Base-catalysed Double-bond Isomerizations of Cannabinoids: Structural and Stereochemical Aspects

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Base-catalysed double-bond isomerization offers a convenient, high-yield route to a variety of new cannabinoids, as well as to compounds of this group which are accessible with some difficulty. By this route we have obtained optically active Δ^2-tetrahydrocannabinols and Δ^3-tetrahydrocannabinols, the Δ^6-isomer of cannabidiol, and other novel cannabinoids.

The reactions of cannabinoids with acids have been investigated in considerable detail as befits the terpenoid nature of this class of compounds.[1,2] By contrast only a few reactions proceeding through cannabinoid anions have been reported.[3,4] The application of one of these reactions, which was reported by Fahrenholtz *et al.*,[4] is of considerable importance. It allows the conversion of the easily prepared Δ^6-tetrahydrocannabinol (Δ^6-THC) (**1a**) into Δ^1-THC (**2a**) by the addition of the elements of hydrochloric acid across the double bond of Δ^6-THC (**1a**) to yield (**3**), followed by dehydrohalogenation initiated by the adjacent phenoxide ion formed by a strong base.[5]

We report now that by base-promoted anionic isomerizations it is feasible to obtain numerous isomers of natural cannabinoids some of which were hitherto unknown.

Two procedures were followed for the production of cannabinoid anions: A, t-pentyl potassium in toluene–hexamethylphosphoric triamide (HMPA) (6:1) at reflux temperature, and B, n-butyl-lithium solution in hexane (1.65M) admixed with HMPA at 0 °C. These procedures were established after considerable experimentation (see Experimental section) with other solvent systems. HMPA was found to be indispensable for the isomerizations described below.

Δ^1-THC (**2a**).—Under the conditions of procedure B, Δ^1-THC (**2a**) produces an 8:1 mixture of (1*S*,4*R*)-Δ^2-THC (**4a**), m.p. 153—154 °C, and (1*R*,4*R*)-Δ^2-THC (**5a**), m.p. 54—55 °C. Procedure A leads to a 1:9 mixture of (**4a**) to (**5a**) respectively. As isomer (**4a**) has a pseudoaxial methyl substituent on C-1, while (**5a**) has a pseudoequatorial one, these reactions can be interpreted to mean that procedure A leads mainly to the thermodynamically more stable product while procedure B initially promotes a kinetically controlled reaction. Neither isomer reacts appreciably under the conditions of procedure A or procedure B during a period of *ca.* 0.5 h. However, when either (**4a**) or (**5a**) is left in a solution of butyl-lithium in hexane–HMPA (conditions of procedure B) at room temperature for *ca.* 12 h or heated for 0.5 h at 100 °C, identical mixtures [1:9 (**4a**):(**5a**)] are obtained. Boiling either (**4a**) or (**5a**) under the conditions of procedure A for 12—14 h slowly produces the same mixture.

The presence of an allylic-benzylic hydrogen in Δ^1-THC (**2a**) is apparently the main factor for its rapid isomerization; (**4a**) and (**5a**) react at a much lower rate.

Claussen and Korte[6a] have identified racemic Δ^2-THC, m.p. 128 °C, as a minor product formed in the classical synthesis of racemic Δ^3-THC (**6a**) as reported in 1940 by the groups of Adams[7] and Todd.[8] The stereochemistry of racemic Δ^2-THC, m.p. 128 °C, was not established at the time. By comparison of the n.m.r. data reported (and now confirmed by us from a sample kindly supplied by Professor Korte) with those of (1*S*,4*R*)-Δ^2-THC (**4a**) and (1*R*,4*R*)-Δ^2-THC (**5a**) it was established that the racemic compound possesses structure (**5a**) (relative stereochemistry only).

Attempted isomerizations of either (**4a**) or (**5a**) under various basic conditions did not give any appreciable amounts of Δ^3-THC isomers. Hence this isomerization was undertaken with toluene-*p*-sulphonic acid in benzene. Under these conditions (1*R*,4*R*)-Δ^2-THC (**5a**) led to (1*R*)-Δ^3-THC (**6b**), $(\alpha)_D$ +114°; (1*S*,4*R*)-Δ^2-THC (**4a**) led to (1*S*)-Δ^3-THC (**6c**), $(\alpha)_D$ −117°. (1*R*)-Δ^3-THC (**6b**) has previously been prepared from (*R*)-(+)-pulegone (**7**).[9,10] The rotations of (**6b**)[9,10] reported vary from *ca.* +70° to *ca.* +135°. As the absolute stereochemistry of (*R*)-(+)-pulegone has been unequivocally established,[11] this correlation determines the stereochemistry of all THC isomers described above.

Double-bond isomerization of Δ^1-THC takes place also when the free phenolic group is blocked as a methyl ether; the ratio of (**4c**) to (**5c**) is 1:1 when Δ^1-THC methyl ether (**2b**) is isomerized under the conditions of procedure A. By procedure B only one compound, (1*R*,4*R*)-Δ^2-THC methyl ether (**5c**), is obtained.

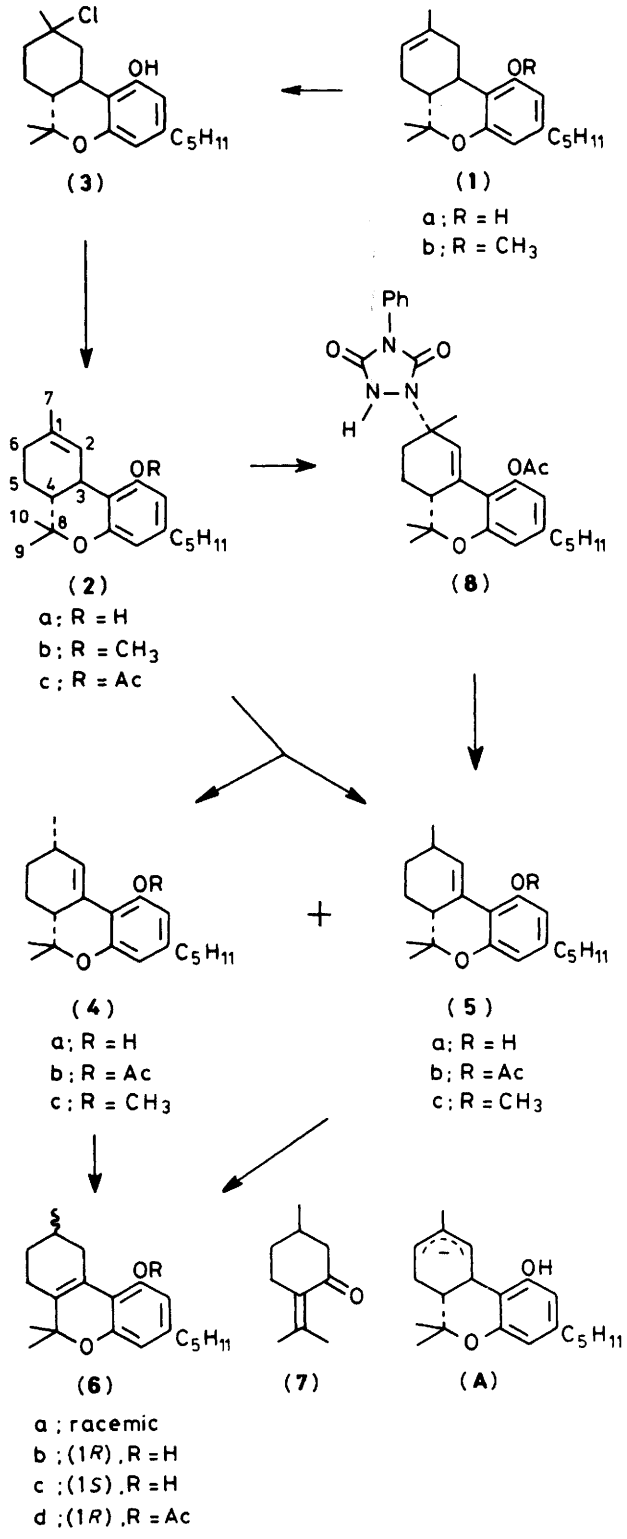
Prior to the investigations on the base-catalysed isomerizations described above we had developed, for biological testing, an alternative route to (1*R*,4*R*)-Δ^2-THC (**5a**). It was based on the ene reaction of Δ^1-THC acetate (**2c**) with 4-phenyl-4*H*-1,2,4-triazole-3,5-dione which led to the adduct (**8**). The stereochemistry indicated for C-1 is based on the known mechanism of the ene reaction:[12] the proton which is removed from C-3 and the group which is newly attached (on C-1) have to be on the same side of the molecule. Sodium borohydride reduction of (**8**) gave (**5a**), identical (except for a minor difference in rotation value) with the product obtained from the anionic rearrangement of Δ^1-THC (**2a**). Acid-catalysed isomerization, as described above, of (**5a**) obtained in this sequence led to (1*R*)-Δ^3-THC (**6b**), $[\alpha]_D$ + 121°.

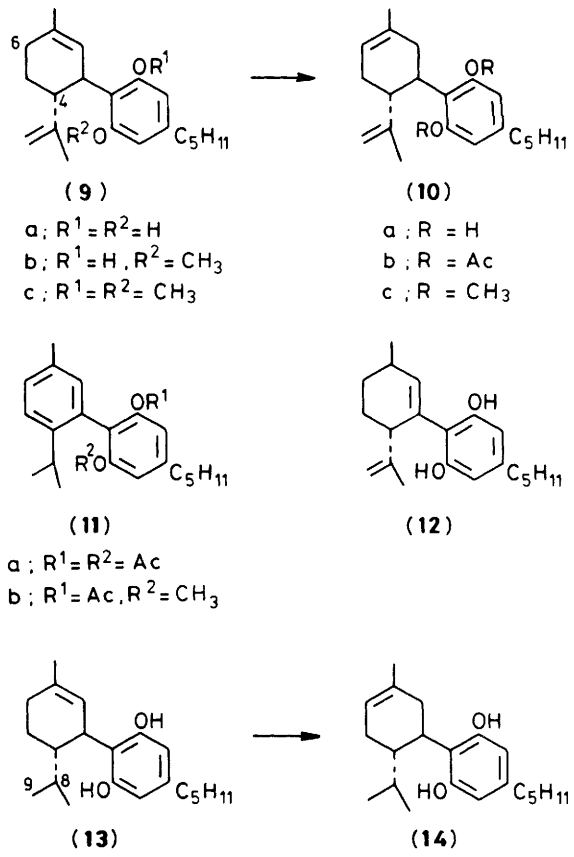
Δ^6-THC (**1a**).—Under the conditions of procedure B, Δ^6-THC (**1a**) isomerizes to a mixture of the Δ^2-THC's (**4a**) and (**5a**) in the ratio *ca.* 3:2. This reaction presumably proceeds through the intermediacy of Δ^1-THC (**2a**). Unexpectedly, Δ^6-THC remains unchanged under the conditions of procedure A.

The methyl ether of Δ^6-THC, (**1b**), does not isomerize under the conditions of procedures A or B. We assume that the Δ^6-THC isomerization proceeds *via* the formation of a phenoxide ion which abstracts the allylic C-2 proton, producing the delocalized ion (A) which may lead to Δ^2-THC (**4a**) and/or (**5a**). The methyl ether (**1b**) obviously cannot undergo the initial stage of this rearrangement process.

Cannabidiol (**9a**).—Under the conditions of procedure A, cannabidiol (**9a**) isomerizes in a high yield to the Δ^6 isomer (**10a**). Procedure B leads to the same isomer although in lower yield.

While the chemistry and pharmacology of Δ^6-THC (**1a**) have been investigated in great detail, the Δ^6 isomer of cannabidiol,



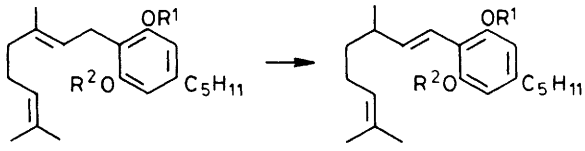


(10a), has not been reported up to now. The racemate of the Δ^6 isomer of dimethylcannabidiol, **(10c)**, has been synthesized by Korte *et al.*[13] *via* a rather lengthy route. Recently, in connection with a project involving the determination of structure–activity relationships of cannabinoids as antiepileptic agents, we prepared **(10a)** *via* a three-step sequence.[14]

Neither monomethylcannabidiol **(9b)** nor dimethylcannabidiol **(9c)** isomerize to the respective Δ^6 isomers under the conditions of either of our procedures. On prolonged heating (procedure A) of **(9b)** the fully aromatic compound **(11b)** is produced (after acetylation) as the major identifiable product. Under no conditions were we able to identify Δ^2 isomers of cannabidiol, **(12)**.

8,9-Dihydrocannabidiol **(13)** does not undergo an isomerization under the conditions of procedure B (at 0 °C, for 24 h). On being heated, however, **(13)** smoothly isomerizes to **(14)**, the double bond moving from the β,γ position relative to the aromatic ring to the γ,δ position (rather than to the α,β conjugated one). While the 1,2 double bond in both cannabidiol **(9a)** and in 8,9-dihydrocannabidiol **(13)** isomerizes to the same position, the rate of this reaction in **(9a)** is considerably higher. This may be due, in part, to the possible formation in **(9a)** of a C-4 carbanion by intramolecular abstraction of the C-4 proton by the phenoxide ion, which is placed in the same plane as the C-4 proton. This C-4 anion may then lead to the C-6 anion by a proton shift. In **(13)** such a reaction is less probable as the C-4 proton is not allylic.

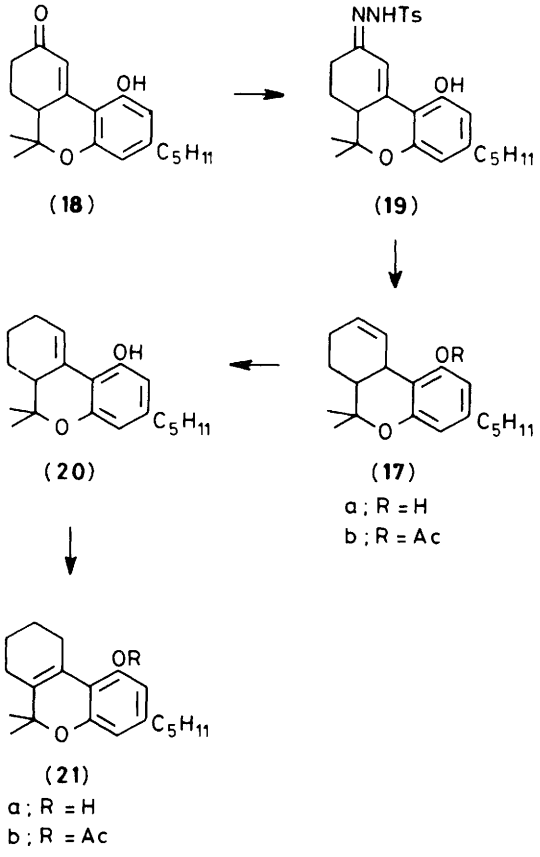
Cannabigerol **(15a)**.—Cannabigerol undergoes isomerization to the conjugated isomer **(16a)** under the conditions of pro-



cedure B on heating. The monomethyl ether (**15b**) produces the corresponding ether (**16b**); unexpectedly, however, cannabigerol dimethyl ether (**15c**) is stable.

On the basis of the large coupling constant observed for the protons of the conjugated double bond (J 16.8 Hz) in (**16a**) the stereochemistry of this double bond is established as *E*.

3,4-cis-7-*Nor*-Δ^1-*tetrahydrocannabinol* (**17a**).—This material was prepared from the known racemic 7-nor-1-oxo-Δ^2-THC (**18**)[4] *via* the hydrazone (**19**) which was then reduced with sodium borohydride (*cf.* ref. 15). We place the double bond in (**17a**) in the 1,2 position, rather than in the alternative 1,6 position, on the basis of the considerable shift of the C-2 olefinic proton observed on acetylation. Such a shift would not be expected if the double bond were in the 1,6 position (*cf.* ref. 16). The relative stereochemistry of the hydrogen atoms at positions C-3 and C-4 is *cis*. This is based on the well documented[4,17] differences between the chemical shifts of the C-9 and C-10 methyl groups in the *cis* series (*ca.* 0.08—0.15 p.p.m.) and those in the *trans* series (*ca.*0.25—0.35 p.p.m.). In (**17a**) and (**17b**) the difference observed is 0.14 p.p.m.



Under the conditions of procedure A nor-Δ^1-THC (**17a**) isomerizes smoothly to 7-nor-Δ^2-THC (**20**) in high yield. Further isomerization (potassium t-butoxide–toluene–HMPA, see Experimental section) leads to the known[9,18] 7-nor-Δ^3-THC (**21a**).

Discussion

In the above described reactions the initial stage presumably is the formation of phenoxy and/or hydrocarbon anions, the latter being probably of delocalized (π) character. The nature of these anions, the stereochemistry of the initial olefin, and the reagent used are presumably the main factors which are responsible for the formation of kinetically and/or thermodynamically preferred products. The interplay between these factors is apparently quite subtle.

The isomerization of Δ^1-THC (**2a**) to the conjugated Δ^2-THC's (**4a**) and (**5a**) takes place regardless of whether the phenolic group is free or blocked, although the yields and the ratios of the products obtained are influenced by the state of the phenolic group.

In the cannabidiol series no conjugation takes place. We assume that, as the two rings are almost perpendicular to each other,[19] they are not suitably orientated to enhance conjugation. The requirement that both phenolic groups be free for the isomerization of the double bond from the Δ^1 to the Δ^6 position to take place in the cannabidiol-type compounds apparently indicates an intramolecular phenoxy-anion-assisted reaction. The nature of this reaction is yet unknown.

In the cannabigerol series conjugation takes place as long as at least one of the phenolic groups is free. As in the cannabidiol series the nature of this reaction is obscure.

In summary, through the various isomerization procedures described above it is possible to obtain the optical isomers of Δ^2-THC and Δ^3-THC, the Δ^6 isomer of cannabidiol, and other novel cannabinoids with ease and in excellent yields.

Experimental

Unless otherwise stated the following apply. Mass spectra were recorded on a LKB 2091 Gas Chromatograph–Mass Spectrometer at 70 eV. I.r. spectra were recorded as thin films (for oils) and in Nujol mulls or in KBr discs (for solids) on a Perkin–Elmer, Grating Infrared Spectrophotometer, model 457. U.v. spectra were taken for solutions in ethanol on a Varian U.v.–Vis spectrophotometer, model 635. ^{1}H N.m.r. spectra were determined at 60 MHz on a Bruker W.P. 60 or at 300 MHz on a Brucker W.H. 300 instrument. M.p.s are uncorrected. They were measured in closed capillaries in a Thomas-Hoover instrument. Column chromatography was performed by medium-pressure liquid chromatography (m.p.l.c.) with an FMI pump on Merck Kieselgel 60, 230—400 mesh ASTM, with mixtures of diethyl ether (ether) and light petroleum (b.p. 60—80 °C) in the ratios 2:98 or 5:95. HMPA was purified by distillation under reduced pressure over calcium hydride. Butyl-lithium in hexane was commercially obtained from Aldrich. Potassium t-butoxide was purchased from Fluka.

Reagent Systems.—Procedure A. Metallic potassium (0.6—1.2 g, 15—30 mg-atom) was added to t-pentyl alcohol (50 ml) and the mixture was boiled under nitrogen until the disappearance of potassium was complete (*ca.* 1 h). The excess of alcohol was distilled off and a mixture of dry toluene (50 ml) and HMPA (8 ml) was added to the slurry. After a clear solution was obtained the cannabinoid (3 mmol) was added either as a solid or, for oils, as a solution in toluene (2 ml). The solution was boiled under reflux for the desired amount of time, cooled, poured over 1M hydrochloric acid in ice, and extracted with ether (2 × 50 ml). The extracts were washed successively with water, saturated aqueous sodium hydrogen carbonate, and saturated sodium chloride, then dried ($MgSO_4$) and evaporated. The reaction products were chromatographed by m.p.l.c.

Procedure B. A solution of butyl-lithium in hexane (1.65 mol) (*ca.* 5 ml) was injected under nitrogen into a stirred solution of the appropriate cannabinoid (3mmol) in HMPA (25 ml) at 0 °C until a dark cherry red colour was observed. The reaction mixture was then poured onto 1M hydrochloric acid and worked up as described in procedure A.

Various other procedures were tried: t-pentylpotassium in boiling toluene, sodium hydride in boiling toluene, a 1:1 mix-

ture of 2M sodium hydroxide–acetonitrile at reflux temperature, and n-butyl-lithium in toluene–HMPA (50:8 v/v) gave no reaction with cannabidiol (**9a**). n-Butyl-lithium (1:65M in hexane) in boiling toluene gave an intractable mixture with cannabidiol. When commercially available potassium t-butoxide (Fluka) was substituted for the t-pentylpotassium in procedure A, mixtures of Δ^2-THC's (**4a**) and (**5a**) and Δ^3-THC's (**6b**) and (**6c**) were obtained from Δ^1-THC (**2a**).

Isomerization of Δ^1*-THC* (**2a**).—*Procedure A*. The reaction solution containing Δ^1-THC (942 mg, 3mmol) was boiled for 1 h. On chromatography two compounds were obtained. The first compound eluted was (1*R*,4*R*)-Δ^2-THC (**5a**) (0.754 mg, 80%), m.p. (solidification at −5 °C) 54—55 °C; $[\alpha]_D$ −70°; $\lambda_{max.}$ 227 (ε 25 700), 265 (15 770), and 271sh nm (13 440); $\nu_{max.}$ (Nujol) 3 480, 1 620, 1 570, 1 450, 1 365, 1 265, 1 235, 1 180, 1 145, and 1 045 cm^{-1}; δ($CDCl_3$) 0.87 (3 H, t, ω-CH_3), 1.09 (3 H, d, *J* 7.2 Hz, 7-H_3), 1.12 and 1.39 (2 × 3 H, 2 s, 9- and 10-H_3), 2.44 (2 H, t, benzylic), 5.42 (OH, s), 6.21 and 6.24 (2 × 1 H, 2 s, ArH), and 6.46 (1 H, m, vinylic); *m/z* 314 (M^+, 100%), 299 (92), 285 (8), 271 (42), 258 (25), 243 (21), and 231 (33) (Found: C, 80.1; H, 9.7. $C_{21}H_{30}O_2$ requires C, 80.21; H, 9.62%). The second compound eluted was (1*S*,4*R*)-Δ^2-THC (**4a**) (0.085 mg, 9%), m.p. 153—154 °C (from cold pentane); $[\alpha]_D$ −133°; $\lambda_{max.}$ 226 (ε29 000), 264 (16 254), and 272sh nm (13 484); $\nu_{max.}$ (Nujol) (3 470, 1 620, 1 570, 1 450, 1 375, 1 175, and 1 050 cm^{-1}; δ($CDCl_3$) 0.87 (3 H, t, ω-CH_3), 1.07 (3 H, d, *J* 7.4 Hz, 7-H_3), 1.13 and 1.43 (2 × 3 H, 2 s, 9- and 10-H_3), 2.43 (2 H, t, benzylic), 5.38 (OH, s), 6.20 and 6.23 (2 × 1 H, 2 s, ArH), and 6.60 (1 H, d, *J* 5.4 Hz, vinylic); *m/z* 314 (M^+, 100%), 299 (70), 285 (6), 271 (46), 258 (36), 247 (20), 244 (16), 231 (80), and 193 (18) (Found: C, 80.3; H, 9.35. $C_{21}H_{30}O_2$ requires C, 80.25; H, 9.55%).

Procedure B. Under the conditions of this procedure the ratio of (**4a**) to (**5a**) obtained was 8:1. The acetates of the above two Δ^2-THC's were both oils: (1*R*,4*R*)-Δ^2-THC acetate (**5b**), $[\alpha]_D$ −44°; $\lambda_{max.}$ 257 (ε 10 920), 265sh (9 494), 298 (3 680), and 305 nm (3 560); $\nu_{max.}$(thin film) 1 770, 1 625, 1 560, 1 430, 1 370, 1 205, 1 180, 1 150, 1 100, 1 050, 895, and 870 cm^{-1}; δ($CDCl_3$) 0.87 (3 H, t, *J* 6.6 Hz, ω-CH_3), 1.05 (3 H, d, *J* 7.2 Hz, 7-H_3), 1.10 and 1.38 (2 × 3 H, 2 s, 9- and 10-H_3), 2.27 (3 H, s, CH_3CO), 2.48 (2 H, t, *J* 7.8 Hz, benzylic), 6.34 (1 H, s, ArH), 6.37 (1 H, d, *J* 1.5 Hz, ArH), and 6.52 (1 H, d, *J* 1.5 Hz vinylic); *m/z* 356 (M^+, 100%), 341 (20), 314 (85), 299 (70), 297 (90), 271 (30), 258 (15), 243 (18), and 231 (20); (1*S*,4*R*)-Δ^2-THC acetate (**4b**), $[\alpha]_D$ −107°; $\lambda_{max.}$ 256 (ε 12 234), 265sh (10 426), 300 (4 043), and 307 nm (3 830); $\nu_{max.}$(thin film) 1 770, 1 620, 1 560, 1 425, 1 365, 1 200, 1 175, 1 045, 890, and 860 cm^{-1}; δ($CDCl_3$) 0.87 (3 H, t, ω-CH_3), 1.06 (3 H, d, *J* 7.2 Hz, 7-H_3), 1.11 and 1.40 (2 × 3 H, 2 s, 9- and 10-H_3), 2.27 (3 H, s, CH_3CO), 2.48 (2 H, t, *J* 7.2 Hz, benzylic), 6.37 and 6.52 (2 × 1 H, 2 d, *J* 1.8 Hz, ArH), and 6.48 (1 H, d, *J* 3.9 Hz, 2-H); *m/z* 356 (M^+, 88%), 341 (28), 314 (96), 299 (100), 271 (40), 258 (20), 243 (24), and 231 (28).

Isomerization of O-Methyl-Δ^1*-THC* (**2b**).—Isomerization of (**2b**) (328 mg, 1 mmol) under the conditions of procedure A gave the following two C-1 isomers in 85% total yield in the ratio 1:1:(1*R*,4*R*)-Δ^2-THC methyl ether (**5c**) (140 mg, 43%), m.p. 71—72 °C (from cold pentane); $[\alpha]_D$ −72°; $\lambda_{max.}$ 269 nm (ε 15 490); $\nu_{max.}$ (Nujol) 1 610, 1 560, 1 420, 1 365, 1 230, 1 185, 1 175, 1 145, 1 100, 900, 880, 860, and 810 cm^{-1}; δ($CDCl_3$) 0.87 (3 H, t, ω-CH_3), 1.10 and 1.37 (2 × 3 H, 2 s, 9- and 10-H_3), 2.49 (2 H, t, benzylic), 3.82 (3 H, s, OCH_3), 6.27 (2 H, br s, ArH), and 6.83 (1 H, br s, vinylic); *m/z* 328 (M^+, 83%), 313 (100), 297 (10), 285 (21), 257 (13), and 245 (16) (Found: C, 80.4; H, 9.6. $C_{22}H_{32}O_2$ requires C, 80.44; H, 9.82%); (1*S*,4*R*)-Δ^2-THC methyl ether (**4c**), m.p. 80—81 °C (from cold pentane); $[\alpha]_D$ −115°; $\lambda_{max.}$ 268 nm (ε 15 070); $\nu_{max.}$ (Nujol) 1 610, 1 560, 1 420, 1 370, 1 230, 1 185, 1 175, 1 115, 1 105, 1 050 cm^{-1}; δ($CDCl_3$) 0.89 (3 H, t, ω-CH_3), 1.12 and 1.40 (2 × 3 H, 9- and 10-H_3), 2.50 (2 H, t, benzylic), 3.83 (3 H, s, OCH_3), 6.29 (2 H, s, ArH), and 7.01 (1 H, br d, vinylic); *m/z* 328 (M^+, 94%), 313 (100), 297 (9), 285 (21), 257 (15), and 245 (15) (Found: C, 80.2; H, 9.1%). Isomerization of (**2b**) under the conditions of procedure B gave (**5c**) (85%).

The ethers (**4c**) and (**5c**) were also prepared for comparative purposes from (**4a**) and (**5a**) respectively by a standard methylation [methyl iodide, potassium carbonate in dimethylformamide (DMF) at room temperature for 30 min]. Compounds (**4c**) and (**5c**) prepared by the two procedures were identical (m.p., n.m.r. spectra, t.l.c.).

(1R)-Δ^3-*THC* (**6b**).—(1*R*,4*R*)-Δ^2-THC (**5a**) (314 mg, 1 mmol) was boiled in benzene (10 ml) containing toluene-*p*-sulphonic acid (100 mg) for 0.5 h. The benzene solution was washed successively with saturated aqueous sodium hydrogen carbonate and saturated sodium chloride, and evaporated. The reaction product was chromatographed (m.p.l.c.) to yield (1*R*)-Δ^3-THC (**6b**) (299 mg, 95%), an oil, $[\alpha]_D$ +114°; $\lambda_{max.}$ 272 nm (ε 14 190); $\nu_{max.}$(film) 3 400, 1 620, 1 570, 1 425, 1 360, 1 260, 1 195, 1 165, 1 045, 965, 910, and 800 cm^{-1}; δ($CDCl_3$) 0.87 (3 H, t, ω-CH_3), 1.01 (3 H, d, *J* 5.5 Hz, 7-H_3), 1.20 and 1.41 (2 × 3 H, 2 s, 9- and 10-H_3), 2.45 (2 H, t, benzylic), 4.79 (OH), and 6.12 and 6.30 (2 × 1 H, 2 d, *J* 1.5 Hz, ArH); *m/z* 314 (M^+, 12%), 299 (100), 283 (2), 271 (2), 258 (3), 243 (3), and 231 (2) {lit.,[10] $\lambda_{max.}$ 275 (ε 11 500) and 229 nm (25 120); $[\alpha]_D$ +134.8° or +118.4° depending on synthetic route; lit.,[6] $\lambda_{max.}$ 273 (ε 13 200) and 227 nm (30 200) and identical n.m.r. data. The data in ref. 6 refer to racemic Δ^3-THC, prepared according to ref. 7, though further purified by modern methods.}

(1R)-Δ^3-*THC Acetate* (**6d**).—This compound, prepared by acetylation of (**6b**) (acetic anhydride–pyridine, 1:10 at room temp.) was obtained (90%) as an oil, $[\alpha]_D$ +114°; $\lambda_{max.}$ 266 (ε 8 628) and 303 nm (4 930); $\nu_{max.}$(thin film) 1 760, 1 620, 1 560, 1 420, 1 365, 1 205, 1 190, 1 155, 1 050, 910, and 730 cm^{-1}; δ($CDCl_3$) 0.88 (3 H, t, ω-CH_3), 1.00 (3 H, d, *J* 6.6 Hz, 7-H_3), 1.22 and 1.42 (2 × 3 H, 2 s, 9- and 10-H_3), 2.27 (3 H, s, CH_3CO), 2.51 (2 H, t, benzylic), and 6.39 and 6.58 (2 × 1 H, 2 d, *J* 1.2 Hz, ArH); *m/z* 356 (M^+, 8%), 341 (100), and 299 (54).

(1S)-Δ^3-*THC* (**6c**).—This isomer was obtained from (1*S*,4*R*)-Δ^2-THC (**4a**) exactly as described for the preparation of (1*R*)-Δ^3-THC (**6b**) from (1*R*,4*R*)-Δ^2-THC (**5a**). The isomer (**6c**), $[\alpha]_D$ −117°, is identical with (**6b**) (i.r., u.v., n.m.r., mass spectrum) except for optical rotation.

Reaction of Δ^1*-THC Acetate* (**2c**) *with* 4-*Phenyl*-4H-1,2,4-*triazole*-3,5-*dione*.—Δ^1-THC acetate (**2c**) (780 mg, 2.2 mmol) was dissolved in dry acetone (100 ml) and a solution of 4-phenyl-4*H*-1,2,4-triazole-3,5-dione (1.27 g, 7.25 mmol) in dry acetone (30 ml) was added under nitrogen during 5 min at −83 °C. The deep red reaction mixture was kept at this temperature for 30 min, when neutral alumina (activity V; 2.5 g) was added and the reaction mixture was left at room temperature for 3 h, filtered, and evaporated to dryness. The oily residue (1.8 g) was chromatographed on a dry column (for details of the preparation of the column and of the chromatography see ref. 20). Elution with 10% ethyl acetate in light petroleum followed by 25% ethyl acetate in light petroleum gave the adduct (**8**) (430 mg, 36.8%), $[\alpha]_D$ −13°; $\lambda_{max.}$ 222 (ε 20 046), 255 (14 477), and 300 nm (4 454); $\nu_{max.}$ ($CHCl_3$) 1 730, 1 710, 1 610, 1 590, and 1 430 cm^{-1}; δ($CDCl_3$) 0.88 (3 H, t, ω-CH_3), 1.06 and 1.38 (2 × 3 H, 2 s, 9- and 10-H_3), 1.54 (3 H, s, 7-H_3), 2.26 (3 H, s, $COCH_3$), 2.56 (2 H, t, benzylic), 2.82 (1 H, m), 6.40 (1 H, ArH), 6.50 (2 H, br, ArH and 2-H), and 7.38 (5 H, NPh); *m/z* (F.D.) 531 (M^+, 32%), 489 (10), 354 (100), 312 (14), 177 (100), and 58 (10).

(1R,4R)-Δ^2-*THC* (**5a**) *from Adduct* (**8**).—Adduct (**8**) (100 mg, 0.19 mmol) was dissolved in tetrahydrofuran (50 ml) and sodium borohydride (700 mg, 18 mmol) was added. The reaction mixture was boiled under reflux for 0.5 h, and water (50 ml) and ether (2 × 50 ml) were added. The organic layer was washed successively with water and brine, dried ($MgSO_4$), evaporated, and the residue chromatographed (preparative layer chromatography). Two compounds were obtained. One (11 mg, 18%) of them was identical with natural Δ^1-THC (**2a**) (i.r., u.v., n.m.r., and t.l.c. comparisons). The second was shown to be identical with (**5a**) (17 mg, 28%) (mass spectrum, n.m.r., u.v., t.l.c., i.r. comparisons). The optical rotation determined was $[\alpha]_D$ −80°. On being boiled with toluene-*p*-sulphonic acid in benzene, as described above for (**5a**) from the base-catalysed sequence, (1*R*)-Δ^3-THC (**6b**) was obtained, $[\alpha]_D$ +121°; identical (i.r., u.v., n.m.r., t.l.c.) with (**6b**) described above.

Isomerization of Δ^6-*THC* (**1a**).—Under the conditions of procedure B, Δ^6-THC (**1a**) gives a mixture of the Δ^2-THC's (**4a**) and (**5a**) in the ratio *ca.* 3:2. Under the conditions of procedure A (24 h) Δ^6-THC remains unchanged. The methyl ether of Δ^6-THC, compound (**1b**), remains unchanged under the conditions of procedures A (24 h) or B (24 h).

1,2-*Dihydro*-1,6-*didehydrocannabidiol* (**10a**).—Under the conditions of procedure A, cannabidiol (**9a**) (314 mg, 1 mmol) gave 1,2-dihydro-1,6-didehydrocannabidiol (**10a**) (189 mg, 60%) as an oil, $[\alpha]_D$ +9.4°; $\lambda_{max.}$ 274 (ε 820) and 281 nm (780); $\nu_{max.}$ 3 400, 1 620, 1 590, 1 435, 1 380, 1 360, 1 260, 1 200, 1 155, 1 060, 1 030, 1 015, 890, 830, and 790 cm^{-1}; $\delta(CDCl_3)$ 0.88 (3 H, t, ω-CH_3), 1.58 and 1.67 (2 × 3 H, 2 s, 7- and 10-H_3), 2.42 (2 H, t, benzylic), 4.55 (1 H, m, 9-H), 4.70 (3 H, m, 2 OH and 9-H), 5.13 (1 H, br s, 6-H), and 6.12 (2 H, s, ArH); *m/z* 314 (M^+, 36%), 299 (3), 271 (9), 258 (21), 246 (18), 231 (100), and 193 (39). Under the conditions of procedure B compound (**10a**) was obtained in 20% yield only. 1,2-Dihydro-1,6-didehydrocannabidiol diacetate (**10b**) was obtained from (**10a**) as a crystalline solid, m.p. 78—79 °C (from cold pentane); $[\alpha]_D$ −10°; $\lambda_{max.}$ 266 (ε 1 390) and 274 nm (1 194); $\nu_{max.}$ (Nujol) 1 765, 1 420, 1 370, 1 195, 1 180, 1 030, and 890 cm^{-1}; $\delta(CDCl_3)$ 0.89 (3 H, t, ω-CH_3), 1.53 and 1.66 (2 × 3 H, 2 s, 7- and 10-H_3), 2.32 (6 H, s, $COCH_3$), 2.57 (2 H, t, benzylic), 4.62 (2 H, m, 9-H_2), 5.42 (1 H, br s, 6-H), and 6.76 (2 H, s, ArH); *m/z* 398 (M^+, 28%) (Found: C, 75.5; H, 8.6. $C_{25}H_{34}O_4$ requires C, 75.34; H, 8.60%).

When cannabidiol (**9a**) was heated under the conditions of procedure A in the absence of t-pentyl alcohol only dehydrogenation took place and (after acetylation) 8,9-dihydrocannabinodiol diacetate (**11a**) was obtained as an oil (60%), $\lambda_{max.}$ 212 (ε 32 032), 267 (1 201), and 273sh nm (1 056); $\nu_{max.}$(thin film) 1 770, 1 625, 1 560, 1 485, 1 470, 1 420, 1 365, 1 180, 1 040, 890, and 820 cm^{-1}; $\delta(CDCl_3)$ 0.92 (3 H, t, ω-CH_3), 1.09 (6 H, d, *J* 6.6 Hz, 9- and 10-H_3), 1.87 (6 H, CH_3CO), 2.27 (3 H, s, 7-H_3), 2.62 (2 H, t, *J* 6.8 Hz, benzylic), 6.83 (1 H, m, ArH), 6.88 (2 H, s, ArH), and 7.18 (2 H, m, ArH); *m/z* 396 (M^+, 9%), 354 (26), and 312 (100).

8,9-*Dihydro*-O-*methylcannabinodiol Monoacetate* (**11b**).—Under the conditions of procedure B, cannabidiol monomethyl ether (**9b**) did not react during 0.5 h. If the reaction mixture was heated overnight at 50 °C, 8,9-dihydro-*O*-methylcannabinodiol monoacetate (**11b**) was obtained (after acetylation) as an oil, (45%), $\lambda_{max.}$ 208 (ε 32 589) and 275 nm (3 795); $\nu_{max.}$(thin film) 1 770, 1 615, 1 570, 1 465, 1 420, 1 365, 1 200, and 1 180 cm^{-1}; $\delta(CDCl_3)$ 0.93 (3 H, t, ω-CH_3), 1.10 (6 H, d, *J* 8.1 Hz, 9- and 10-H_3), 1.86 (3 H, s, $COCH_3$), 2.30 (3 H, s, 7-H_3), 2.65 (2 H, t, *J* 7.8 Hz, benzylic), 3.72 (3 H, s, OCH_3), 6.60 (1 H, s, ArH), 6.68 (1 H, s, ArH), 6.86 (1 H, s, ArH), 7.15 (1 H, m, ArH), and 7.23 (1 H, s, ArH); *m/z* 368 (M^+, 34%), 326 (100) 311 (11), and 284 (13).

1,6-*Didehydrotetrahydrocannabidiol* (**14**).—8,9-Dihydrocannabidiol[16b] (**13**) (316 mg, 1 mmol) under the conditions of procedure B did not react to any appreciable extent during 24 h. If, however, the mixture was heated at 100 °C (2 h) 1,6-didehydrotetrahydrocannabidiol (**14**) (79 mg, 25%) was obtained as an oil, $[\alpha]_D$ −40°; $\lambda_{max.}$ 273 nm (ε 1 457); $\nu_{max.}$(thin film) 3 460, 1 625, 1 585, 1 430, 1 255, 1 205, 1 155, 1 095, 1 060, 1 045, and 1 010 cm^{-1}; $\delta(CDCl_3)$ 0.72 (3 H, d, *J* 10.6 Hz, isopropyl CH_3), 0.83 (3 H, d, *J* 11.0 Hz, isopropyl CH_3), 0.89 (3 H, t, ω-CH_3), 1.66 (3 H, s, 7-H_3), 2.46 (2 H, t, *J* 7.2 Hz, benzylic), 3.23 (2 H, m), 4.73 (2 H, s, OH), 5.46 (1 H, br s, 6-H), and 6.16 (2 H, s, ArH); *m/z* 316 (M^+, 84%), 301 (4), 273 (12), 260 (27), 248 (64), 246 (44), 231 (93), and 193 (100).

2-(3,7-*Dimethylocta*-1,6-*dienyl*)-5-*pentylresorcinol* (**16a**).—Under the conditions of procedure B cannabigerol (**15a**) (316 mg, 1 mmol) remained unchanged after 0.5 h. On being heated at 50 °C for 1 h, however, it gave 2-(3,7-dimethylocta-1,6-dienyl)-5-pentylresorcinol (**16a**) (253 mg, 80%) as an oil, $\lambda_{max.}$ 224 (ε 29 604) and 266 nm (18 960); $\nu_{max.}$(thin film) 3 440, 1 630, 1 580, 1 440, 1 165, 1 025, 980, and 825 cm^{-1}; $\delta(CDCl_3)$ 0.88 (3 H, t, ω-CH_3), 1.12 (3 H, d, *J* 6.6 Hz, 7-H_3), 1.60 and 1.69 (2 × 3 H, 2 s, 3′- and 7′-CH_3), 2.46 (2 H, t, *J* 7.5 Hz, benzylic), 5.12 (1 H, m, olefinic), 5.17 (2 H, s, OH), 5.98 (1 H, dd, $J_{7,8}$ 16.8, $J_{6,7}$ 8.1 Hz, 2′-H), 6.26 (1 H, d, *J* 16.8 Hz, 1′-H), and 6.30 (2 H, s, ArH); *m/z* 316 (M^+, 45%), 301 (5), 273 (35), 260 (24), 247 (10), 233 (62), 231 (60), and 193 (100).

O-*Methylcannabigerol* (**15b**) *and* O,O-*Dimethylcannabigerol* (**15c**).—Methyl iodide (2.84 g, 20 mmol) was added to a stirred suspension of cannabigerol (**15a**) (6.32 g, 20 mmol) and potassium carbonate (5 g) in DMF (50 ml). The suspension was stirred for 3 h, diluted with water, and extracted with ether. The extract was washed with brine, dried, and chromatographed (m.p.l.c.). Elution with 1% ether in light petroleum gave first *O,O*-dimethylcannabigerol (**15c**) (2.7 g, 40%), $\lambda_{max.}$ 272 (ε 862) and 280sh nm (730); $\nu_{max.}$(thin film) 1 610, 1 590, 1 455, 1 420, 1 225, 1 185, 1 165, and 1 120 cm^{-1}; $\delta(CDCl_3)$ 0.90 (3 H, t, ω-CH_3), 1.58 (3 H, s, olefinic CH_3), 1.64 (3 H, s, olefinic CH_3), 1.74 (3 H, s, olefinic CH_3), 2.55 (2 H, t, *J* 6.6 Hz, benzylic), 3.31 (2 H, d, *J* 7.3 Hz, 1′-H_2), 3.80 (6 H, s, OCH_3), 5.62 (2 H, m, olefinic), and 6.37 (2 H, s, ArH); *m/z* 344 (M^+, 11%), 301 (3), 287 (3), 275 (33), 267 (9), and 221 (100). Further elution with the same solvent gave *O*-methylcannabigerol (**15b**) (2.31 g, 35%), $\lambda_{max.}$ 273 (ε 1 296) and 279sh nm (1 248); $\nu_{max.}$(thin film) 3 420, 1 610, 1 570, 1 450, 1 420, 1 205, 1 160, 995, and 820 cm^{-1}; $\delta(CDCl_3)$ 0.89 (3 H, t, ω-CH_3), 1.67, 1.72, 1.78 (3 × 3 H, 3 s, olefinic CH_3s), 2.51 (2 H, t, *J* 6.8 Hz, benzylic), 3.34 (2 H, d, *J* 8.5 Hz, 1′-H_2), 3.79 (3 H, s, OCH_3), 5.08 (3 H, m, OH and olefinic), and 6.34 (2 H, ArH); *m/z* 330 (M^+, 8%), 299 (3), 288 (3), 274 (4), 261 (26), 246 (17), and 207 (100).

2-(3,7-*Dimethylocta*-1,6-*dienyl*)-O-*methyl*-5-*pentylresorcinol* (**16b**).—Under the conditions of procedure B (reaction time 10 min) compound (**16b**) was obtained (205 mg, 65%) as an oil, $\lambda_{max.}$ 268 nm (ε 20 682); $\nu_{max.}$(film) 3 500, 1 610, 1 570, 1 450, 1 420, 1 210, 1 160, 1 100, 1 080, 980, and 815 cm^{-1}; $\delta(CDCl_3)$ 0.89 (3 H, t, ω-CH_3), 1.10 (3 H, d, *J* 6.6 Hz, 3′-CH_3), 1.60 and 1.68 (2 × 3 H, 2 s, olefinic CH_3s), 2.54 (2 H, t, *J* 6.6 Hz, benzylic), 3.79 (3 H, s, OCH_3), 5.10 (1 H, m, 6′-H), 5.47 (1 H, br s, OH), and 5.66—6.50 (4 H, m, ArH and 1′- and 2′-H); *m/z* 330 (M^+, 50%), 287 (33), 274 (21), 273 (17), 247 (63), 245 (35), and 207 (100). A longer reaction time produced a mixture.

Under the conditions of procedure B (at 0 or at 50 °C) cannabigerol dimethyl ether (**15c**) did not react; at 100 °C a complicated mixture was obtained.

(±)-7-*Nor-oxo*-Δ^2-*tetrahydrocannabinol Tosylhydrazone* (**19**).—Toluene-*p*-sulphonohydrazine (tosylhydrazine) (651 mg,

3.5 mmol) was added to a solution of compound (**18**)[4] (1 g, 3.1 mmol) in ethanol (5 ml). The reaction mixture was boiled under reflux overnight, the volatiles were removed under reduced pressure, and the residue was chromatographed on silica gel Woelm TSC (dry column chromatography). Elution with methanol–methylene dichloride (1:99) gave *compound* (**19**) (650 mg, 44%) as an amorphous solid, $\lambda_{max.}$ 324 nm (ε 34 190); $\nu_{max.}$ (Nujol) 3 420, 3 200, 1 620, 1 570, 1 430, 1 160, and 1 055 cm^{-1}; δ($CDCl_3$) 0.9 (3 H, t, ω-CH_3), 1.10 and 1.43 (2 × 3 H, 2 s, 9- and 10-H_3), 2.43 (3 H, s, tosyl CH_3), 6.14 (2 H, m, OH or NH and ArH), 6.27 (1 H, s, ArH), 7.25 (2 H, d, *J* 8.0 Hz, tosyl ArH), and 7.89 (2 H, d, *J* 8.0 Hz, tosyl ArH); *m/z* (F.D.) 482 (M^+, 100%), 464 (10), and 157 (23) (Found: C, 67.3; H, 7.3; N, 5.6; S, 6.2. $C_{27}H_{34}N_2O_4S$ requires C, 67.20; H, 7.10; N, 5.80, S, 6.64%).

3,4-cis-7-*Nor*-Δ^1-*tetrahydrocannabinol* (**17a**).—Excess of sodium borohydride (10 mmol) was added to a stirred solution of compound (**19**) (428 mg, 1 mmol) in glacial acetic acid (5 ml). The reaction mixture was then stirred for 1 h at room temperature and for 1.5 h at 70 °C. After being cooled the reaction contents were poured onto ice–aqueous sodium hydroxide (1M) and extracted with pentane; the extract was washed with brine and dried ($MgSO_4$). The volatiles were removed under reduced pressure and the residue was chromatographed on preparative t.l.c. plates (silica; 10% ether in light petroleum as developer) to yield racemic 3,4-*cis*-7-nor-Δ^1-tetrahydrocannabinol (**17a**) (150 mg, 50%), $\lambda_{max.}$ 274 (ε 2 075) and 282sh nm (1 750); $\nu_{max.}$(thin film) 3 480, 1 620, 1 570, and 1 420 cm^{-1}; δ($CDCl_3$) 0.87 (3 H, t, ω-CH_3), 1.27 and 1.42 (2 × 3 H, 2 s, 9- and 10-H_3), 3.57 (1 H, br s, 3-H), 4.90 (1 H, s, OH), 5.73 (1 H, m, 1-H), 6.10 (1 H, d, *J* 2.0 Hz, ArH), 6.23 (1 H, d, *J* 2.0 Hz, ArH), and 6.53 (1 H, m, 2-H); *m/z* 300 (M^+, 100%), 285 (43), 271 (5), 257 (77), 244 (55), 232 (22), 229 (27), 217 (38), and 193 (16). The acetate (**17b**) showed δ($CDCl_3$) 0.86 (3 H, t, ω-CH_3), 1.25 and 1.39 (2 × 3 H, 2 s, 9- and 10-H_3), 2.30 (3 H, s, CH_3CO), 2.49 (2 H, t, benzylic), 3.47 (1 H, br s, 3-H), 5.84 (1 H, br s, 1-H), 6.07 (1 H, br d, 2-H), 6.42 and 6.51 (2 × 1 H, 2 d, *J* 2.0 Hz, ArH).

7-*Nor*-Δ^2-*tetrahydrocannabinol* (**20**).—3,4-*cis*-7-Nor-Δ^1-tetrahydrocannabinol (**17a**) (300 mg, 1 mmol) under the conditions of procedure B gave 7-*nor*-Δ^2-*tetrahydrocannabinol* (270 mg, 90%), m.p. 85—87 °C (from light petroleum, b.p. 30—40 °C); $\lambda_{max.}$ 267 nm (ε 15 170); $\nu_{max.}$ (Nujol) 3 480, 1 625, 1 575, 1 435, 1 370, 1 280, 1 190, 1 165, 1 130, 1 080, 1 065, 1 045, 1 000, 960, 890, 860, 840, 820, and 800 cm^{-1}; δ($CDCl_3$) 0.87 (3 H, t, ω-CH_3), 1.13 and 1.39 (2 × 3 H, 2 s, 9- and 10-H_3), 2.44 (2 H, t, benzylic), 5.37 (1 H, OH), 6.20 (2 H, m, ArH), and 6.44 (1 H, br s, 2-H); *m/z* 300 (M^+, 100%), 285 (50), 257 (69), and 244 (44) (Found: C, 80.05; H, 9.5. $C_{20}H_{28}O_2$ requires C, 79.96; H, 9.39%).

7-*Nor*-Δ^3-*tetrahydrocannabinol* (**21a**).—The isomerization of (**20**) to (**21a**) under acid catalysis as described above for the conversion of (**4a**) into (**6c**) and (**5a**) into (**6b**) gave a complicated mixture. However, this reaction took place under basic catalysis. Procedure A was followed except that potassium t-butoxide (rather than t-pentyl salt) was employed. 7-Nor-Δ^2-THC (**20**) (300 mg, 1 mmol) gave a 1:1 mixture of the starting material (**20**) and the desired material (**21a**). When compound (**21a**) was submitted to the same reaction a 1:1 equilibrium mixture was obtained again. 7-Nor-Δ^3-tetrahydrocannabinol (**21a**) (120 mg, 40%) was an oil, $\lambda_{max.}$ 228 (ε 29 650) and 275 nm (11 648); $\nu_{max.}$(thin film) 3 400, 1 615, 1 570, 1 420, 1 380, 1 365, 1 260, 1 195, 1 155, and 1 045 cm^{-1}; δ($CDCl_3$) 0.87 (3 H, t, ω-CH_3), 1.31 (6 H, s, 9- and 10-H_3), 2.43 (2 H, t, benzylic), 4.88 (1 H, s, OH), 6.10 and 6.30 (2 × 1 H, 2 d, *J* 1.5 Hz, ArH); *m/z* 300 (M^+, 10%), 285 (100), and 229 (6) [lit.,[18] $\lambda_{max.}$ (ethanol) 274 nm (ε 10 100)]. 7-*Nor*-Δ^3-*tetrahydrocannabinol acetate* (**21b**) was obtained from (**21a**) as a crystalline solid, m.p. 43—44 °C (from pentane); $\lambda_{max.}$ 266 (ε 9 920) and 302 nm (5 360); $\nu_{max.}$ (KBr) 1 760, 1 620, 1 560, 1 420, 1 360, 1 310, 1 260, 1 200, 1 155, 1 100, 1 040, 1 010, 960, 930, 890, 880, 875, 850, 830, and 800 cm^{-1}; δ($CDCl_3$) 0.88 (3 H, t, ω-CH_3), 1.30 (2 × 3 H, 2 s, 9- and 10-H_3), 2.25 (3 H, t, CH_3CO), and 6.37 and 6.57 (2 × 1 H, 2 s, ArH); *m/z* 342 (M^+, 17%), 327 (100), and 285 (60) (Found: C, 76.9; H, 8.9. $C_{22}H_{30}O_3$ requires C, 77.19; H, 8.77%).

References

1 R. Mechoulam in 'Marijuana. Chemistry, Pharmacology, Metabolism and Clinical Effects,' ed. R. Mechoulam, Academic Press, New York, 1973, pp. 60—67; R. Mechoulam, N. K. McCallum, and S. Burstein, *Chem. Rev.*, 1976, **76**, 75; R. K. Razdan in 'The Total Synthesis of Natural Products,' vol. 4, ed. J. ApSimon, Wiley-Interscience, New York, 1981, pp. 185—262.

2 L. Crombie, W. M. L. Crombie, C. J. Palmer, and S. V. Jamieson, *Tetrahedron Lett.*, 1983, **24**, 3129; R. A. Archer, W. B. Blanchard, W. A. Day, D. W. Johnson, E. Lavagnimo, C. W. Ryan, and J. E. Baldwin, *J. Org. Chem.*, 1977, **42**, 2277; G. R. Handrick, R. K. Razdan, D. B. Uliss, H. C. Dalzell, and E. Boger, *ibid.*, p. 2563.

3 R. Mechoulam, Z. Ben-Zvi, and Y. Gaoni, *Tetrahedron*, 1968, **24**, 5615; R. K. Razdan, H. G. Pars, W. R. Thompson, and F. E. Granchelli, *Tetrahedron Lett.*, 1974, 4315; R. Mechoulam, N. Lander, I. Tamir, Z. Ben-Zvi, and Y. Kimmel, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 543.

4 K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Am. Chem. Soc.*, 1966, **88**, 2079; 1967, **89**, 5934.

5 R. Mechoulam, P. Braun, and Y. Gaoni, *J. Am. Chem. Soc.*, 1967, **89**, 4552; 1972, **94**, 6159; T. Petrzilka and C. Sikemeier, *Helv. Chim. Acta*, 1967, **50**, 2111; T. Petrzilka, W. Haefliger, and C. Sikemeier, *ibid.*, 1969, **52**, 1102.

6 (*a*) U. Claussen and F. Korte, *Naturforscher*, 1966, **21b**, 594; (*b*) F. Korte, H. Sieper, and S. Tira, *Bull. Narc.*, 1965, **17**, 35.

7 R. Adams and B. R. Baker, *J. Am. Chem. Soc.*, 1940, **62**, 2405.

8 R. Ghosh, A. R. Todd, and S. Wilkinson, *J. Chem. Soc.*, 1940, 1121, 1393.

9 R. Adams, C. M. Smith, and S. Loewe, *J. Am. Chem. Soc.*, 1941, **63**, 1973.

10 G. Leaf, A. R. Todd, and S. Wilkinson, *J. Chem. Soc.*, 1942, 185.

11 W. Klyne and J. Buckingham, 'Atlas of Stereochemistry,' Chapman and Hall, London, 1974, p. 42; E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, 1955, **77**, 3383.

12 W. Oppolzer and V. Snieckus, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 476; H. M. R. Hoffmann, *ibid.*, 1969, **8**, 566; J. Brynjolffssen, A. Emke, D. Hands, J. M. Midgley, and W. B. Whaley, *J. Chem. Soc., Chem. Commun.*, 1975, 633; W. H. Pirkle and J. C. Stickler, *Chem. Commun.*, 1967, 760.

13 F. Korte, E. Hackel, and H. Sieper, *Ann. Chem.*, 1965, **685**, 122.

14 N. Lander, R. Mechoulam, and P. Consroe, submitted for publication in *Experientia*.

15 R. O. Hutchins, M. Kacher, and L. Rua, *J. Org. Chem.*, 1975, **40**, 923; R. O. Hutchins and R. Natale, *ibid.*, 1978, **43**, 2299.

16 (*a*) R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Org. Naturst.*, 1967, **25**, 175; (*b*) Y. Gaoni and R. Mechoulam, *Isr. J. Chem.*, 1968, **8**, 679; (*c*) M. Srebnik and R. Mechoulam, *Tetrahedron*, 1984 in the press.

17 D. B. Uliss, G. R. Handrick, H. C. Dalzell, and R. K. Razdan, *Tetrahedron*, 1978, **34**, 1885; D. B. Uliss, R. K. Razdan, H. C. Dalzell, and G. R. Handrick, *ibid.*, 1977, **33**, 2055 and refs. cited therein.

18 P. B. Russell, A. R. Todd, S. Wikinson, A. D. Macdonald, and G. Woolfe, *J. Chem. Soc.*, 1941, 169.

19 R. Mechoulam and Y. Shvo, *Tetrahedron*, 1963, **19**, 2073; P. G. Jones, L. Falvello, O. Kennard, and R. Mechoulam, *Acta Crystallogr.*, 1977, **B33**, 3211; I. Tamir, R. Mechoulam, and A. Y. Meyer, *J. Med. Chem.*, 1980, **23**, 220.

20 A. Goldblum and R. Mechoulam, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1889.

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