9-Hz splitting in this signal, which originates from trans-diaxial coupling to H<sub>10α</sub>, 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<sub>10α</sub>. Smaller unresolved splittings, which cause broadening of the C<sub>10α</sub> doublet, originate from homonuclear coupling to both the C<sub>1</sub> methylene and C<sub>3</sub> methyl protons.

In the partial spectra of δ<sup>8</sup>-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<sub>5</sub> spectra, respectively. The former signal is assigned to H<sub>10α</sub> since this proton is located trans diaxial to two protons, namely H<sub>10α</sub> and H<sub>10β</sub> axial (and is therefore expected to give rise to a triplet with coupling in the order of 9–11 Hz), and axial-equatorial to H<sub>10α</sub> equatorial (and is therefore expected to give rise to further small splitting (2–5 Hz) of each of the triplet lines). The latter doublet of doublet signal, formerly misassigned to H<sub>10α</sub> equatorial, is herein correctly assigned to H<sub>10α</sub> equatorial.

The remaining broad low-field doublet signals, which are assigned to the axial methyl isomer. Further evidence for this comes from nuclear Overhauser effect results which are discussed later in this section. The partial spectrum of \( \Delta^{9}(10a) \)-THC (2) exhibits broad doublets \((J = 17.0 \text{ Hz})\) centered at \( \delta = 2.67 \) and 3.11 in both deuteriochloroform and pyridine-\( d_{5}\) solvents, respectively, while in the latter solvent an additional signal, a broad doublet \((J = 17.0 \text{ and } 9.2 \text{ Hz})\) centered at \( \delta = 2.79 \), is also present. Since \( H_{10a} \) is absent in 2, these signals can arise only from the \( C_{6} \) methylene protons. Thus, the broad doublet signals arising at low field in both solvents are assigned to \( H_{10a} \) equatorial, whereas \( H_{10b} \) axial, which must be oriented \( \text{trans} \) diaxial to the \( C_{9} \) proton since \( J_{c_{9}c_{10}} = 9.8 \text{ Hz} \) (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 \((\delta = 2.1)\) which causes both the \( C_{10a} \) and \( C_{10b} \) 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 \( C_{9} \) protons is smaller in 3 \((J_{c_{9}c_{10}} = 13.5 \text{ Hz})\) than in 5 and 2 \((J_{c_{9}c_{10}} = 17.0 \text{ Hz})\). This is consistent with the accepted structures for 2, 3, and 5 since it is well established that \( \pi \) bonds adjacent to methylene protons cause \( J_{c_{9}c_{10}} \) 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 \((H_{2} \text{ and } H_{3})\). 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 saturation 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 \( \alpha \) configuration) and spatially remote from the low-field methyl group (which is accordingly assigned \( \beta \) configuration). Of the two possible ring B conformations for compounds 1, 3, and 5, \( \alpha \text{ or } \beta \) as shown in Figure 3, only conformation B can reasonably account for the occurrence of an NOE between \( H_{10a} \) and the 6\( \alpha \) methyl group since, in this con-


5204

Journal of the American Chemical Society | 92:17 | August 26, 1970
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 increases of approximately 12-13% are observed for the OH function, while the remaining unaffected doublet chemical shift information.

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$_2$. 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$_{10a}$ 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 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$_2$D$_2$N 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-

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

<table>
<thead>
<tr>
<th>Compd</th>
<th>Proton(s) irradiated δ, ppm</th>
<th>Proton obsd δ, ppm</th>
<th>$%$ area increase$^b$</th>
<th>Internuclear distance$^c$, Å</th>
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<tbody>
<tr>
<td>HHC (3)</td>
<td>High-field methyl [1.15]</td>
<td>H$_{10a}$ [2.99]</td>
<td>Nil</td>
<td>2.33</td>
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<tr>
<td></td>
<td>Low-field methyl [1.41]</td>
<td>H$_{10a}$ [2.99]</td>
<td>Nil</td>
<td>2.33</td>
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<tr>
<td></td>
<td>OH</td>
<td>H$_2$ [6.09] [6.66]</td>
<td>Nil</td>
<td>3.0</td>
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<td>10$_{10a}$ (eq) [2.89]</td>
<td>OH</td>
<td>Nil</td>
<td>3.18</td>
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<tr>
<td>6$\alpha$-THC (2)</td>
<td>OH [4.85] [4.88]</td>
<td>H$_2$ [6.12] [6.74]</td>
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<tr>
<td></td>
<td>OH</td>
<td>H$_4$ [6.31] [6.62]</td>
<td>Nil</td>
<td>5.59</td>
</tr>
</tbody>
</table>

$^a$ Values in parentheses and brackets indicate resonance positions in CDCl$_3$ and C$_2$D$_2$N solutions, respectively. $^b$ See Experimental Section. $^c$ These values were obtained from the Westheimer calculations, except for the distances in Δ$\alpha$-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.

(33) Distances obtained from the Westheimer calculations (See Table II) on Δ$\alpha$-THC.
Experience 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 C10 methylene protons (see Table I). Thus, in 2, relative to 3 and 5, both the C10 protons resonate to lower enough field (in CD3OD) to be readily identifiable and, in addition, both H5eq axial and H6eq equatorial experience smaller (but similar) solvent deshielding effects (Δ = 0.44 and 0.35 ppm, respectively) than corresponding protons in 3 and 5. Since the magnitude of pyridine solvent shifts is distance dependent, 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 C10 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 H6eq is considerably closer to the phenolic OH (and hence the large solvent shift) than H5eq axial. These conclusions are in good accord with the internuclear distance, r, between the phenolic oxygen and C10 protons obtained from the Westheimer method. Thus, in 1 (rH1a-O, = 2.30 Å) and 3 (rH1a-O, = 2.34 Å and rH5eq-O, = 3.46 Å), H10 and H6eq are in close proximity to the phenolic oxygen, whereas in 2 (rH5eq-O, = 2.65 Å and rH10eq-O, = 2.48 Å), H8eq and H10eq are located at nearly equal but intermediate distances from the phenolic oxygen.

Abstract: The proton magnetic resonance (pmr) spectra of a series of aminophosphines, R2NPXY, have been examined over the temperature range 40° to -150°C. 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-l-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 π-π bonding. In contrast to an earlier report it is found that the symmetrical aminophosphines, R2NPX2, are still undergoing rapid P-N bond rotation on the nmr time scale at -80°C. The observation of diastereotopic R groups below -120°C, together with steric considerations, suggests that the gauche-type conformation is adopted at low temperatures. The pmr spectra of C6H4AsCl(N(CH3)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-

Experimental Section

1-Δ4-THC (1) and 6-Δ4-THC (5) were obtained from R. Mechoulam, Laboratory of Natural Products, School of Pharmacy, The Hebrew University, Jerusalem, Israel. Gas-liquid partition chromatography (glpc)14 indicated that the purity of these samples was about 95%. The 3α-hexyl analog of Δ6-Δ4-THC (2) ("synhexyl") was obtained from Abbott Laboratories. Glpc indicated that the sample was at least 90% pure. 1α-trans-Hexahydrocannabinol (3)34 was prepared by taking a 313 mg sample of Δ2-THC (5) in 35 ml of ethanol and hydrogenating over 50 mg of PtO2 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 increase in signal height was integrated at least ten times with and without optimum power and NOE's calculated from the average values.

Acknowledgments. We are grateful to Max M. Marsh for stimulating this work and for helpful discussions.


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1 This work was supported by the Air Force Office of Scientific Research, through Grant No. AF-AFOSR-050-67, the National Science Foundation, through Grant GP-9518, and the Robert A. Welch Foundation.

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