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HASHISH—VII[1]

THE ISOMERIZATION OF CANNABIDIOL TO TETRAHYDROCANNABINOLS

Y. GAONI and R. MECHOULAM
Institute of Organic Chemistry, the Weizmann Institute of Science, Rehovoth, Israel

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Abstract—Depending on the reaction conditions used, the physiologically active products obtained by Adams on isomerization of the inactive cannabidiol (Ia) with acids are shown to be either $\Delta^{1(6)}$ tetrahydrocannabinol (II) or a mixture of II, Δ^1 tetrahydrocannabinol (IIIa) and the two isomers of 1-ethoxy hexahydrocannabinol (VIIIa, VIIIb).

IN A series of papers Adams[2] reports that the inactive marihuana constituent cannabidiol isomerizes readily in the presence of a number of acidic reagents to give tetrahydrocannabinols possessing marihuana-type physiological activity. The general structure of these products was established by dehydrogenation to cannabinol (IV) whose constitution had previously been determined by synthesis.[3] Dependent upon the conditions used, the oily tetrahydrocannabinols were reported to have different specific rotations. Very dilute ethanolic hydrochloric acid converted cannabidiol to a tetrahydrocannabinol, $(\alpha)_D$ $-130° \pm 5°$, while reflux with *p*-toluenesulphonic acid in benzene gave a compound $(\alpha)_D$ $-265° \pm 5°$. Under the latter conditions the tetrahydrocannabinol $(\alpha)_D$ $-130°$ was converted into a product which had a rotation of $-200°$ to $-225°$. It was assumed that a partial isomerization had taken place. The UV data excluded the possibility that the double bond was conjugated to the aromatic ring. Upon reduction of a tetrahydrocannabinol of any rotation between $(\alpha)_D$ $-130°$ and $-270°$ there was always formed a 'homogeneous hexahydro product of constant rotation $(\alpha)_D$ $-70°$'. The following structures were tentatively suggested: II for the isomer with a rotation of $(\alpha)_D$ $-265°$ and Va for the $(\alpha)_D$ $-130°$ form (without stereochemical assignments).

Wollner *et al.*[4] have reported that a tetrahydrocannabinol, $(\alpha)_D$ $-193°$ isolated from Indian charas was not identical with either of the above two isomers.[5] Recently,[6] we showed that the correct structure of cannabidiol is Ia and not Vb as previously assumed.[2] We have also reported[7] that a solution of cannabidiol (Ia) in absolute

[1] Part VI: R. Mechoulam and Y. Gaoni, *J. Amer. Chem. Soc.* **87**, 3273 (1965).

[2] [a] R. Adams, D. C. Pease, C. K. Cain, B. R. Baker, J. H. Clark, H. Wolff and R. B. Wearn, *J. Amer. Chem. Soc.* **62**, 2245 (1940); [b] R. Adams, D. C. Pease, C. K. Cain and J. H. Clark, *Ibid.* **62**, 2402 (1940); [c] R. Adams, S. Loewe, D. C. Pease, C. K. Cain, R. B. Wearn, R. B. Baker and H. Wolff, *Ibid.* **62**, 2566 (1940); [d] R. Adams, C. K. Cain, W. D. McPhee and R. B. Wearn, *Ibid.* **63**, 2209 (1941). See also F. Šantavý, *Acta Univ. Palackianea Olomuc.* **35**, 5 (1964); *Chem. Abstr.* **62**, 4057 (1965).

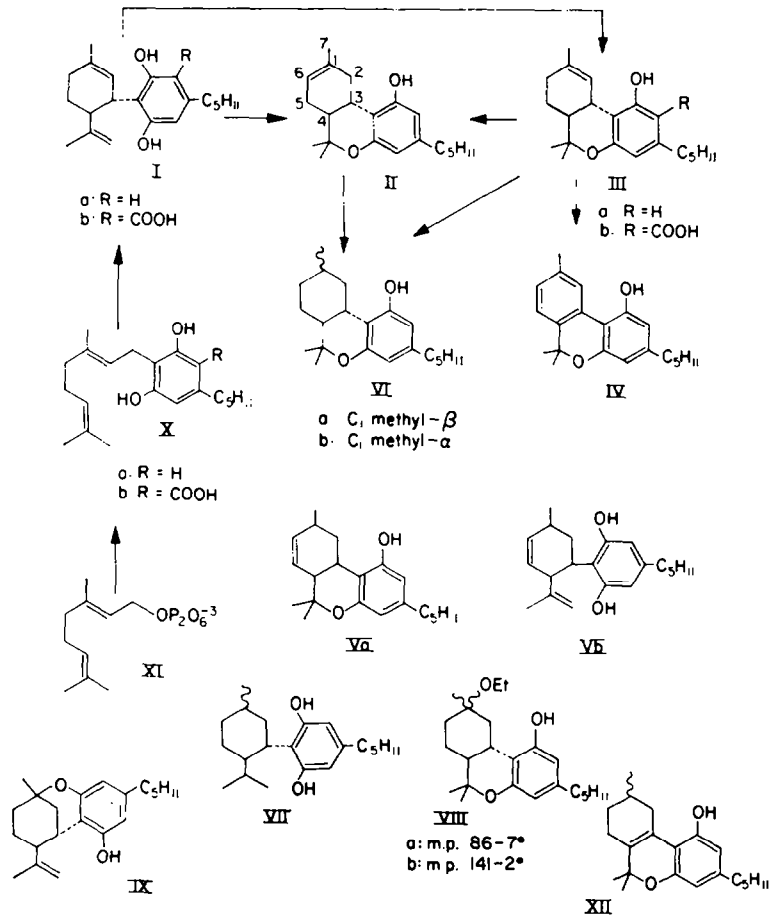
[3] [a] R. Adams, R. B. Baker and R. B. Wearn, *J. Amer. Chem. Soc.* **62**, 2204 (1940); [b] R. Ghosh, A. R. Todd and S. Wilkinson, *J. Chem. Soc.* 1393 (1940).

[4] H. J. Wollner, J. R. Matchett and J. Levine, *J. Amer. Chem. Soc.* **64**, 26 (1942).

[5] It is possible that Wollner's tetrahydrocannabinol was not homogeneous for its acetylation is reported to give a product different than the acetate from which the tetrahydrocannabinol was originally obtained by hydrolysis.

[6] R. Mechoulam and Y. Shvo, *Tetrahedron* **19**, 2073 (1963).

[7] Y. Gaoni and R. Mechoulam, *J. Amer. Chem. Soc.* **86**, 1646 (1964).



ethanol containing 0·05% hydrogen chloride on 2 hr boiling gives a mixture of the starting material and Δ^1 tetrahydrocannabinol (IIIa) identical with the natural active constituent of *Cannabis sativa*. In order to clarify this rather confusing situation, we have now reexamined the reaction products reported by Adams using analytical methods which were not available in the early forties, when his work was done.

Cannabidiol (Ia) in benzene containing *p*-toluenesulphonic acid on heating under reflux gives indeed $\Delta^{1(6)}$ tetrahydrocannabinol (II). The shift of the double bond from the Δ^1 to the $\Delta^{1(6)}$ position can be explained by decrease in steric strain. The phenolic group hinders the C-2 protons in the $\Delta^{1(6)}$ isomer (II) to a much lesser extent than it hinders the proton in the same position in the Δ^1 isomer (IIIa). The UV data of II and of the Δ^1 isomer IIIa are essentially identical. The IR spectra are similar but not superimposable. In addition to minor differences in all parts of the 6·5–11·5 μ region, the $\Delta^{1(6)}$ isomer has two bands which are absent in the Δ^1 one, namely a strong peak at 9·26 μ and a medium one at 8·69 μ. The position of the double bond in II is determined by comparison of its NMR spectrum with that of IIIa. These spectra are essentially identical except for the chemical shift of the olefinic proton (Table). In the Δ^1 isomer this proton appears at 6·35 ppm while in the $\Delta^{1(6)}$ compound it is at 5·35.

In the Δ^1 isomer the vinylic proton is in (or nearly in) the plane of the aromatic ring, which causes the observed deshielding effect. In the $\Delta^{1(6)}$ isomer such a magnetic interaction is geometrically impossible. The chemical shift, though not the splitting pattern, of the C-3 proton in both isomers (II and IIIa) is similar, notwithstanding that in IIIa it is allylic while in II it is not. Apparently there is only a small contribution from the π electrons of the double bond to the shielding of the C-3 proton. This is supported by the fact that the C-3 proton appears in the same region even in the saturated compounds in this series (Table). If it is assumed that the character of the long range shielding associated with the carbon-carbon double bond is similar to that of the carbonyl group[8] one would expect that the shielding will be positive in the conical regions extending above and below the plane of the double bond and negative in the plane. Dreiding models of IIIa show that the C-3 proton is sterically fixed due to the rigidity of the tricyclic system and falls between the regions of positive and negative shielding. This is apparently not the case of cannabidiol (Ia) *versus* tetrahydrocannabidiol (VII)[9] which are not tricyclic. The reduction of the double bonds in Ia causes an upfield shift of 0·85 ppm of the C-3 proton.

Catalytic reduction of either II or IIIa gave a mixture of the two possible C-1 epimers, albeit in slightly different proportions. These two isomers (VIa and VIb) are separated on chromatoplates and can be obtained in pure form, although with difficulty, by column chromatography. The identity of the corresponding epimers, obtained from either II or IIIa was shown by direct comparison (chromatoplate, IR and NMR spectra). The UV and mass spectra[10] of VIa and VIb are identical. The IR spectra, however, are not superimposable. The chromatographically less polar epimer VIa has peaks of medium size at 9·40 and 9·60 μ which are absent in VIb, while the latter has peaks of similar size at 9·24, 9·50 and 9·82 μ which are absent in VIa. On the basis of these IR differences it can be grossly estimated that in the crude reduction product of II, VIa and VIb are found in the relative proportion of ca. 3:1, while under the same reaction conditions these isomers are formed from IIIa in a ratio of 1:2. A crystalline 3,5 dinitrobenzoate, m.p. 125–127° could be prepared from VIa. The same ester from VIb could not be induced to crystallize.

Comparison of the NMR spectra of VIa and VIb permits a tentative assignment of the stereochemistry of the methyl groups at C-1. The proton at C-3 in VIa appears as a broad doublet centered at 2·85 ppm. In VIb this broad doublet is centered at 3·05 ppm. It has been pointed out[11] that in rigid cyclohexane ring systems an *axial* substituent on a γ carbon should increase the shielding of the protons on the α carbon, while an equatorial substituent being too far removed, probably would not influence their chemical shift. As both VIa and VIb are rigid systems, we suggest that in VIa the methyl group at C_1 is axial and *trans* to the aromatic ring while in VIb it is equatorial.

Boiling cannabidiol (Ia) with dilute hydrochloric acid in ethanol for 18 hr, as described by Adams[2d] gave a complicated mixture of compounds which was only

[8] L. M. Jackman, *NMR Spectroscopy in Organic Chemistry* p. 129. Pergamon Press, New York (1959).

[9] The chemical shift of the C-3 proton in VII was wrongly reported[6] as being in the 2·6 ppm region. We have reexamined the spectrum. The correct position is 3·0 ppm (br).

[10] H. Budzikiewicz, R. T. Aplin, D. A. Lightner, C. Djerassi, R. Mechoulam, Y. Gaoni, *Tetrahedron* **21**, 1881 (1965).

[11] Ref. 8 p. 118.

TABLE 1. NMR SPECTRA TETRAHYDROCANNABINOL ISOMERS AND DERIVATIVES[a]

	Solvent	C_3–H	C_4–H	Aromatic-H	ω–CH_2	C_1–CH_3	C_6–CH_3	Miscellaneous
Δ^1-Tetrahydro-cannabinol IIIa	CCl_4	6·35 (s, br) (1)	3·14 (d, br) J = 10 c/s (1)	6·00 (d; J = 2 c/s) (1) 6·18 (d; J = 2 c/s) (1)	0·88 (t) (3)	1·65 (s, br)	1·08 (s) 1·38 (s)	
$\Delta^{1(6)}$Tetrahydro-cannabinol II	CCl_4	5·35 (s, br) (1)	3·18 (d, br) (1)	5·90 (d; J = 2 c/s) (1) 6·13 (d; J = 2 c/s) (1)	0·88 (t) (3)	1·68 (s, br)	1·08 (s) 1·32 (s)	
Hexahydro-cannabinol VIa	CCl_4		2·85 (d, br) (1)	5·85 (d; J = 2 c/s) (1) 6·08 (d; J = 2 c/s) (1)	0·88 (t) (3)	1·05 (s)[b] 1·30 (s)	1·15[b]	
Hexahydro-cannabinol VIb	CCl_4		3·05 (d, br) (1)	5·85 (d; J = 2 c/s) (1) 6·08 (d; J = 2 c/s) (1)	0·90 (t) (3)	0·97[b] 1·30 (s)	1·00 (s)	

1-Ethoxyhexa-hydrocanna-binol VIIIa	$CDCl_3$	3·15 (s, br) (1)	6·15 (d; J = 2 c/s) (1) 6·28 (d; J = 2 c/s) (1)	0·88 (t) (3)	1·18 1·38	1·30[c]	C_1-OCH_3CH_3 3·58 (q)(2)
1 ethoxy hexahydro-cannabinol VIIIb m.p. 141	$CDCl_3$	3·20 (s, br) (1)	6·14 (d; J = 2 c/s) 6·28 (d; J = 2 c/s)	0·90 (t) (3)	1·08 1·24[d]	1·18 1·36	C_1-OCH_3CH_3 3·55 (q)(2)
IX (?)	CCl_4	3·35 (br) (1)	5·90 (d; J = 2 c/s) 6·15 (d; J = 2 c/s)	0·90 (t) (3)	1·25 (s)	1·80 (s)	$>C = CH_2$ 4·85 (br)(2)

[a] Spectra were determined on a Varian A-60 spectrometer. Values given in ppm relative to tetramethylsilane as internal standard (frequency zero). Number in parentheses denote number of protons, determined by integration of areas. Letters in parentheses denote singlet (s); doublet (d); triplet (t); quartet (q); broad (br) and multiplet (m).

[b] Peak of *ca* half the height of the other —CH_3 peaks. Probably it is part of the doublet of the C_1–CH_3.

[c] The ethoxylmethyl triplet is hidden amongst the hump of other signals.

[d] Low peak, probably part of the ethoxymethyl triplet.

partially separated on chromatography. Two of the isolated compounds, VIIIa, m.p. 86–87°, and VIIIb, m.p. 141–142° were shown to be the two isomers of 1-ethoxy hexahydrocannabinol. The structure of these two compounds is deduced from their analysis, mol wt. (mass spectrum)[10] and NMR spectra (Table). In these spectra no olefinic protons are observed. A well defined quartet appears, centered at 3·60, which is attributed to the methylene protons of the ethoxyl group. Boiling with *p*-toluene-sulphonic acid in benzene converts VIIIb into $\Delta^{1(6)}$ tetrahydrocannabinol (II). This reaction lends further support to the proposed structures. Addition to the alicyclic double bond has previously been observed in this series. Adams has reported[2d] that a labile monochloro compound is formed from "tetrahydrocannabinol $(\alpha)_D$ −130°" and hydrochloric acid. Δ^1 Tetrahydrocannabinol (IIIa) and the $\Delta^{1(6)}$ isomer (II) were also isolated from the reaction mixture. These two compounds undoubtedly account for the reported[2d] biological activity of the crude product, for both VIIIa and VIIIb are devoid of any ataxia activity. We isolated also a very small amount of an oil, whose NMR spectrum fits structure IX.

Recently, in a review article, Downing[12] has expressed doubt as to whether the active constituent of hashish (IIIa) isolated by us[7] is the natural material or is an artefact, formed by double bond isomerization. We believe that this scepticism is unfounded on both biogenetic and purely chemical grounds. In addition to IIIa, five hashish constituents (cannabidiol (Ia)[6], cannabigerol (Xa)[15], cannabidiolic acid (Ib)[16], cannabigerolic acid (Xb)[16] and tetrahydrocannabinolic acid (IIIb)[17]) have been isolated in which the double bond occupies the same position as in IIIa. No naturally occuring compounds of the cannabis group are known in which the double bond is present in some other position in the terpene part of the molecule. These findings fit the generally accepted theory[18] that in Nature monoterpenes are formed from geranyl pyrophosphate (XI). In the cannabis series the biogenetic sequence is presumably XI → X → I → III.

The observations on the double bond isomerizations reported in this paper together with published data also support the view that IIIa is not an artefact. The $\Delta^{1(6)}$ isomer (II) and the synthetic Δ^3 isomer,[3b,13](XII) are stable on acidic treatment and do not revert to the labile Δ^1 isomer. The yet unknown Δ^2, Δ^4 and Δ^5 isomers, if unstable, would be expected to isomerize to II or XII but not to IIIa. It should also be pointed out that the isolation procedures employed by us excluded acidic treatment. Chromatography on silica gel, Florisil or alumina gave always the same compounds. On these grounds we believe that Δ^1 tetrahydrocannabinol is a naturally occuring active constituent of hashish.

[12] D. F. Downing in *Psychopharmacological Agents* (Edited by M. Gordon) pp. 555, 618. Academic Press, New York (1964). This review repeats a number of mistakes occurring in texts and previous reviews. Thus Wolner *et al.*[4] did not assign structure XII or any other definite structure to the material isolated by them. Also Adams' group did not synthesize a naturally occurring active principle but the isomer XII[13] (or rather a mixture of isomers[14]). Both a partial[7] and a total[1] syntheses have only recently been accomplished.

[13] R. Adams and B. R. Baker, *J. Amer. Chem. Soc.* **62**, 2401, 2405 (1940).

[14] F. Korte and H. Sieper, *Liebigs Ann.* **630**, 71 (1960).

[15] Y. Gaoni and R. Mechoulam, *Proc. Chem. Soc.* 82 (1964).

[16] R. Mechoulam and Y. Gaoni, *Tetrahedron* **21**, 1223 (1965).

[17] F. Korte, M. Haag and U. Claussen, *Angew. Chem.* **77**, 862 (1965).

[18] J. H. Richards and J. B. Hendrickson *The Biosynthesis of Steroids, Terpenes and Acetogenins.* W. A. Benjamin, New York (1964).

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer Infracord 137-B (I). UV spectra were recorded on Cary 14 in EtOH. Thin layer chromatoplates (TLC), made of Kieselgel-G Merck, were eluted with pentane–ether (88:12) and sprayed with a $KMnO_4$ solution. Gas chromatographs (VPC) were run at 230° using a 20 ft column of 0·1% silicon SE-30 on glass beads with a He flow of 100 cc/min. Column chromatographs were done on Merck acid washed alumina. Microanalyses were performed by the microanalytical department of the Weizmann Institute.

$\Delta^{1(6)}$-Tetrahydrocannabinol (II) *from cannabidiol* (Ia)

Cannabidiol (3, 14 g.) dissolved in benzene (100 ml) containing *p*-toluenesulphonic acid (200 mg), was boiled for 2 hr. The reaction mixture was poured into water. The upper layer was separated, washed with a 5% $NaHCO_3$aq., then with water, dried and evaporated. The remaining viscous oil gave a negative Beam test, showed mainly one spot on TLC and mainly one peak on VPC. The oil was dissolved in pentane (25 ml) and chromatographed on alumina (300 g). Elution with pentane–ether (95:5) gave fractions containing oily material which were checked for purity by TLC. Fractions showing only one spot were combined, yielding 2·0 g. Distillation of this oil (b.p. 175–178°/0·1 mm) gave pure II as a slightly yellow, highly viscous oil whose IR, UV and NMR spectra, as well as R_f (of TLC) were essentially the same as those of the undistilled material. Pure II has $(\alpha)_D^{CHCl_3}$ −266°, λ_{max}^{EtOH} 275, 282 mμ (ε 1260. 1320), mol. wt. (mass spectrum) 314. (Found: C, 80·15; H, 9·50. Calc. for $C_{21}H_{30}O_2$: C, 80·21; H, 9·62%.) We were unable to prepare a crystalline *p*-phenylazobenzoate, a dinitrophenyl urethane or a dinitrobenzoate of II. The oily derivatives obtained had the expected NMR spectra.

$\Delta^{1(6)}$-Tetrahydrocannabinol (II) *from Δ^1 tetrahydrocannabinol* (IIIa)

The above described procedure was employed, starting with IIIa and *p*-toluenesulphonic acid in benzene. The compound obtained moved as a single spot on TLC with R_f equivalent to that of an authenic sample of II, from the previous reaction. Identification was further established on the basis of IR and NMR comparisons.

Catalytic hydrogenation of II *to hexahydrocannabinols* (VI)

Compound II (3·1 g) in acetic acid (50 ml) was catalytically hydrogenated with Adam's catalyst (300 mg) at atm. press. Absorption stopped after an uptake of 22 ml. The catalyst was filtered off and most of the solvent was removed under vacuum, without warming. Ether was added and the solution was washed with water, $NaHCO_3$aq and water, and then dried (Na_2SO_4). Removal of the solvent yielded a glassy oil, which showed only one peak on VPC. This oil was distilled, b.p. 174–177°/0·1 mm. (Found: C, 79·39; H, 9·97. $C_{21}H_{32}O_2$ requires: C, 79·70; H, 10·19.) On TLC however two close spots were observed indicating that, as expected, a mixture of epimers had been formed. In order to separate the two components 1·7 g of the pure oil was chromatographed on 800 g alumina. Fractions of 100 ml were collected. The elution pattern was as follows: fractions 1–35 were eluted with pentane–ether (97:3), fractions 36–200 with the same solvents (95:5) and fractions 201–230 also with the same solvents (93:7). The separation trend was checked by TLC. Fractions 97–103 contained pure VIa (0·7 g) and fractions 193–225 contained pure VIb (0·25 g). The intermediate fractions were a mixture of the two epimers. Isomer VIa has $(\alpha)_D^{CHCl_3}$ −109°, λ_{max}^{EtOH} 275, 282 mμ (ε, 1180, 1180). (Found: C, 79·36; H, 10·08. $C_{21}H_{32}O_2$ requires: C, 79·70; H, 10·19%). Isomer VIb has $(\alpha)_D^{CHCl_3}$ −107°, λ_{max}^{EtOH} 275, 282 mμ (ε 1250, 1220). (Found: C, 79·44; H, 9·99. $C_{21}H_{32}O_2$ requires: C, 79·70; H, 10·19%.)

Dinitrobenzoate of VIa

Compound VIa (250 mg) was warmed at 70° with 3·5 dinitrobenzoyl chloride (400 mg) for ½ hr without a solvent. Benzene (20 ml) was then added and the insoluble dinitrobenzoic acid was filtered off. The solution was washed with 5% $NaHCO_3$aq and water, then dried over Na_2SO_4. The residue obtained upon removal of the solvent was chromatographed on 50 g silica gel and eluted with pentane–ether 97:3. The dinitrobenzoate obtained was recrystallized twice from pentane, giving crystals m.p. 125–127°. (Found: C, 65·77; H, 6·65; N, 5·79. $C_{35}H_{44}N_2O_7$ requires: C, 65·87; H, 6·71; N, 5·49%.)

Catalytic hydrogenation of Δ^1*-tetrahydrocannabinol* (IIIa) *to hexahydrocannabinols* (VI)

Compound IIIa (0·7 g) was hydrogenated as described for isomer II. The reduced product showed two spots on TLC, with R_f values identical with those of VIa and VIb. The mixture was chromatographed on 200 g alumina. Elution with pentane–ether 97:3 and 95:5 partially separated the mixture. The pure fractions (TLC) were combined giving 37 mg of epimer VIa and 80 mg of epimer VIb. These epimers were compared with the corresponding ones obtained from the hydrogenation of II and were found to be identical. The comparisons were both spectral (IR and NMR) and chromatographic (TLC and VPC).

In order to show that IIIa is not converted into II during the hydrogenation, thus accounting for the same reduction products, a blank experiment was done. Pure IIIa was dissolved in acetic acid in the presence of Adam's catalyst and was left for 2 hr at room temp. The solution was then worked up as described for the hydrogenation reactions. The starting material (II) was recovered unchanged (IR, NMR, VPC and TCL comparisons).

Reaction of cannabidiol with ethanolic hydrochloric acid

A solution of Ia (3·0 g) in abs EtOH (100 ml) containing 0·05% HCl was boiled for 18 hr. The solution was then poured into water and extracted with ether. The ether solution was washed with water, dried (Na_2SO_4) and evaporated. The oil obtained was a mixture giving numerous spots on TLC. This mixture was chromatographed on alumina (400 g). The following compounds were isolated:

1-*Ethoxyhexahydrocannabinol* (VIIIa) was the first compound to be eluted (pentane–ether, 98:2). The fractions containing only VIIIa were combined. The oil obtained (370 mg) slowly solidified and was recrystallized from MeOH–water giving crystals m.p. 86–87°, $(\alpha)_D^{CHCl_3}$ −84°, λ_{max}^{EtOH} 272, 280 mμ (ε 870, 870), mol. wt. (mass spectrum) 360. (Found: C, 76·71; H, 10·03. $C_{23}H_{36}O_2$ requires: C, 76·62; H, 10·07%.)

Tetrahydrocannabinols (II, IIIa) were eluted, together with small amounts of some other components of the mixture, with pentane–ether (95:5) giving an oil, 1·8 g. On repeated chromatography both the less polar $\Delta^{1(6)}$ isomer (II) and the more polar IIIa could be isolated in a pure state. They were compared with authenic samples by NMR, IR, VPC and TLC. In one case we were able to isolate a minor component of polarity between that of II and IIIa. This compound, to which we tentatively assign structure IX is an oil, b.p. 210/1mm, $(\alpha)_D^{CHCl_3}$ −65°, λ_{max}^{EtOH} 274,280 mμ (ε 1110, 1100), ν_{max} 1640 (shoulder), 890 cm^{-1} (—C=CH_2). (Found: C, 80·19; H, 9·59. $C_{21}H_{30}O_2$ requires: C, 80·21; H. 9·62%).

1-*Ethoxyhexahydrocannabinol* (VIIIb) was the last component to be eluted (pentane–ether, 93:7). The fractions containing only VIIIb were combined. On evaporation of the solvent solid material was obtained giving 350 mg crystals on recrystallization from pentane, m.p. 141–142° $(\alpha)_D^{CHCl_3}$ −50°, λ_{max}^{EtOH} 275, 282 mμ (ε 1130, 1160), mol. weight (mass spectrum) 360. (Found: C, 76·64; H, 9·87; $C_{23}H_{36}O_2$ requires: C, 76·62; H, 10·07%).

$\Delta^{1(6)}$*-Tetrahydrocannabinol* II *from* VIIIb

A solution of VIIIb (100 mg) in benzene (15 ml) containing *p*-toluenesulphonic acid (20 mg) was boiled for 1½ hr. The cooled solution was washed with water, dried and the solvent was evaporated. The residual oil was shown to be pure II by direct comparison (IR, NMR, VPC and TLC).

Note added in proof (Jan. 30, 1966): Taylor, Lenard and Shvo[19] have published a total synthesis of D,L-II. Apparently these authors were unaware that II was first prepared by Adams[2] from cannabidiol (Ia), the racemic form of which has recently been synthesized by us.[1] Adams has also reported the physiological potency of II.

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[19] E. C. TAYLOR, K. LENARD and Y. SHVO, *J. Amer Chem. Soc.* **88**, 367 (1966).