

# HASHISH—I

## THE STRUCTURE OF CANNABIDIOL<sup>1</sup>

R. MECHOULAM and Y. SHVO  
Daniel Sieff Research Institute, The Weizmann Institute of Science,  
Rehovoth, Israel

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**Abstract**—Cannabidiol, one of the major components of hashish, has been shown to possess structure IIIa.

HASHISH (marihuana), the psychotomimetically active resin of the female flowering tops of *Cannabis sativa* L., is one of the most widely used drugs in the illicit market of narcotics in many parts of the world. The chemistry of the constituents of hashish has been the subject of numerous publications since the beginning of this century.<sup>2</sup> Due mainly to the masterly investigations<sup>2</sup> of Cahn, Adams and Todd, substantial progress has been made in this field. However up till now the structure of only one compound of the cannabis group, namely the physiologically inactive cannabinol (I), has been fully elucidated.

We have initiated a program aimed at clarifying some of the remaining problems connected with the chemistry of the constituents of hashish. This paper deals with the structure and stereochemistry of cannabidiol, one of the major components of hashish. Cannabidiol was isolated by Adams<sup>3</sup> and Todd<sup>4</sup> from marihuana and Indian hemp resin, respectively. Structure II (without stereochemical assignments) was suggested for cannabidiol.<sup>5a,d</sup> The carbon skeleton and the position of the hydroxyl groups are undoubtedly correctly represented by II, for cannabidiol has been converted<sup>6b</sup> into cannabinol (I), whose structure has been proved by synthesis.<sup>6</sup> The terminal position of the double bond has been adequately proved by chemical means.<sup>6c</sup> The position of the double bond in the alicyclic ring,<sup>6c</sup> however, seemed to require additional corroboration. We now present evidence that cannabidiol in fact possesses structure IIIa.

The UV spectral analysis of cannabidiol reported by Adams<sup>5a,c,d</sup> unequivocally shows that the double bond in the terpene ring is conjugated neither to the terminal

<sup>1</sup> A portion of this study has been reported at a Meeting of the Israeli Chemical Society, Jerusalem, April 1963 [R. Mechoulam, *Bull. Research Council Israel* **12A**, 57 (1963)].

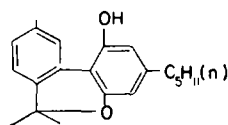
<sup>2</sup> For reviews on the subject see D. F. Downing, *Quart. Rev.* **16**, 133 (1962); A. R. Todd, *Experientia* **2**, 55 (1946); R. Adams, *Harvey Lectures* **37**, 168 (1942); see also the series of papers by R. Adams, the latest one of which is R. Adams, M. Harfenist and S. Loewe, *J. Amer. Chem. Soc.* **71**, 1624 (1949).

<sup>3</sup> R. Adams, M. Hunt and J. H. Clark, *J. Amer. Chem. Soc.* **62**, 196 (1940).

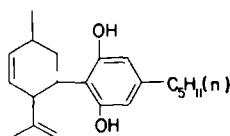
<sup>4</sup> A. Jacob and A. R. Todd, *J. Chem. Soc.* 649 (1940).

<sup>5</sup> R. Adams and co-workers, *J. Amer. Chem. Soc.* <sup>a</sup> **62**, 2566 (1940); <sup>b</sup> **62**, 2402 (1940); <sup>c</sup> **62**, 2215 (1940); <sup>d</sup> **63**, 2209 (1941); <sup>e</sup> **62**, 2194 (1940).

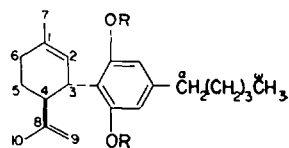
<sup>6</sup> R. Adams, B. R. Baker and R. B. Wearn, *J. Amer. Chem. Soc.* **62**, 2204 (1940); R. Ghosh, A. R. Todd and S. Wilkinson, *J. Chem. Soc.* 1121, 1393 (1940).



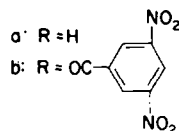
I



II



III



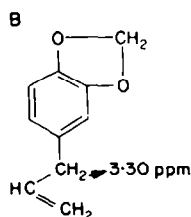
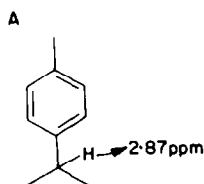
methylene group nor to the aromatic nucleus. Therefore the only three possible positions are  $\Delta^1$ ,  $\Delta^{1(6)}$  and  $\Delta^5$ .

The NMR spectra of cannabidiol (IIIa) and of its dinitrobenzoate (IIIb) (see Table) show the presence of three olefinic protons only. Two of these are the terminal methylene group protons, while the third one is on the alicyclic ring double bond. The presence of just one proton on this double bond excludes its formerly accepted position ( $\Delta^5$ ) in the proposed structure (II). This is further supported by the presence of two vinylic methyl groups, and only one methyl on a saturated carbon ( $\omega$ -methyl), as shown by the NMR spectra. It is necessary now to decide between positions 1 and 1(6) for the location of the nuclear double bond.

Of special interest in the NMR spectra is the signal at 3.85 ppm in cannabidiol (IIIa) and at 3.58 ppm in its ester (IIIb). In both compounds the area of this signal corresponds to one proton and we assign it to the hydrogen attached to  $C_3$ . Such a chemical shift is rather low for a proton  $\alpha$  to a phenyl ring only, and it is therefore postulated that the additional deshielding contribution must arise from an adjacent olefinic center.<sup>7</sup> Placing the double bond at  $\Delta^1$  and not at the alternative  $\Delta^{1(6)}$  position will satisfy this requirement. The  $C_3$  proton couples its spin with the  $C_4$  proton, and the former appears as a doublet ( $J = 11$  cps) with only minimal splitting from the adjacent  $C_2$  vinylic proton with which it forms an angle of  $\phi = 85^\circ (\pm 5)$ ,<sup>8</sup> taking into account the stereochemistry of the molecule (*vide infra*). The doublet is somewhat broad, which is probably due to a long range interreaction with the 7 methyl protons.

Further support for these assignments is obtained from the NMR spectrum of tetrahydrocannabidiol<sup>9</sup> (IV) in which the two olefinic double bonds are reduced. The signal originally found at 3.85 ppm in the spectrum of IIIa, moves upfield to the

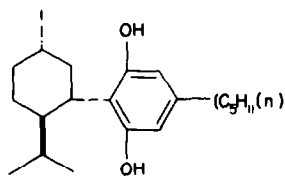
<sup>7</sup> In *p*-cymene (A) the proton on the tertiary carbon  $\alpha$  to the phenyl ring has a signal at 2.87 ppm, while in saffrol (B) the corresponding signal is at 3.30 ppm (N.S. Bhacca, L. F. Johnson and J. N. Shoolery, *NMR Spectra Catalog*, Varian Associates, 1962).



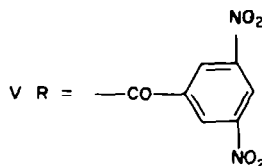
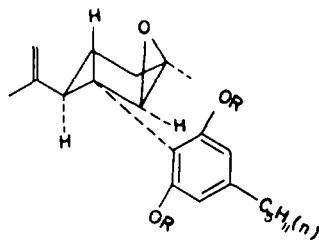
<sup>8</sup>  $\phi$  values were measured from Dreiding models.

<sup>9</sup> R. Adams, M. Hunt and J. H. Clark, *J. Amer. Chem. Soc.* **62**, 735 (1940).

2-60 ppm region, and is masked by the signals arising from the two additional protons  $\alpha$  to the phenyl ring on the side chain ( $C_\alpha$  protons). Such a shift of this signal is consistent with its assignment to the  $C_3$  proton in IIIa provided the double bond is situated at  $\Delta^1$ . If the  $C_3$  proton in IIIa were not allylic, hydrogenation of the double bond would not have appreciably effected its chemical shift.



IV



In order to confirm the position of the alicyclic double bond it seemed desirable to convert this double bond into another chemical function and study the NMR properties of the adjacent protons. Epoxidation, being an electrophilic reaction, seemed to offer a facile route for a selective attack on the ring double bond without a reaction on the terminal olefinic group, as the electron density on the latter is lower than in the former.<sup>10</sup> Indeed epoxidation of cannabidiol bisdinitrobenzoate (IIIb) with one mole of perbenzoic acid yielded the monoepoxide V, m.p. 120–122°. The NMR spectrum of the epoxide was instructive. It retained the signals due to the two terminal olefinic protons at  $C_9$  but lacked the signal for the proton on the alicyclic ring double bond, indicating therefore that only the latter double bond had undergone epoxidation. Furthermore a sharp new singlet appeared at 3.01 ppm due to a proton  $\alpha$  to an epoxide oxygen atom.<sup>11</sup> It has been demonstrated that the coupling constant between two protons on adjacent carbon atoms is a function of the dihedral angle ( $\phi$ ).<sup>12</sup> One of the implications of this relationship is that for  $\phi = 70\text{--}110^\circ$  the coupling constant ( $J$ ) is quite small.<sup>11–13</sup> In the case of epoxides fused to rigid cyclohexane systems, the dihedral angles between the proton  $\alpha$  to the epoxide oxygen and the two adjacent methylene protons are of such an order as to give rise to observable splitting with one of the latter protons only.<sup>11</sup> As an unsplit signal was observed in the NMR spectrum of V for the proton  $\alpha$  to the epoxide oxygen

<sup>10</sup> For some recent examples of selective epoxidations see J. S. Showell, J. R. Russell and D. Swern, *J. Org. Chem.* **27**, 2853 (1962); F. C. Frostick, B. Phillips and P. S. Starcher, *J. Amer. Chem. Soc.* **81**, 3350 (1959); L. S. Silbert, Z. B. Jacobs, W. E. Palm, L. P. Witnauer, W. S. Port and D. Swern, *J. Polymer Sci.* **21**, 161 (1956).

<sup>11</sup> A. D. Cross, *J. Amer. Chem. Soc.* **84**, 3206 (1962).

<sup>12</sup> M. Karplus, *J. Chem. Phys.* **30**, 11 (1959).

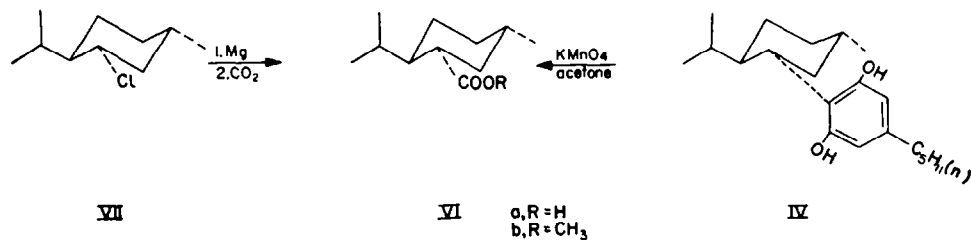
<sup>13</sup> K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.* **83**, 4623 (1961).

atom ( $C_2$  proton), it must be concluded that this proton is flanked by only one adjacent proton. This can be realized only if the epoxide occupies the 1,2 and not the alternative 1,6 position. Indeed the dihedral angle ( $H-C_2-C_3-H$ ) in epoxide V was found to be  $105^\circ (\pm 10^\circ)$  and should not give rise to an observable splitting. The  $C_3$  proton in the NMR spectrum of V appears as a sharp doublet at 3.24 ppm ( $J = 11$  cps) which is consistent with structure V for the epoxide. The  $C_3$  proton couples its spin only with the single proton at  $C_4$ ; no splitting could be observed due to the  $C_2$  proton which is in accordance with the above interpretation. If the epoxide oxygen atom were on  $C_1-C_8$  then the signal of the  $C_3$  proton should not have changed from that of the starting material and its splitting pattern should have been much more complex.

On the ground of the above experimental results we propose the modified structure IIIa for cannabidiol.

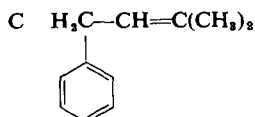
It is noteworthy that neither basic nor acidic treatment of cannabidiol induces isomerization of the  $\Delta^1$  double bond *into conjugation* with the aromatic system.<sup>4,5a,d,e</sup> The reason for this rather surprising observation might be due to hyperconjugation.<sup>14</sup> Conformational factors also must be taken into account. Due to the numerous substituents in the vicinity of the carbon-carbon bond between the phenyl and the alicyclic rings, a double bond in the alicyclic ring conjugated to the phenyl ring will not be in the same plane as the phenyl ring. Hence, the driving force for an isomerization leading to conjugation with the phenyl ring may be considerably diminished.

Adams<sup>9</sup> has shown that oxidation of tetrahydrocannabidiol (IV) with potassium permanganate in acetone gives a menthane carboxylic acid (VIa), which is identical with the acid obtained from menthyl chloride (VII) through a Grignard reaction with carbon dioxide. Grignard reactions of this type have been shown to give the thermodynamically more stable acid. Thus Shoppee<sup>15</sup> has reported that carbonation



of a Grignard reagent prepared from either  $3\alpha$ -bromo-cholestane or  $3\beta$ -bromo-cholestane gives the same cholestane- $3\beta$ -carboxylic acid in which the carboxyl group is equatorial. By equilibration experiments we have now shown that the carboxylic group in (VIa) is also equatorial. Methyl menthane carboxylate (VIb) when boiled with sodium methoxide in benzene or in absolute methanol gave back unchanged starting

<sup>14</sup> It has been observed that the unconjugated 1,1 dimethyl-3-phenyl propene (C) is more stable than the isomeric styrene (above  $150^\circ$ , at which temp the experiments were performed). (H. Pines and J. Shabtai, unpublished data communicated to us by Dr. J. Shabtai).



<sup>15</sup> G. Roberts, C. W. Shoppee and R. J. Stephenson, *J. Chem. Soc.* 2705 (1954).

material. Gastambide<sup>16</sup> has also assigned structure VIa to menthane carboxylic acid by comparing the rotations of different menthyl and neomenthyl derivatives.

If it is assumed that during the relatively mild oxidation of tetrahydrocannabidiol no inversions have taken place, then the stereochemistry of cannabidiol is correctly represented by IIIa. Further support for this stereochemistry assignment can be found in the NMR spectra. The large coupling constant ( $J = 11$  cps) between the  $C_3$  and  $C_4$  protons in both III and V indicates that the dihedral angle between them is that of two trans diaxial hydrogens.<sup>11-13</sup>

The stereochemistry of the epoxide ring in V can also be deduced from the NMR spectrum. It was shown already that the  $C_3$  proton, which appears as a doublet in the NMR spectrum of the epoxide V, forms an angle of  $105 (\pm 10^\circ)$  with the  $C_2$  proton. These two hydrogens are therefore in a trans relationship, and it follows that the epoxide ring and the phenyl ring are also trans oriented, as depicted in V.

Some insight into the conformation of the bisdinitrobenzoate ester of cannabidiol (IIIb) could be gained by inspection of its NMR spectrum. It can be seen from the Table that the dinitrobenzoylation of the two phenolic groups induces a significant upfield shift of all protons associated with the cyclohexene ring structure. Such shifts can be accounted for in terms of diamagnetic currents arising from the aromatic nuclei. However the cyclohexene ring must be at least partially disposed above (or below) the plane of one of the 3,5 dinitrobenzene rings to account for its shielding. Since the phenolic ring carries two bulky ortho substituents it is probably forced out of planarity with the cyclohexene ring and a situation where the 3,5-dinitrobenzene rings fold over and below the cyclohexene ring can be readily attained.\*

TABLE—NMR SPECTRA OF CANNABIDIOL AND ITS DERIVATIVES<sup>a</sup>

|   | $C_2$ -H       | $C_9$ -H             | $C_3$ -H                           | 10 & 7-methyls       | $\omega$ -methyl  |
|---|----------------|----------------------|------------------------------------|----------------------|-------------------|
| Cannabidiol<br>(IIIa)                             | 5.59(s)<br>(1) | 4.66, 4.58(s)<br>(2) | 3.85(br)(d)<br>(1)                 | 1.80, 1.68(s)<br>(6) | 0.88(t)<br>(3)    |
| Cannabidiol-<br>bisdinitroben-<br>zoate (IIIb)    | 5.33(s)<br>(1) | 4.73, 4.55(s)<br>(2) | 3.58(br)(d)<br>(J = 11 cps)<br>(1) | 1.59, 1.22(s)<br>(6) | 0.92(t)<br>(3)    |
| Tetrahydro<br>cannabidiol (IV)                    |                |                      |                                    | 0.91                 | 0.81 (br)<br>(12) |
| Epoxy-canna-<br>bidiol bis<br>dinitrobenzoate (V) | 3.01(s)<br>(1) | 4.75, 4.55(s)<br>(2) | 3.24(d)<br>(J = 11 cps)<br>(1)     | 1.56                 | 0.90<br>(9)       |

<sup>a</sup> Spectra were determined on a Varian A-60 spectrometer in deuteriochloroform. Values given in p.p.m. relative to tetramethylsilane as internal standard. Numbers in parentheses denote number of protons, determined by integration of areas. Letters in parentheses denote singlet (s); doublet (d); triplet (t); and broad (br).

\* Note added in proof

Prof. F. Šantavy of Palacký University, Olomouc, Czechoslovakia has kindly informed us that, mainly on the basis of optical rotation data, he has reached the same conclusions as reported in this paper regarding the structure of cannabidiol and that his manuscript is in preparation.

A. J. Bose<sup>16a</sup> has found, by a method different than ours, that methane carboxylic acid has structure VIa.

<sup>16</sup> B. Gastambide, *Ann. Chim., (Paris)* **9**, 257 (1954).

<sup>16a</sup> A. K. Bose, S. Harrison and L. Farber, *J. Org. Chem.* **28**, 1223 (1963).

EXPERIMENTAL<sup>17</sup>

*Monoepoxycannabidiol bisdinitrobenzoate* (V). To a cooled solution of perbenzoic acid (207 mg, by titration) in 20 cc chloroform was added 1.05 g cannabidiol bis 3,5-dinitrobenzoate. The solution was left in the dark at 20° for 16 hr, washed with cold 5% sodium hydroxide solution, then several times with water and was dried (sodium sulphate). After evaporation a solid residue was recrystallized from acetone-pentane, giving 900 mg monoepoxy cannabidiol bis 3,5-dinitrobenzoate, m.p. 116–120°. The analytical sample showed m.p. 120–122°, ( $\alpha$ )<sub>D</sub>-54° (CHCl<sub>3</sub>). Purity was determined by chromatoplate. (Found: C, 58.68; H, 4.78; N, 7.84. C<sub>28</sub>H<sub>34</sub>O<sub>18</sub>N<sub>4</sub> requires: C, 58.49; H, 4.77; N, 7.80%.)

*Equilibration experiments of methyl menthane carboxylate* (VIb). (–)Menthane carboxylic acid<sup>18</sup> (m.p. 65–66°; 200 mg) ( $\alpha$ )<sub>D</sub>-44° (CHCl<sub>3</sub>) was reacted with freshly distilled diazomethane. The resulting methyl ester was dissolved in benzene, sodium methoxide (1 g) was added and the reaction mixture was boiled for 16 hr. After acidification with 5% hydrochloric acid, the benzene solution was washed with water, dried (sodium sulphate) and evaporated. The resulting oil was identical with the starting ester by its IR spectrum, by chromatoplate, and by vapour phase chromatography (on 7% silicon oil, temp 110°, gas flow 430 cc/min, on a Perkin Elmer vapour fractometer model 154 as well as on 10% Apiezon L, APL, temp 146°, gas flow 70 cc/min on a Pye Argon Chromatograph). In another run the methyl menthyl carboxylate was not isolated, but after the equilibration water was added to the reaction mixture which was boiled for another 1 hr. After cooling the aqueous phase was washed with ether, acidified with 5% hydrochloric acid and extracted with ether. Evaporation of the ether solution gave pure (–) menthane carboxylic acid, m.p. 65–66°, ( $\alpha$ )<sub>D</sub>-44°, identical with the starting material (IR, mixture m.p., NMR spectra). Identical results were obtained when the experiments were performed with sodium methoxide in absolute methanol rather than in benzene.

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<sup>17</sup> Microanalyses were carried out by our microanalytical laboratory under the supervision of Mr. R. Heller.

<sup>18</sup> N. I. Kursanov, *J. Russ. Phys. Chem. Soc.* **46**, 815 (1914); *Chem. Abstr.* **9**, 1751 (1915); J. G. Smith and G. F. Wright, *J. Org. Chem.* **17**, 1116 (1952).