Metabolism of Cannabis

XI.* Synthesis of Δ^7-Tetrahydrocannabinol and 7-Hydroxytetrahydrocannabinol

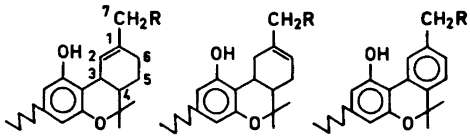
J. LARS G. NILSSON, INGER M. NILSSON and STIG AGURELL

Faculty of Pharmacy, University of Uppsala, Box 6804, S-113 86 Stockholm, Sweden

BJÖRN ÅKERMARK and INGER LAGERLUND

Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm 70, Sweden

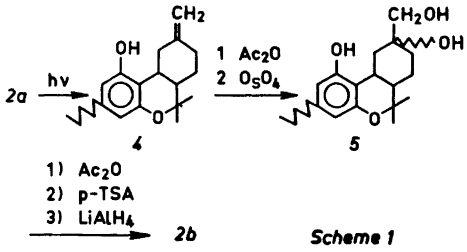
During the last few years, a number of cannabinoids have been isolated from *Cannabis sativa*.[1] So far only Δ^1- and $\Delta^{1(6)}$-tetrahydrocannabinol (Δ^1- and $\Delta^{1(6)}$-THC; *1a* and *2a*) have been shown to be psychotomimetically active.[2]



The primary reaction in the metabolic conversion of *1a*,[3,4] *2a*,[5,6] and *3a*[7] (an apparently psychotomimetically 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*.[3,6]

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 isomerisation [8,9] of $\Delta^{1(6)}$-THC (*2a*) furnished the cannabinoid *4*. We originally intended to convert this to a mixture of the hydroxylated compounds



Scheme 1

1b and *2b* by addition of singlet oxygen [10] 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 $LiAlH_4$ gave 7-hydroxy-$\Delta^{1(6)}$-THC (*2b*) in an over all yield of 25 % from the compound *4*.

Experimental. Gas chromatography was carried out with a Varian Aerograph Model 2100 chromatograph (FID) using 6 ft × 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 N_2/min. Retention times: at 190°: Δ^1-THC [11] (*1a*) 8.5 min, $\Delta^{1(6)}$-THC [11] (*2a*) 8.2 min, Δ^7-THC [12] (*4*) 7.6 min, and at 230°: 7-hydroxy-Δ^1-THC [3] (*1b*) (diacetate) 5.6 min, and 7-hydroxy-$\Delta^{1(6)}$-THC [13] (*2b*) (diacetate) 5.3 min. The two diacetates were prepared by on-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 $CDCl_3$ solutions. Mass spectra were recorded using an LKB 9000 apparatus at 70 eV. Redistilled light petroleum b.p. 40–60° was used throughout.

Δ^7-Tetrahydrocannabinol (4). $\Delta^{1(6)}$-Tetrahydrocannabinol [11] (*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 Δ^7-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 Δ^7-tetrahydro-

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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 (32). 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.[14,15]

7-Hydroxy-$\Delta^{1(6)}$-tetrahydrocannabinol 2b. A solution of Δ^7-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 (Na_2SO_4) 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 $NaHSO_3$ (2 g) in water (30 ml) and pyridine (20 ml).[13] This mixture was stirred over night at room temperature and then filtered through Celite. The filtrate was extracted with CH_2Cl_2 (3×20 ml) and the extract dried (Na_2SO_4) and evaporated. This yielded 0.5 g of an oil, identified as the alcohol *5* by its IR-spectrum and chromatographic behaviour. (ν_{max} 3400 cm^{-1}, broad, OH; R_F=0.1 on silica gel G developed in ether-lignt 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*-toluenesulphonic acid (50 mg) for 4 h. The solution was then shaken with 10 % $NaHCO_3$-solution, dried (Na_2SO_4) and evaporated. The oily residue was dissolved in dry ether (100 ml) $LiAlH_4$ (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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