Metabolism of Cannabis
XI.* Synthesis of Δ⁶-Tetrahydrocannabinol and 7-Hydroxytetrahydrocannabinol
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During the last few years, a number of cannabinoids have been isolated from Cannabis sativa.1 So far only Δ⁶- and Δ⁹⁶-tetrahydrocannabinol (Δ⁶- and Δ⁹⁶-THC; 1a and 2a) have been shown to be psychomimetically active.⁵

The primary reaction in the metabolic conversion of 1a,⁴ 2a,⁴ and 3a⁷ (an apparently psychomimetically inactive cannabinoid) is oxidation to the 7-hydroxy derivatives 1b - 3b. The hydroxylated forms 1b and 2b may be the biologically active forms of the two tetrahydrocannabinols 1a and 2a.⁴

We have now carried out the synthesis of the active metabolite 2b as indicated in Scheme 1. The synthetic procedures described now make the two compounds 2b and 4 readily available for biological investigations.

Photo-induced isomerisation⁴ of Δ⁹⁶-THC (2a) furnished the cannabinoid 4. We originally intended to convert this to a mixture of the hydroxylated compounds

1b and 2b by addition of singlet oxygen¹⁰ followed by reduction. However, compound 4 did not react with singlet oxygen. It was therefore acetylated and hydroxylated to the alcohol 5 by treatment with osmium tetroxide. Acetylation followed by elimination of water and removal of the acetyl groups using LiAlH₄ gave 7-hydroxy-Δ⁶⁶-THC (2b) in an overall yield of 25% from the compound 4.

Experimental. Gas chromatography was carried out with a Varian Aerograph Model 2100 chromatograph (FID) using 6 ft. x 1/8 in. i.d. glass columns, packed with 3 % J × R on 100/120 mesh Gas Chrom Q (Serva Feinbiochemica, Heidelberg). Flow rate was 25 ml N₂/min. Retention times: at 190°C: Δ⁶-THC¹¹ (1a) 8.5 min, Δ⁹⁶-THC¹¹ (2a) 8.2 min, Δ⁶-THC¹² (4) 7.6 min, and at 230°C: 7-hydroxy-Δ⁶⁶-THC¹³ (1b) (diacetate) 5.6 min, and 7-hydroxy-Δ⁹⁶-THC¹³ (2b) (diacetate) 5.3 min. The two diacetates were prepared by one-column-acetylation using acetic anhydride.

IR-spectra were recorded with a Perkin-Elmer 237 spectrophotometer and NMR spectra with a Varian A 60 instrument using CDCl₃ solutions. Mass spectra were recorded using a LKB 9000 apparatus at 70 eV. Redistilled light petroleum b.p. 40–60° was used throughout.

Δ⁶-Tetrahydrocannabinol (4). Δ⁹⁶-Tetrahydrocannabinol¹³ (2a, 2.5 g) in a mixture of 2-propanol (900 ml) and p-xylene (10 ml) was irradiated with a Hanovia 90 W medium pressure mercury lamp until all of the starting material had been transformed (14 days). The major product was Δ⁶-THC, but a number of other products were also formed as indicated by GLC and TLC. The solvent was evaporated, the residue dissolved in light petroleum and chromatographed on a column of silica gel (100 g). This was eluted with light petroleum-ether mixtures of increasing polarity.

Elution with 3 % ether in light petroleum (1000 ml) gave almost pure Δ⁶-tetrahydoro-

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cannabinol (4, 0.75 g, 30%). Compound 4 was identified by comparison with an authentic sample (IR, NMR, GLC and TLC) prepared according to Fahrenholtz et al.12

The mass spectrum showed prominent peaks at m/e (intensity %) 316 (80), 273 (100), 260 (84), 193 (80) and 136 (22). The peak at m/e 316 corresponds to M+2, indicating that the double bond is readily reduced in the mass spectrometer. Similar results have been obtained for compounds that have easily reducible double bonds.13

7-Hydroxy-Δ[6]4-tetrahydrocannabinol 2b. A solution of Δ[6]4-THC (4) (0.45 g; 1.45 mmol) in dry pyridine (5 ml) and acetic anhydride (4 ml) was heated at 100° for 30 min. It was then poured into water (50 ml), stirred for 30 min at room temperature and extracted with ether. After drying (Na2SO4) and removal of the solvent, the residue was dissolved in dry ether (25 ml) and a solution of osmium tetroxide (0.4 g; 1.6 mmol) was added. The mixture immediately turned black. It was left at room temperature for 6 days whereupon the ether was evaporated, the residue dissolved in pyridine (20 ml) and added to a solution of NaHSO3 (2 g) in water (30 ml) and pyridine (20 ml). This mixture was stirred over night at room temperature and then filtered through Celite. The filtrate was extracted with CH2Cl2 (3 × 20 ml) and the extract dried (Na2SO4) and evaporated. This yielded 0.5 g of an oil, identified as the alcohol 4 by its IR-spectrum and chromatographic behaviour. \( \nu_{\text{max}} 3400 \text{ cm}^{-1}, \) broad, O-H; \( R_f = 0.1 \) on silica gel G developed in ether-light petroleum 1:1. The material was used in the next step without purification.

The alcohol 5 was acetylated as described above and the diacetate was dissolved in benzene (50 ml) and refluxed with p-toluene-sulphonic acid (50 mg) for 4 h. The solution was then shaken with 10% NaHCO3-solution, dried (Na2SO4) and evaporated. The oily residue was dissolved in dry ether (100 ml) LiAlH4 (0.3 g) was added and the mixture was stirred at room temperature over night. After the usual work-up procedure, the residual material was subjected to preparative TLC, developed in ether-light petroleum 1:1 with authentic material as reference. This yielded 120 mg (25%) of 2b, having GLC and TLC behaviour and IR, NMR, and MS properties identical to those of an authentic sample.13

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