Hashish (1): Ceric Ammonium Nitrate Oxidation of $\Delta^{6a,10a}$-Tetrahydrocannabinols (THC's)

Raj K. Razdan, Haldean C. Dalzell and Patricia Herlihy*

Sisa Incorporated, 767B Concord Ave., Cambridge, MA 02138

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A procedure is described for the conversion of acetates of $\Delta^{6a,10a}$-THC's (**2** and **4a**) to their corresponding 7-oxo-derivatives (**3a**, **b**, **d** and **4b**) by oxidation with ceric ammonium nitrate. The differences between the nmr spectra of these 7-oxo-derivatives and the 10-oxo-THC (**1**) are discussed. The 7-oxo-derivatives show THC-like activity in mice albeit less than their corresponding THC's.

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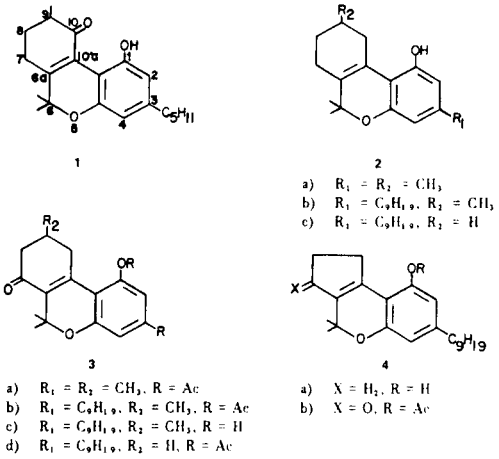
The recently reported isolation of 10-oxo-$\Delta^{6a,10a}$-THC (**1**) (2) from *Cannabis sativa* prompts us to record our findings on the formation of similar compounds when $\Delta^{6a,10a}$-THC's (**2** and **4a**) as their acetates are oxidized with ceric ammonium nitrate. We have found that with this reagent, under the experimental conditions used by us, the oxidation gave the corresponding 7-oxo derivatives (**3a**, **b**, **d** and **4b**), while no 10-oxo derivatives were isolated. With various $\Delta^{6a,10a}$-THC's, the yield varied from 10-23%. The position of oxidation at the allylic C_7 rather than the alternate allylic C_{10} was established on the basis of the nmr spectra. In all cases, the oxidation resulted in deshielding of the geminal methyl groups which is consistent with the oxo-group at C_7. In accord with this reasoning is the finding that no such deshielding of the geminal methyl groups was found in the 10-oxo-THC (**1**) (2). To avoid complications in the nmr spectra due to the aliphatic side chain in THC's, the simplified orcinol derivative (3) (**2a**) was prepared and it was found that the geminal methyl signals appeared as singlets in **2a** (as the acetate) at δ 1.26 and 1.4 compared to 1.38 and 1.7 in the 7-oxo-THC acetate (**3a**).

Another noteworthy point in the nmr spectra of these compounds is the influence of the assymetric center at C_9 on the position of the geminal methyl group. Thus in compounds (**3a,b,c**), which have a C_9-CH_3, the geminal methyl groups are non equivalent and appear as two singlets. This separation is a consequence of a strong conformational preference induced by the C_9-CH_3. On the other hand, in compound **3d** and **4b**, which do not have a C_9-CH_3, the geminal methyl groups are equivalent and appear as a singlet (see Experimental).

The 7-0x0 derivatives are biologically active albeit less than their corresponding THC's. Thus compound **3d** showed THC-like activity in mice at 2.0 mg./kg. (iv) and had antinociceptive properties, ED_{50}, 38 mg./kg. (po) in the mouse hot-plate test (4). Compound **3c** had ED_{50} of 9.0 mg./kg. (po) in the same test. Similarly the cyclopenteno analog **4b** showed THC-like activity in mice at 5.0 mg./kg. (iv).



EXPERIMENTAL (5)

1-Acetoxy-7,8,9,10-tetrahydro-3,6,6,9-tetramethyl-6*H*-dibenzo-[*b*,*d*]pyran (Acetate of **2a**).

A soultion of 9.07 g. (0.035 mole) of **2a** (3) and 7.1 g. (0.07 mole) of acetic anhydride in 25 ml. of pyridine was warmed over a steam bath for 2 hours. After cooling, the pyridine was removed by evaporation under reduced pressure. Water was added to the residue, and the aqueous mixture was extracted with three portions of ether. The ethereal extracts were combined, washed with water, 6 *N* hydrochloric acid, again with water, dried over sodium sulfate and concentrated under reduced pressure to 9.5 g. (90%) of a colorless solid, m.p. 115-119°; ir (mull): 1760 (s),

1740(shoulder), 1630(s), 1610(s) cm^{-1}; nmr (deuteriochloroform): δ 1.1 (d, 3H, J = 6 Hz), 1.26 (s, 3H), 1.4 (s, 3H), 1.6-2.6 (broad m, 7H), 2.26 (s, 6H), 6.4 (s, 1H), 6.6 (s, 1H).

Anal. Calcd. for $C_{19}H_{24}O_3 \cdot 1/2\ H_2O$: C, 73.79; H, 8.14. Found: C, 73.97; H, 7.82.

1-Acetoxy-7-oxo-7,8,9,10-tetrahydro-3,6,6,9-tetramethyl-6*H*-dibenzo[*b*,*d*]pyran (**3a**).

To a stirring mixture of 0.6 g. (2 mmoles) of **2a** as the acetate in 7 ml. of 50% acetic acid and 5 ml. of chloroform held under a nitrogen atmosphere, was added dropwise a solution of 4.39 g. (8 mmoles) of ceric ammonium nitrate in 12 ml. of 50% acetic acid. After addition was complete, the reaction mixture was stirred over a steam bath. After 3 hours, the mixture was poured on crushed ice. The product was extracted into ether, washed to neutrality with 5% sodium bicarbonate solution, washed with water, dried over sodium sulfate and concentrated under reduced pressure. Elution of the product from a Florisil column with graded ether (10-40%)/petroleum ether gave 0.12 g. (14.2%) of **3a**. It showed a blue fluorescent spot on tlc (R_f silica gel 0.67, 40% ethyl acetate/hexane); ir (neat): 1770(m), 1740(s), 1660(s), 1640(s), 1620(m) cm^{-1}; nmr (deuteriochloroform): δ 1.08 (d, 3H, J = 4 Hz), 1.38(s, 3H), 1.7(s, 3H), 2.3(s, 6H), 1.0-3.0 (broad m, 5H), 6.5(s, 1H), 6.62(s, 1H); uv λ max (ethanol): 350 nm (ε, 6,516), 300 nm (11,898).

Anal. Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.06. Found: C, 72.53; H, 7.12.

3-(1,2-Dimethylheptyl)-1-hydroxy-7-oxo-7,8,9,10-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran (**3c**).

Compound **2b** (6) was converted to its acetate (gum; 93% yield) by the procedure described above for the preparation of the acetate of **2a**.

Oxidation with ceric ammonium nitrate as in **3a** gave **3b** as a resin in 23% yield; ir (mull): 1770 cm^{-1} (acetate); nmr (deuteriochloroform): δ 1.38, 1.73 (2s, 6H, $C(CH_3)_2$), 6.51, 6.66 (2s, J = 2 cps, 2H, aromatic). On hydrolysis of **3b** with 3 *N* sodium hydroxide on a steam bath for 10 minutes, a gum was obtained which was purified by chromatography on Florisil and eluted with graded ether (10-20%)/petroleum ether mixtures. Compound **3c** was obtained (57% yield) as a gum; ir (mull): 3250(OH), 1640(shoulder, C=C-C(=O)–) cm^{-1}; uv λ max (ethanol): 335 nm (ε, 15,726); nmr (deuteriochloroform): δ 1.43, 1.77 (2s, 6H, $C(CH_3)_2$), 6.37 (s, 2H, aromatic), 7.53 (s, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{25}H_{36}O_3$: C, 78.10; H, 9.4. Found: C, 77.98; H, 9.38.

1-Acetoxy-6,6-dimethyl-3-(1,2-dimethylheptyl)-7-oxo-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran (**3d**).

The acetate (7) of **2c** was oxidized and isolated as in the preparation of **3a**, to give **3d** as a resin (10% yield). It was crystallized from dilute ethanol as a tan solid, m.p. 81-83°; uv λ max (ethanol): 350 nm (ε, 9,365), 300 nm (ε, 15,556); nmr (deuteriochloroform): δ 1.6 (s, 6H, $C(CH_3)_2$), 2.3 (s, 3H, $COCH_3$), 6.46, 6.61 (2s, aromatic); mass spectrum: m/e 412 ($M.^+$).

Anal. Calcd. for $C_{26}H_{36}O_4 \cdot 3/2\ H_2O$: C, 71.03; H, 8.94. Found: C, 71.30; H, 8.64.

9-Acetoxy-4,4-dimethyl-7-(1,2-dimethylheptyl)-3-oxo-1,2,3,4-tetrahydrocyclopenta[*c*][1]benzopyran (**4b**).

It was prepared from **4a** (8) (as the acetate) following the procedure for **3a**. The material was rechromatographed (thick plate, Merck, 15% ether/petroleum ether) to give a gum; ir (neat): 1770, 1690 cm^{-1}; nmr (deuteriochloroform): δ 1.6 (s, 6H, $C(CH_3)_2$), 2.33 (s, 3H, $COCH_3$), 6.53, 6.63 (2s, J = 2 Hz, 2H, aromatic); mass spectrum: m/e 398 ($M.^+$); uv λ max (ethanol): 330 nm (ε, 18,750).

Anal. Calcd. for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 74.68; H, 8.77.

REFERENCES AND NOTES

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(5) Melting points are uncorrected and were determined on a Thomas-Hoover Capillary melting point apparatus. Nmr spectra were determined on a Varian T-60 Spectrometer. Ir and uv spectra were recorded on a Perkin-Elmer Model 700 and Varian Techtron Model 635 Spectrometers respectively.

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