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THE *ISO*-TETRAHYDROCANNABINOLS*

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ABSTRACT

Synthetic routes are described which lead to iso-tetrahydrocannabinols, a new series of structural isomers of the natural Δ^1-tetrahydrocannabinol. In this group of compounds a dihydrobenzopyran ring system is formed by cyclization of one of the phenolic groups of a cannabinoid with the C_1 carbon in the terpene moiety of the molecule.

The acid catalyzed cyclization of cannabidiol (I) to 1-Δ^1-*trans*-tetrahydrocannabinol (1-Δ^1-*trans*-THC) (II), the major psychotomimetic principle in hashish, as well as to 1-$\Delta^{1(6)}$-*trans*-THC (III) has been described [3, 4 5, 6]. In this reaction a dihydrobenzopyran ring system is formed by internal ether formation of one of the phenolic groups with the Δ^8 double bond. Under the experimental conditions described (p-toluene sulfonic acid in benzene or dilute hydrochloric acid in ethanol) cyclization with the Δ^1 double bond is generally not observed. In one instance only [4] "a very small amount of an oil" was isolated whose NMR spectrum fitted structure IV. The almost exclusive formation of normal THC's i.e. those in which C_8 is part of the heterocyclic ring seemed rather surprising and we therefore undertook an investigation into the synthetic routes leading to ring closure of one of the phenolic groups with C_1 to give *iso*-THC's. We wish to report now** that the formation of *iso*-compounds is of common occurrence in the cannabinoid† series and in some cases it is actually preferred over that leading to the normal isomers.

The reaction of natural 1-cannabidiol (I) with boron trifluoride-etherate in methylene chloride or chloroform gave a mixture containing 13% 1-Δ^8-*iso*-THC (IV).

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* Hashish, Part XIV. For Part XIII see [1].

** Part of the material described in this paper has been the subject of a Communication to the Editor [2].

† The term cannabinoids has been proposed for the group of C_{21}-compounds typical of, and present in Cannabis sativa L., as well as for their analogs and transformation products [6].

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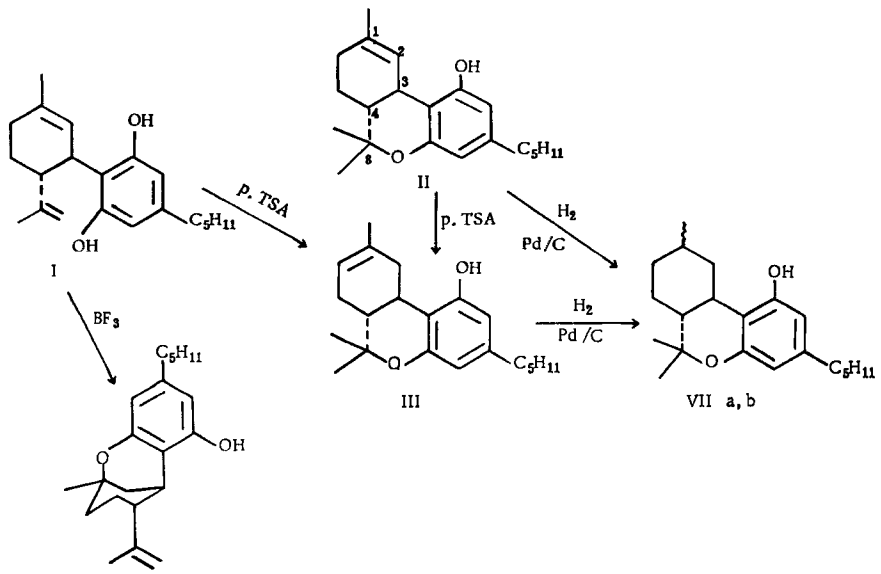
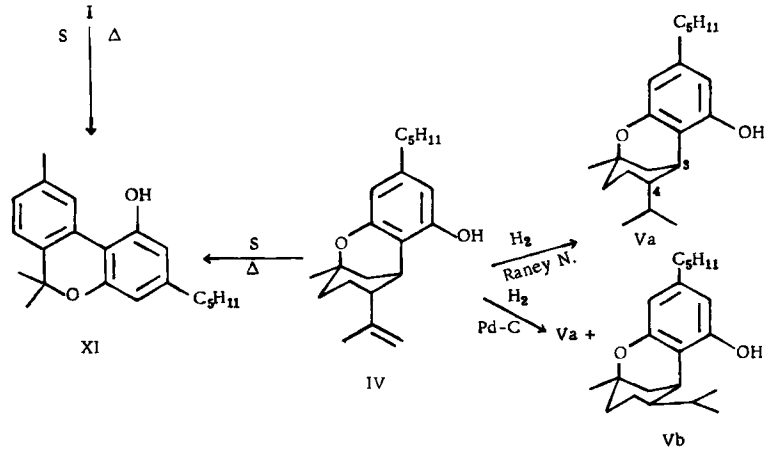
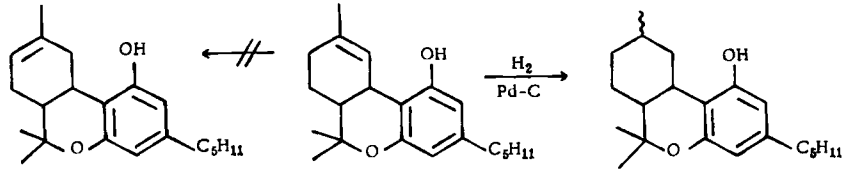
The structure of the iso-cannabinoid IV was deduced on the basis of the following physical data and chemical reactions and correlations: In the IR spectrum a strong band at 892 cm^{-1} indicates the presence of a terminal methylene group. In the NMR spectrum the two protons of this group appear at 4.85 ppm. No other olefinic protons are observed. In the normal series the single olefinic proton appears at a much higher frequency [6]. Hydrogenation of IV over Raney nickel gave 1-3, 4-*trans*-*iso*-hexahydrocannabinol (Va), (Scheme 2) which has no band in the 890 cm^{-1} region. In the NMR spectrum of Va the signals of the protons of the olefinic methyl group and of the two terminal methylene protons present in IV are no longer observed. Hydrogenation of IV over a palladium-charcoal catalyst gave two isomers, Va and the 1-3,4 *cis*-*iso*-hexahydrocannabinol Vb. It seems that the palladium catalyst causes an initial, partial isomerization of IV to VI which on hydrogenation gives the two possible C-4 isomers. Isomerizations of this type during hydrogenations catalysed by palladium are known [7 - 11], though the exact mechanism of the reaction is apparently obscure. The NMR of Vb is very similar to that of Va, the differences being mainly in the splitting pattern of the isopropyl methyl groups. Compounds Va and Vb are different (IR, NMR, TLC) from the 1-*trans*-hexahydrocannabinols VIIa and VIIb, (Scheme 1), obtained [4] on hydrogenation of 1-Δ^1-*trans*-THC (II). They are also different from the dl-*cis*-hexahydrocannabinols VIIIa and VIIIb obtained on catalytic hydrogenation of the recently reported [12] dl-Δ^1-*cis*-THC (IX) (Scheme 3). These observations show that 1-Δ^8-*iso*-THC (IV) does not possess the same ring system as the normal tetrahydrocannabinols.



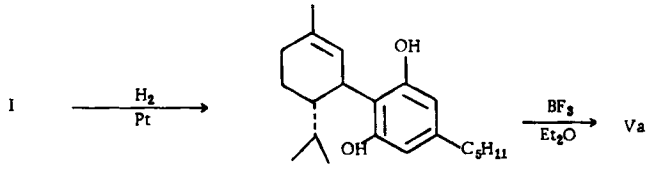
Scheme 1



Scheme 2



Scheme 3



Scheme 4

Compound Va was also prepared by an unequivocal route. Cannabidiol (I) was partially hydrogenated to dihydrocannabidiol (X) (Scheme 4) [13]. The TLC indicated the presence of one compound only, except for some starting material. The IR spectrum of pure X lacked the terminal methylene band at 890 cm^{-1}; in the NMR spectrum the signal of the C-2 olefinic proton (at 5.45 ppm) could still be observed, while those of the terminal methylene group present in the parent compound were missing. Acid catalysed cyclization of X gave Va, fully identical with the product obtained by reduction of IV.

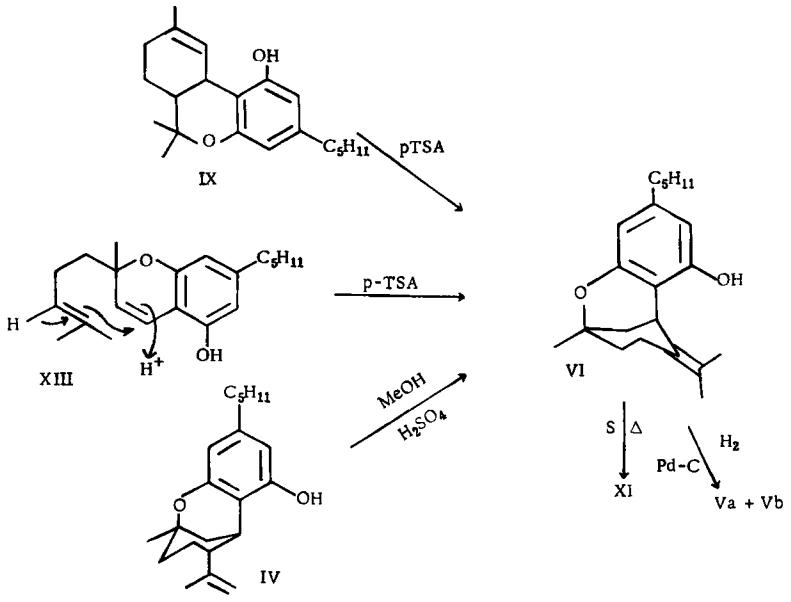
The possibility that the *iso*-THC IV obtained in the acid isomerization of cannabidiol is not a cyclization product but a rearrangement one can be eliminated on the basis of its dehydrogenation with sulfur which gives cannabinol (XI) (Scheme 2). This dehydrogenation which involves a ring opening followed by ring closure and dehydrogenation is not exceptional from a mechanistic point of view. Since in cannabinol the pattern of the carbon atoms is unrearranged as regards both the normal THC's and the proposed structure for the *iso*-THC's this dehydrogenation represents a proof for the non-rearranged skeletal structure of the *iso*-series.

Another compound of the *iso* series, dl-$\Delta^{4(8)}$-*iso*-THC (VI), can be obtained by acid isomerization of dl-Δ^{1}-*cis*-THC (IX). This reaction has been reported [12] to give dl-$\Delta^{1(6)}$-*cis*-THC (XII) (Scheme 3) being thus parallel to the well known Δ^{1}-*trans*-THC (II) to $\Delta^{1(6)}$-*trans*-THC (III) isomerization [4, 5, 12] (Scheme 1). However, the driving force for the latter reaction is the relief of steric strain, the C-2 hydrogens in III being less hindered than the olefinic C-2 hydrogen in II. From examination of Dreiding models we concluded that in the *cis* series there was no such driving force and hence the suggested Δ^{1} to $\Delta^{1(6)}$-*cis*-THC isomerization was reexamined (Scheme 5). The NMR data reported for "$\Delta^{1(6)}$-*cis*-THC" (XII) are not compatible with the suggested structure. A singlet at 4.19 ppm is assigned to an olefinic proton while no peak at all is attributed to the C-3 proton. The unusually high field assignment for the olefinic proton which is essentially outside the influence of a major shielding factor is hard to explain. The NMR data however fit $\Delta^{4(8)}$-*iso*-THC (VI), the 4.19 ppm peak being due to the allylic-benzylic C-3 proton, which is in the plane of the aromatic ring and is therefore strongly deshielded.*

While dl-Δ^{1}-*trans*-THC acetate (II, acetate) is converted almost quantitatively into dl-$\Delta^{1(6)}$-*trans*-THC acetate (III, acetate) on boiling with p-toluene sulfonic acid in benzene, dl-Δ^{1}-*cis*-THC acetate (IX, acetate) remains unchanged under these conditions. Although the last experiment, being a negative one, should be viewed upon with some reservation, we believe that the above observations point towards two conclusions: (a) The acid catalysed isomerization of Δ^{1}-*cis*-THC (IX) is not a simple double bond migration, but involves the free phenolic group; (b) the formation of $\Delta^{4(8)}$-*iso*-THC (VI) from IX is not a stepwise reaction of a ring cleavage at C-8 followed by a cyclization at C-1, but is apparently a concerted one. Were this a stepwise reaction the formation of $\Delta^{4(8)}$-*cis*-THC acetate (VI, acetate) from Δ^{1}-*cis*-THC acetate (VI, acetate) would have been observed. The intermediate hypothetical monophenol, mono acetate, which would be freely rotating, could have cyclized at C-1 giving VI, acetate.

Boiling 1-Δ^{8}-*iso*-THC (IV) with sulfuric acid in methanol gives 1-$\Delta^{4(8)}$-*iso*-THC (VI) $[\alpha]_{D}^{CHCl_3}$ - 300° (Scheme 5). This isomerization probably proceeds through addition of methanol to the double bond followed by elimination. The 1-$\Delta^{4(8)}$-*iso*-THC (VI) thus obtained is identical in all respects, except optical rotation, with the dl-product obtained from dl-Δ^{1}-*cis*-THC (IX) as described above.

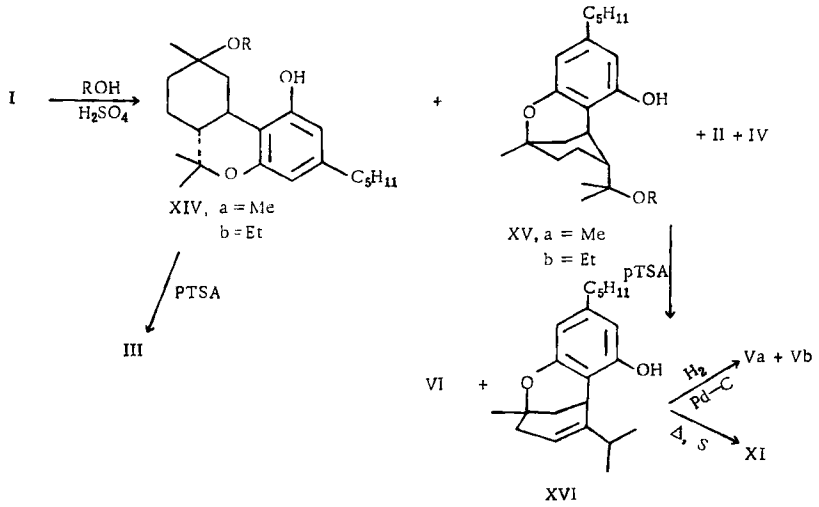
* This assignment is compatible with that reported for a proton in an essentially identical environment in monomethyl-gamboginate [14]. It also fits with the NMR of IV, where the C-3 proton appears at 3.35 ppm. The additional allylic deshielding thus causes a paramagnetic shift of 0.84 ppm.



Scheme 5

dl-$\Delta^{4(8)}$-*iso*-THC (VI) was also synthesized from cannabichromene (XIII) [15, 16, 17] by acid cyclization (Scheme 5). The mechanism of this reaction (see arrows in XIII) is probably identical with that suggested by Ollis and co-workers [14] for the closely related conversion of gambogic to gamboginic acid. The absence of rotation in VI formed from the natural, supposedly optically active cannabichromene (XIII) can be explained either by assuming that in the cyclization the assymmetric center is somehow destroyed, an assumption without a sound mechanistic basis, or that natural cannabichromene is a racemate, the optical activity reported for it (oil, $[\alpha]_D$ -9° [15] crystals, m. p. 144 - 6° and $[\alpha]_D$ + 3.4 [16]) being due to impurities. We believe that the latter supposition is the correct one. We have now subjected natural cannabichromene to further purification. The final product obtained, although identical by NMR and IR to the compound previously reported by us [15] has virtually no rotation*.

* Cannabichromene, in our hands, could not be induced to crystallize. A TLC comparison of our oily cannabichromene [15] with a minute sample of crystalline cannabichromene [16] showed that the two compounds were different. A TLC of a less pure oily cannabichromene (this sample as well as the crystalline one were kindly supplied to us by Dr. U. Claussen) showed the presence of two compounds. One of them was identical (by TLC only) with the cannabichromene isolated by us, while the other — with the crystalline product of Claussen et al. [16]. We believe that the crystalline compound is an impurity in the oily cannabichromene as Dr. Claussen has now informed us.



Scheme 6

1-$\Delta^{4(8)}$-*iso*-THC (VI) was also prepared through a different sequence of reactions. Treatment of cannabidiol (I) with sulfuric acid in methanol gave a mixture of mainly four compounds (Scheme 6), which could be separated into 1-8-methoxy-*iso*-hexahydro-cannabinol (XVa), 1-Δ^{8}-*iso*-THC (IV), 1-Δ^{1}-THC (II) and 1-1-methoxyhexahydrocannabinol (XIVa). The 1-methoxy isomer XIVa, which possesses the expected NMR spectrum, was quantitatively converted into 1-$\Delta^{1(6)}$-THC (III) by boiling with p-toluene sulfonic acid in benzene. The NMR spectrum of XVa, an isomer of XIVa, is very similar to that of latter and we were initially led to believe that we had the second 1-methoxy isomer. However, XVa on boiling with p-toluene sulfonic acid in benzene gave 1-$\Delta^{4(8)}$-*iso*-THC (VI) together with the unknown d-Δ^{4}-*iso*-THC (XVI) (Scheme 6). In the NMR spectrum of XVI the C-3 proton appears at 3.75 ppm., being deshielded both by the aromatic ring and by the double bond.

Both 1-$\Delta^{4(8)}$-*iso*-THC (VI) and d-Δ^{4}-*iso*-THC (XVI) on hydrogenation over palladium gave a mixture of the *iso*-hexahydrocannabinols Va and Vb, identical with the products obtained on palladium hydrogenation of 1-Δ^{8}-*iso*-THC (IV). Compounds VI and XVI on dehydrogenation with sulfur gave cannabinol (XI). These correlations provide further support to the proposed structures.

In a previous paper [4] we have reported that cannabidiol reacts with ethanol in the presence of hydrochloric acid giving a mixture of II, III, IV and the two possible 1-ethoxy-hexahydrocannabinols (XIVb) (Scheme 6). While the structure of one of these, XIVb, m. p. 141 - 2°, was substantiated by conversion into 1-$\Delta^{1(6)}$-THC (III), the other ethoxy isomer, m. p. 86 - 7°, was assumed to possess the assigned structure on the basis of analogy only. In view of the results reported above we have repeated this reaction. The ethoxy compound, m. p. 86 - 7°, for which we previously suggested structure

XIVb, possesses in fact structure XVb. On boiling with p-toluene sulfonic acid in benzene XVb gives a mixture of VI and XVI.

Experimental

Instrumentation: IR: Perkin-Elmer Model 137. NMR: Varian A-60. TLC: Kieselgel G. Merck, elution with pentane-ether (4:1). V. P. C.: 0.1% SE-30 on glass beads, column 20 ft., at 230°, He flow 100 cc/min.

Isomerization of Cannabidiol (I) with Boron Trifluoride

To a solution of I (4.8 g) in methylene chloride (200 ml) was added, with stirring, 1 ml of boron trifluoride etherate and the solution was set aside at r. t. for 30 min. Et. (200 ml) and water (200 ml) were added, the organic layer was separated and washed with sodium bicarbonate solution and with saturated sodium chloride solution and dried (Na_2SO_4). NMR examination of the crude oily mixture obtained by evaporation of the solvent showed a terminal methylene to vinylic hydrogen ratio of 1:2. Separation of the mixture was effected by chromatography on Florisil (500 g) and elution was carried out with pentane and with increasing proportions of et. in pentane, a total of 15 l. of solvent being used. Alternating fractions of 250 and 100 ml were collected, the 100 ml fractions were evaporated under reduced pressure and examined by TLC, IR and NMR.

The first compound to be eluted (0.66 g; 1% ether in pentane), showing one spot on TLC, was identified as 1-Δ^8-*iso*-THC (IV) (4), b. p. 200-210° (bath)/1 mm.

1-Δ^8-iso-THC 3,5-dinitrobenzoate

The dinitrobenzoate of IV was prepared by warming IV (0.16 g) with excess 3,5-dinitrobenzoyl chloride and 0.2 ml of pyr. in a bath at 120° for 1½ h. Bz. was added and the mixture was directly chromatographed of silica gel (10 g). Elution was carried out with 2% et. in pentane. Fractions showing one spot on TLC (slightly less polar than starting material) were combined yielding an uncrystallizable 3,5-dinitrobenzoate (0.13 g). $\delta(CCl_4)$ 1.33s, 1.58s (C_1- and C_8-Me), 3.25s, br (C_3-H), 4.8s, br (—C=C$\underline{H}_2$), 6.45s, 6.53s (two aromatic protons; slightly split) 9.20s (nitro aromatic ring protons).

Catalytic Hydrogenation of 1-Δ^8-iso-THC (IV)

(a) With Raney nickel. Distilled IV was reduced in EtOH over freshly prepared Raney nickel until the rapid uptake of hydrogen had ceased. The compound obtained after filtration of the catalyst and evaporation of the solvent showed only one spot on TLC and was identical by IR, NMR and TLC to the second isomer, Va, obtained by reduction of 1-$\Delta^{4(8)}$-*iso*-THC (VI) (see below).

(b) With palladium on charcoal. Compound IV (0.17 g.) was reduced in ethanol, at atmospheric pressure, over 10% palladium on

charcoal catalyst until the uptake of hydrogen had ceased (1 molar equivalent). The reduced material showed two spots on TLC in a ratio of ca. 1:1 (by area of spots). Chromatography on Florisil (20 g) and elution with pentane-ether 99:1 separated the two epimers, which were identical by TLC, IR and NMR with those (Va and Vb) obtained by reduction of compound VI (see below).

8, 9-Dihydrocannabidiol (X)

Cannabidiol (I) (1 g) was reduced in EtOac (30 ml) over Adam's catalyst (100 mg) at atm pressure. The hydrogenation was stopped after an uptake of 72 ml of hydrogen. TLC of the total material showed the formation of one compound, with some starting material still present. The mixture obtained upon evaporation of the solvent was chromatographed on alumina (100 g; Merck Acid-washed). Elution with 4% et. in pentane yielded 8, 9-dihydrocannabidiol (X), b. p. 200 - 220° (bath)/1 mm, $[\alpha]_D^{CHCl_3}$ -87, λ_{max}^{EtOH} 274, 282 mμ (ε 1080, 1080). δ(CCl_4) 0.78, 0.88 (isopropyl), 1.76s (C_1-Me), 3.84s, br (C_3-H), 5.45s, br (C_2-H), 6.05s (2 aromatic protons). Molecular weight (mass spectrum), 316 (calculated -316). (Fd.: C, 79.91; H, 10.08. $C_{21}H_{32}O_2$ req.: C, 79.90; H, 10.19%).

Isomerisation of 8,9-dihydrocannabidiol (X) to Va

To a solution of distilled X (0.2 g) in methylene chloride (5 ml) was added boron trifluoride etherate (0.1 ml) and after 15 min at r. t. the solution was worked-up by the addition of et. and washing with water, with sodium bicarbonate solution and with saturated sodium chloride solution. The dried solution (Na_2SO_4) yielded quantitatively a compound showing one spot on TLC which was distilled and, identified as the dihydro-*iso*-THC Va, $[\alpha]_D^{CHCl_3}$ -18.5°, identical by TLC, IR and NMR with Va, the second epimer from the reduction of VI (see below).

Reduction of d, 1-3, 4-cis-Δ^1-THC (IX)

Compound IX [12] (80 mg) was reduced in EtOH over 10% palladium on charcoal catalyst until the uptake of hydrogen had ceased. TLC of the total reduced material showed two spots. NMR of the total material showed no unsaturation. Chromatography on Florisil (15 g) was monitored by TLC. Elution with 1% et. in pentane yielded two epimeric compounds. The first epimer obtained as a distillable oil, was the 3, 4-*cis*-hexahydrocannabinol VIIIa, δ(CCl_4) 0.92, 1.21, 1.33 (methyl signals), 3.25 br (C_3—H), 5.90s, 6.10s (aromatic protons). Molecular weight (mass spectrum) 316 (calculated -316). (Fd.: C, 79.95; H, 9.95; $C_{21}H_{32}O_2$ req.: C, 79.70; H, 10.19%). The second isomer was the 3.4-*cis*-hexahydrocannabinol VIIIb, m. p. 82 - 83° (pentane), δ(CCl_4) 0.88, 0.92, 1.27, 1.37 (methyl signals), 2.75 - 3.16 br (C_3—H), 5.90s, 6.10s (aromatic protons). Molecular weight (mass spectrum), 316 (calculated -316). (Fd.: C, 79.82; H, 10.15; $C_{21}H_{32}O_2$ req.: C, 79,70; H, 10.19%).

Dehydrogenation of Δ^4-, $\Delta^{4(8)}$ - *and* Δ^8 *-iso-THC (XVI, VI and IV)*

Dehydrogenation was carried out in all cases by warming the compound with sulfur at 200°, under nitrogen, in a distillation finger for ca. 1 h, by which time evolution of hydrogen sulfide slowed down considerably. The material was then distilled and the distillate, containing sulfur, was taken in pentane and filtered through 1 - 2 gr of alumina. Cannabinol (XI) [6] was the main compound obtained, as evidenced by TLC, IR and VPC (some starting material remained in all cases).

d, 1-$\Delta^{4(8)}$ *-iso-THC (VI) from d, 1-cis-*Δ^1 *-THC (IX)*

Compound IX (0.1 g) was refl. in bz. (20 ml) with p-toluene-sulfonic acid (10 mg) for 30 min. The cooled bz. solution was washed with sodium carbonate solution and with water and dried (Na_2SO_4). Upon evaporation of solvent almost pure $\Delta^{4(8)}$-*iso*-THC (VI) was obtained, as shown by TLC, IR and NMR, of the crude material as compared to pure VI. Further purification was achieved by chromatography on alumina (20 g) coated with silver nitrate (12% by weight). Pentane-ether 19:1 eluted a substance that slowly solidified. It was recrystallized from pentane, yielding pure VI, m. p. 64 - 5°, undepressed upon admixture with an authentic sample, kindly sent to us by Professor W. A. Mosher (cf. [8] and text).

d, 1-3,4-cis-Δ^1 *-THC Acetate and Attempted Isomerisation*

The acetate was prepared from IX (135 mg) with acetic anhydride in pyridine (overnight, r. t.) and purified by chromatography on Florisil (10 g). Elution with 1% et. in pentane yielded the pure acetate as a distillable oil showing one spot on TLC $\delta(CCl_4)$ 0.90 (terminal side chain methyl), 1.25s, 1.35s (methyls α to oxygen), 1.65s (C_1—Me), 2.24s (acetate methyl), 3.33 br (C_3—H), 5.75 br (C_2—H), 6.25s, 6.38 (aromatic protons; slightly split). Molecular weight (mass spectrum) 356 (calculated - 356). (Fd. : C, 77.58; H, 9.15; $C_{23}H_{32}O_3$ req. : C, 77.49; H, 9.05%).

Boiling the acetate in benzene with p-toluensulfonic acid, as for IX above, for a few hours yielded mainly unchanged material. Upon chromatography on alumina IX was recovered by hydrolysis of the ester.

1-3, 4-trans-Δ^1 *-THC Acetate and d, 1-3, 4-trans-*Δ^1 *-THC Acetate*

Acetylation of 1- and d, 1-Δ^1-THC's was carried out on 0.5 g of product in 5 ml of pyridine with 1 ml of acetic anhydride. The crude products were chromatographed on Florisil (20 g) and pentane-ether 99:1 eluted the pure compounds (TLC) which were distilled.

1-acetate $[\alpha]_D^{CHCl_3}$ -180°, λ_{max}^{EtOH} 276, 282 mμ (ε 1980, 1890). $\delta(CCl_4)$ 0.89 (terminal side-chain methyl), 1.05s, 1.33s (two methyls α to oxygen), 1.63s (C_1—Me), 2.16s (acetate methyl), 2.94 d, br (C_3—H), 5.92s, br (C_2—H), 6.25s, 6.40s (aromatic protons; slightly split). (Fd. : C, 77.81; H, 9.30; $C_{23}H_{32}O_3$. req. : C, 77.49; H, 9.05%).

d, 1-acetate identical in all respects, except for rotation, with the 1-acetate. (Fd. : C, 77.69; H, 9.01%).

1-3, 4-trans-$\Delta^{1(6)}$-THC Acetate

Prepared as Δ^1 acetates above. $[\alpha]_D^{CHCl_3}$ -254°, λ_{max}^{EtOH} 276, 282 mμ (ε 2060, 1880). δ (CCl_4) 0.90 (terminal side-chain methyl), 1.07s, 1.32s (two methyls α to oxygen), 1.67s (C_1-Me), 2.16s (acetate methyl), 2.75d, br(C_3—H), 5.38s, br(C_6—H), 6.21s, 6.40s (aromatic protons; slightly split). (Fd. : C, 77.52; H, 9.04%).

Isomerisation of d, 1-3, 4-trans-Δ^1-THC Acetate

The acetate (0.35 g) was refluxed in bz (50 ml) with p-toluensulfonic acid (50 mg) for 1½ hr. The compound obtained after work-up (see above) was practically pure d, 1-3, 4-*trans*-$\Delta^{1(6)}$-THC acetate, as shown by TLC, IR and NMR.

Isomerisation of cannabichromene (XIII) to d, 1-$\Delta^{4(8)}$-iso-THC (VI)

Cannabichromene (XIII) (80 mg) in bz (25 ml) was boiled under refl. for 30 min with p-toluene sulfonic acid (50 mg). The reaction mixture was cooled washed with Na_2CO_3 aq. and NaCl aq., dried and evpd. The material obtained was purified by preparative TLC yielding 37 mg. dl-$\Delta^{4(8)}$-*cis*-THC (VI) identical with the compound obtained from acid isomerization of IX (TLC, IR and NMR comparisons).

Treatment of Cannabidiol (I) with Sulfuric Acid in Methanol

Cannabidiol (I) (1 g) was dissolved in MeOH (20 ml) and conc. sulfuric acid (0.3 ml) was added with stirring and cooling. The solution was left at r. t. for 3 days and was then worked-up by the addition of water (200 ml), extraction with et. washing the et. solution with sodium bicarbonate solution and drying (Na_2SO_4). The total crude material obtained upon evaporation of the solvent showed mainly four spots on TLC, all more polar than I. Chromatography on alumina (100 g) and elution with increasing proportions of et. in pentane yielded four substances identified as follows: (a) 8-methoxy-iso-hexahydrocannabinol (XVa) (0.42 g, eluted with 10% et. in pentane), 3.05 br (C_3 proton), 3.38s ($OC\underline{H}_3$), 6.02, 6.08 (two aromatic protons; slightly split), 7.15 (O<u>H</u>). Molecular weight (mass spectrum) 346 (calculated 346). (Fd. : C, 76.38; H, 9.73. $C_{22}H_{34}O_3$ req. : C, 76.26; H, 9.89%). (b) 1-Δ^8-iso-THC (IV) (0.13 g; eluted with 15% ether in pentane) identified by TLC, IR and NMR, (c) 1-3, 4-trans-Δ^4-THC (II) (0.18 g, eluted with same solvent mixture), containing a small amount of IV. (d) 1-methoxy-hexahydrocannabinol (XIVa) (0.11 g, eluted with 20-40% ether in pentane), m. p. 134-135° (pentane). δ(CCl_4) 1.00s, 1.14s, 1.32s (3 $C\underline{H}_3$ groups), 3.32s ($OC\underline{H}_3$, probably also covers C_3 proton), 5.92, 6.10 (two aromatic protons, slightly split), 6.25 (O<u>H</u>). Molecular weight (mass spectrum) 346 (calculated -346). (Found: C, 76.39; H, 9.87%).

d-Δ^4-iso-THC (XVI)

Compound XVa (0.91 g) was refl. in bz (20 ml) with p-toluensulfonic acid (30 mg) for 2 h. The total material after work-up showed mainly one spot on TLC. Chromatography on silver nitrate-coated alumina and

elution with 15% ether in pentane yielded oily fractions, having all the same Rf value on TLC. IR and VPC showed however that two compounds were obtained. Fractions that were pure by VPC were combined and distilled.

The first compound eluted was identified as d-Δ^4-*iso*-THC, (XVI) $[\alpha]_D^{CHCl_3}$ + 150°, λ_{max}^{EtOH} 276, 282 mμ (ε 1020, 1020). δ(CCl_4) 0.95d (J = 7 cps) (C_8—Me), 1.10d (J = 7 cps) (C_8—Me), 1.45s ($C\underline{H}_3$—C—O—), 3.75 br (C_3—H), 5.1 (O$\underline{H}$), 5.25br (olefinic H), 5.95, 6.25 (aromatic protons, slightly split).
(Found: C, 80.09; H, 9.59. $C_{21}H_{30}O_2$ requires: C, 80.21; H, 9.62%).

3, 5-Dinitrobenzoate (From XVI (0.21 g) and 3, 5-dinitrobenzoyl chloride (0.3 g) by warming without solvent to 150° for 1 h and chromatography on silica gel), m. p. 117 - 118° (pentane).
(Found: C, 66.00; H, 6.22; N, 5.41. $C_{28}H_{32}N_2O_7$ req.: C, 66.13; H, 6.34; N, 5.51%).

The second compound eluted was identified as 1-$\Delta^{4(8)}$-*iso*-THC (VI), $[\alpha]_D^{CHCl_3}$ -300°, identical in all other respects to d, 1-$\Delta^{4(8)}$*iso*-THC.
(Found: C, 80.43; H, 9.47).

3, 5-Dinitrobenzoate (prepared as for XVI above), m. p. 105-106° δ(CCl_4) 1.40s, 1.48s, 1.62s ($C\underline{H}_3$ groups), 4.2 br (C_3H), 6.32, 6.55 (aromatic protons, slightly split).
(Found: C, 65.90; H, 6.16; N, 5.46%).
Compounds XVI and VI were also obtained from XVb (see text) under the same experimental conditions as those used above for XVa.

The above two compounds (XVI and VI), together with 1-$\Delta^{1(6)}$-THC (III) were also obtained by reacting cannabidiol (I) with sulfuric acid in MeOH and refl. the crude reaction mixture in bz with p-toluensulfonic acid. Chromatography on alumina separated first the mixture of XVI and VI from III and the first two compounds were then separated by chromatography on alumina coated with silver nitrate. The amounts of pure compounds thus obtained from 3 g of I were: XVI, 0.22 g; VI, 0.57 g; III, 0.89 g.

1-$\Delta^{4(8)}$-iso-THC (VI) from 1-Δ^8-iso-THC (IV)

Compound IV (0.20 g) was refluxed in MeOH (15 ml) with sulfuric acid (0.5 ml) for 28 h. The resulting crude product was mainly VI, as shown by IR. Chromatography on alumina yielded pure 1-$\Delta^{4(8)}$-*iso*-THC (VI) (0.14 g).

Catalytic Hydrogenation of 1-$\Delta^{4(8)}$-iso-THC (VI)

Hydrogenation of VI (0.45 g) was carried out in EtOH over 10% palladium on charcoal catalyst at atm. pressure, until absorption of hydrogen had ceased. TLC of the crude reduced material showed two spots in a ratio of ca. 3:1. Chromatography on Florisil (50 g) yielded two distillable epimeric compounds. The first compound was the *iso*-hexahydrocannabinol Vb (0.31 g), $[\alpha]_D^{CHCl_3}$ -22°, λ_{max}^{EtOH} 275, 283 mμ (ε 1300, 1300). δ (CCl_4) 0.75d, br (isopropyl methyls; J = 5 c/sec), 0.88 (terminal side chain methyl), 1.3s (methyl α to oxygen), 3.42s, br(C_3—H), 5.92s, 6.15s

(aromatic protons; slightly split). Molecular weight (mass spectrum), 316 (calculated 316). (Fd.: C, 79.90; H, 10.16. $C_{21}H_{32}O_2$ req.: C, 79.70; H, 10.19%).

The second compound was the *iso*-hexahydrocannabinol Va, $[\alpha]_D^{CHCl_3}$ -19°, λ_{max}^{EtOH} 274, 282 mμ (ε 1200, 1200). δ (CCl_4) 0.92d, 1.07d (isopropyl methyls, hiding the terminal side-chain methyl; J = 6.5 c/sec), 3.27s, br(C_3—H), 5.90s, 6.10s (aromatic protons, slightly split). Molecular weight (mass spectrum), 316 (calculated 316). (Fd.: C, 79.87; H, 10.19%).

Catalytic Hydrogenation of d-Δ⁴-iso-THC (XVI)

The reduction was carried out as for VI above yielding the same two epimers Va and b, where Va was much more abundant, as shown by TLC and NMR. The two epimers were separated and characterized as above.

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