HASHISH:[1] OXIDATION OF Δ^8-TETRAHYDROCANNABINOL (THC); SYNTHESIS OF Δ^8-THC-1,2-DIONE AND 2-HYDROXY-Δ^8-THC

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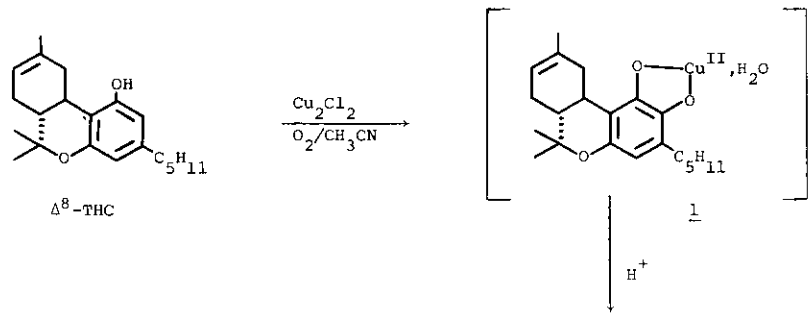
Abstract - The title compounds were synthesized from Δ^8-THC in yields of 65% and 63% respectively. The structure of 3 as a 1,2-dione was supported by NOE data. A structural re-assignment of a previously isolated quinonoid-THC 4 is proposed.

As part of an on-going program in our laboratories on the chemistry of cannabinoids,[2] we examined the effect of copper-catalysed activated molecular oxygen[3] on Δ^8-tetrahydrocannabinol (THC). We were led to these studies because of our interest in copper catalysed reactions[4] and the recently published reports on the use of cuprous chloride with oxygen in aprotic solvents for the oxidation of phenols to catechols and the latter to 1,2-benzoquinones.[5,6] This was of considerable interest to us since this could provide an entry into a novel class of THC's and lead to new information regarding structure-activity relationships in cannabinoids.[2]

We have found that treatment of Δ^8-THC in CH_3CN in the presence of Cu_2Cl_2 with molecular oxygen forms the catechol derivative 2 which then undergoes further oxidation to furnish the 1,2-dione 3. This oxidation of Δ^8-THC most likely proceeds via a copper (II) catecholate intermediate such as 1 (Scheme 1). Precedent for this reaction is seen in the reported oxidation of phenols to catechols and the latter to quinones.[5,6] It was also found that the reaction proceeded similarly with no yield advantage when metallic copper (powder)[6] was added in addition to the Cu_2Cl_2. To obtain the intermediate catechol 2, it was found more advantageous to isolate the 1,2-dione 3 first and then reduce it to 2. This nearly quantitative reduction was achieved by treatment with sodium hydrosulfite solution. As expected, the catechol 2 was prone to oxidation and even careful column chromatography resulted in contamination of 2 with 3. The diacetate of 2 was however quite stable and easy to handle.

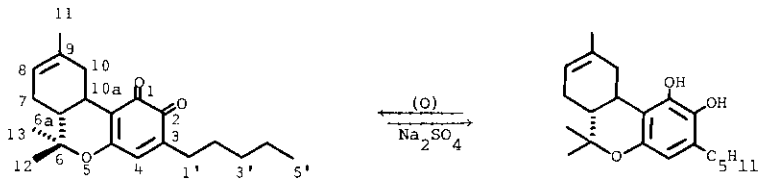
The initial NMR, IR and other physical data clearly pointed to a quinone structure for compound 3. In addition, our synthetic procedure suggested a 1,2- rather than a 1,4-quinone structure. However Nuclear Overhauser Enhancement (NOE) data derived from the ^1H homonuclear double resonance experiments supported the position of the quinone as ortho, i.e. as shown in structure 3. Irradiation of 4-H clearly showed a NOE effect (6±4%) on the benzylic protons of the side

SCHEME 1



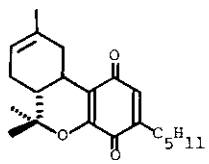
Δ^8-THC

1



3

2



4

chain (1'-H_2) and the 12β-methyl group[7] of the pyran ring. Conversely, irradiation of the 12β-methyl group showed a clear NOE effect (6±4%) on the 4-H. In addition, the coincidental enhancement (6±4%) of the 1'-H_2 protons was observed presumably since the 2'-H_2 or 3'-H_2 protons resonate at the same frequency as the 12β-methyl group (1.45 ppm). Upon irradiation of the 12α-methyl group no NOE effect was observed on the 4-H. These NOE results further suggest that the pyran ring in 3 preferentially exists in a quasi-boat form rather than a quasi-chair form. This is supported by an examination of the Dreiding models which shows that in the former conformation the distance between the 12β-methyl group and the 4-H proton is approximately 3.1A^{o} whereas in the quasi-chair conformation, this distance is ~4.5A^{o}.

The above NOE spectral studies support compound 3 to have a 1,2-dione and not a 1,4-dione (4) structure. In 1968, Mechoulam, Ben-Zvi and Gaoni[8] carried out the m-chloroperbenzoic acid oxidation of Δ^8-THC and reported the isolation of two products. They proposed structure 3 for the minor product and 4 for the major product and assigned the structures mainly on the basis of UV spectra. However, the IR, NMR and UV spectra of our compound 3 corresponds closely to that of Mechoulam et al's major product 4 and hence, a re-examination of their structure assignments is suggested. We have been informed recently by Professor Mechoulam that on the basis of further work in their laboratories, they have independently arrived at similar conclusions.

EXPERIMENTAL

Δ^8-THC-1,2-dione (3). To a solution of 104mg (0.33 mmol) of Δ^8-THC in 0.9 ml of CH_3CN, 5.5 mg (.028 mmol) of freshly prepared Cu_2Cl_2[9] was added. A thin current of air was bubbled through the mixture for 1.5 h after which 50 ml of ether was added. The reaction mixture was washed with H_2O, dried and concentrated. A yellowish oil was obtained which was purified by flash chromatography[10] using 5% ethyl acetate-hexane solution. The dione 3 was obtained as a reddish-yellow gum: 70 mg (65%); NMR (300 MHz; $CDCl_3$) δ 0.86 (t, 3H, 5'-CH_3), 1.12 (s, 3H, 13α-CH_3), 1.2-1.4(3H); 1.45 (s, 3H, 12β-CH_3), 1.45-1.55 (2H); 1.65 (br s, 3H, 9-CH_3), 1.65-1.85 (3H); 2.06-2.12 (m, 2H, 10-H_2), 2.35 (dt, 2H, 1'-H_2), 2.47 (m, 1H, 6a-H), 2.95 (dd, 1H, 10a-H), 5.36 (m, 1H, 8-H), 6.35 (t, J=1.46 Hz, 1H, 4-H); IR (CCl_4) 1600, 1645, 1665 (quinone) cm^{-1}; λ max (EtOH) 269 nm (log ε, 4.06), 362 (2.85), 400 (2.99); [lit.[8] 269 (4.12), 362 (2.84), 400 (2.9)]; mass spectrum, m/z (relative intensity) 328 (M^+, 100), 313 (M^+-15, 29), 272 (M^+-56, 64), 229 (21), 204 (30). Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C,76.60; H, 8.63.

Aliquots taken from reaction mixture and worked up as described above gave mixtures of the dione 3 and the catechol 2 as shown by NMR, IR and TLC. Similar results were obtained when Δ^8-THC (3.6 mmol) was oxidized in the presence of Cu powder (5.5 mmol) and Cu_2Cl_2 (0.23 mmol) followed by similar work-up.

2-Hydroxy-Δ^8-THC (2). To a solution of 315 mg (0.96 mmol) of the Δ^8-THC-1,2-dione (3) in 6 ml of ether, a solution of 334 mg (1.92 mmol) of sodium hydrosulfite in 6 ml of H_2O was added. The

mixture was stirred at 40-45°C for 3 h after which 50 ml of ether was added and the organic layer was separated. It was filtered, dried and concentrated to give 2 as a yellow gum; 302 mg (97%); NMR (CCl_4) δ 0.88 (t, 3H, 5'-CH_3), 1.07, 1.40 (2s, 6H, geminal 12,13-CH_3), 1.66 (br s, 3H, 9-CH_3), 3.0-3.42 (br m, 1H, 10a-H), 5.0-5.2 (m, 2H, OH which disappears on acetylation), 5.33 (br s, 1H, 8-H), 5.88 (br s, 1H, 4-H); IR (CCl_4); 3625, 3570 (OH), 3470, 2980, 2950 cm^{-1}. Anal. Calcd. for $C_{21}H_{30}O_3 \cdot 1/4\ H_2O$: C, 75.29; H, 9.02. Found: C, 75.61; H, 8.83. The diacetate of 2 was formed by treatment of 2 with Ac_2O in pyridine and usual work-up which, after chromatography (15% ethyl acetate-hexane), gave a gum in 70% yield; NMR (CCl_4) δ 2.23 (s, 6H, $2CH_3CO$); IR (CCl_4) 1770 (c=o) cm^{-1}. Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.44; H, 8.27. Found: C, 72.35; H, 8.29.

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