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SYNTHESIS OF Δ^1 AND $\Delta^{1(6)}$ TETRAHYDROCANNABINOL METABOLITES

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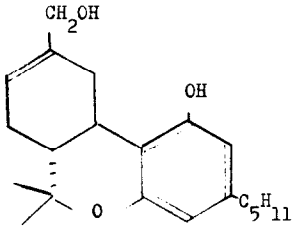
We recently reported[1,2] the isolation, elucidation of structure, and synthesis of 7-hydroxy-$\Delta^{1(6)}$ tetrahydrocannabinol (I), a metabolite of $\Delta^{1(6)}$ tetrahydrocannabinol ($\Delta^{1(6)}$ THC). It was obtained from the urine of rabbits intravenously injected with $\Delta^{1(6)}$ THC (II). The metabolite showed behavioral activity in monkeys comparable to that of the parent material[1,3]. An analogous metabolic pathway has been reported for Δ^1 THC (III) in which IV (7-hydroxy- Δ^1 THC) was found to be the major product[4,5]. It has been tentatively suggested[1,6] that these metabolites are responsible for the psychotomimetic properties of Cannabis in the body.

The potential importance of the THC metabolites in biological investigations has led us to examine additional pathways for the synthesis of I and to seek a route for the preparation of IV. The reported[1] synthesis of I is not a practical one due to its low yield (ca 2%). We wish to report now that selenium dioxide oxidation of $\Delta^{1(6)}$ THC acetate (II, acetate) under strictly defined conditions[7] followed by acetylation gives 7-acetoxy- $\Delta^{1(6)}$-THC acetate (I, diacetate) in workable yield. Thus, selenium dioxide (6.2 mM) in 95% ethanol (13 ml) was added dropwise to a solution containing $\Delta^{1(6)}$ THC acetate (2.5 mM) in 95% ethanol (4 ml) at 50°. The reaction mixture was then raised to reflux. After 7 hours the reaction mixture was cooled, the selenium was removed by filtration and the ethanol was evaporated <u>in vacuo</u>. The residue was taken up in ether, washed with sodium bicarbonate and then water, and dried over magnesium sulphate. The oily mixture was then acetylated (acetic anhydride/pyridine) and chromatographed on silicic acid (compound to silicic acid ratio, 1:250). Elution with 5% ether in petroleum ether (b.p. 65-70) yielded starting material (20%); elution with 10% ether in petroleum ether gave 7-acetoxy- $\Delta^{1(6)}$ THC acetate

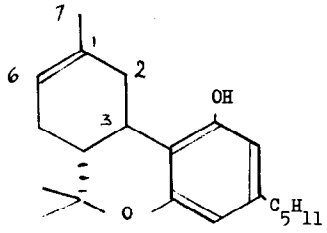
(I, diacetate) in 15% yield. Direct comparison with an authentic sample[1] of I diacetate by infrared and nuclear magnetic resonance (NMR) spectra, thin layer chromatography (TLC), and gas-liquid chromatography (GLC) showed their identity. In view of the relatively ready availability of the starting material this synthesis should now make possible more detailed biological work with this metabolite.

After this work had been completed, Foltz et al[8] described an independent isolation of 7-hydroxy- $\Delta^{1(6)}$ THC from rat liver incubation of $\Delta^{1(6)}$ THC (II). Selenium dioxide oxidation of II was reported[8] to give I in an unspecified yield.

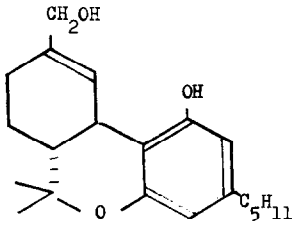
When Δ^{1} THC acetate (III, acetate) was oxidized and acetylated in the same manner, a very complex mixture was obtained which was partially purified by column chromatography on silicic acid and preparative TLC (silica gel PF_{254}). The purified fraction was reduced with lithium aluminum hydride and further purified by two consecutive preparative TLC's (silica gel PF_{254} and silica gel GF_{254} with 20% silver nitrate, plate thickness 0.25 mm). Two compounds were obtained, 7-hydroxy cannabinol (V), [18% yield, m.p. 163°, m.w. 326 (mass spectrum), NMR, δ, 0.82 (tr), 1.50(s) (methyl groups), 2.3 (mult.) (benzylic H), 4.53 (s) (C-7 H), 6.20, 6.33, 7.01. 8.42 (5 aromatic H)] and 7-hydroxy- Δ^{1}THC (IV), 1% yield, m.p. 133°, NMR and mass spectral data identical with published values[4,5]. Direct comparison with authentic material[4] (TLC and GLC) showed its identity with IV. This represents the first synthesis of a Δ^{1} THC metabolite. However, the miniscule yield makes this route unsuitable for practical purposes.



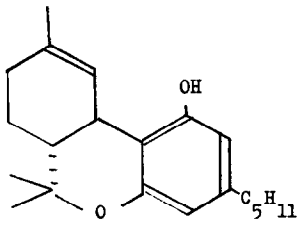
I



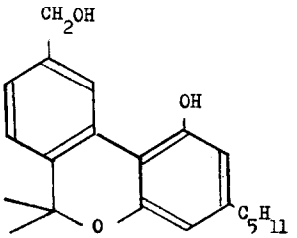
II



IV



III



V

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