Tetrahedron Letters No. 50, pp 4827 - 4830, 1971. Pergamon Press. Printed in Great Britain.

HASHISH[1]: SYNTHESIS OF (-)-7-HYDROXY-$\Delta^{1(6)}$-TETRAHYDROCANNABINOL

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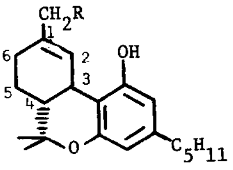
(Received in USA 12 October 1971; received in UK for publication 15 November 1971)

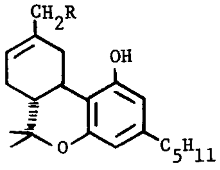
It is well documented[2,3,4,5] that the primary reaction in the metabolism of Δ^1- and $\Delta^{1(6)}$-THCs* (1a and 2a) is oxidation to the 7-hydroxy derivatives 1b and 2b.

As these metabolites are both biologically active their availability and testing has gained importance. The syntheses of the metabolites 1b and 2b have been achieved from 1a and 2a[4,5] but the unsatisfactory yields have led us to examine the synthesis of these metabolites from $\Delta^{1(7)}$-THC (3a).[6] A recent report[7] on the conversion of 3a to 2b prompts us to record our findings at this time. We wish to describe in this communication a facile synthesis of 2b from 3a which makes this material readily available for biological investigations.



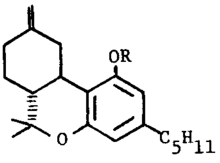
1 a,R = H

b,R = OH



2 a,R = H

b,R = OH



3 a,R = H

b,R = $COCH_3$

We have found that treatment of 3a (36 m.mole) with acetic anhydride (44 m.mole) in pyridine (80 ml) followed by heating on the steam bath for 2 hr and usual work up provided the acetate 3b[8] in nearly quantitative yield. This (45 m.mole) was allowed to react with N-bromoacetamide (48 m.mole) in 260 ml of a mixture of dioxane/chloroform/hexane (20:3:3) containing

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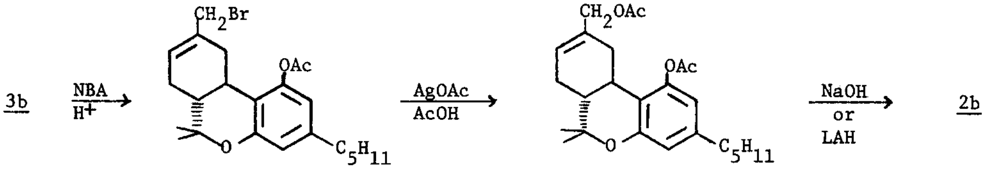
*THC = Tetrahydrocannabinol

about 1.5 ml of 70% perchloric acid.[9] After stirring the mixture for 6 hr at room temperature, it was poured into 1.5 l of water and extracted with hexane to give the 7-bromo-$\Delta^{1(6)}$-THC acetate (4)[10] in 96% yield. Nmr $\delta(CCl_4)$ 0.90 (t, 3H), 1.07, 1.32 (2s, 6H), 2.27 (s, 3H) 3.89 (s, two C-7 protons), 5.85 (br, 1H, vinylic), 6.32, 6.45 (2H, aromatic);



4

5

ir (cm^{-1}, smear) 1765, 1625, 1570, 1215.

Without further purification 4 (39 m.mole) was stirred in the absence of light with a mixture of silver acetate (51 m.mole) in glacial acetic acid (250 ml) at room temperature for 20 hr. The mixture was filtered and excess water was added to the filterate. It was extracted with ethyl acetate, washed, dried and evaporated to leave a gum (66%).[11] Purification of this material by chromatography on Florisil eluting with 5% ether in petroleum ether (bp 30-40) furnished the known[4] 7-acetoxy-$\Delta^{1(6)}$-THC acetate (5). Nmr $\delta(CCl_4)$ 1.95, 2.19 (2s, 6H, acetoxymethyls), 4.40 (AB pattern, 2H, C-7 protons), 5.7 (br, 1H, vinylic), 6.31, 6.47 (2H, aromatic); ir (cm^{-1}, smear) 1780, 1755. Hydrolysis of 5 (4.2 m.mole) was effected by dissolving in 150 ml of a 2:1 mixture of methanol/4% aqueous sodium hydroxide solution and stirring under nitrogen. After 15 hr the solution was acidified, treated with 0.5 l of saturated brine and extracted with ethyl acetate to give the metabolite 2b as a glassy solid (95%), $[\alpha]_D$-270° (EtOH)[12] having nmr, glc, tlc properties identical to those of an authentic sample.[13] The metabolite 2b was also obtained from 5 on treatment with $LiAlH_4$ in ether.

Further work along these lines is in progress and will be reported elsewhere.

Acknowledgment: This work was carried out with the support of Contract No. HSM-42-71-69, National Institute of Mental Health, NIH, HEW.

References

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4. Z. Ben-Zvi, R. Mechoulam and S. H. Burstein, Tetrahedron Lett., 4495 (1970), and earlier references given in this paper.
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6. We have recently reported a total synthesis of (-)-$\Delta^{1(7)}$-THC from (-)-$\Delta^{1(6)}$-THC; see reference 1. For another synthesis of 3a, see J. W. Wildes, N. H. Martin, C. G. Pitt and M. E. Wall, J. Org. Chem., **36**, 721 (1971).
7. J. L. G. Nilsson, I. M. Nilsson, S. Agurell, B. Akermark and I. Lagerlund. Acta Chem. Scand. **25**, 768 (1971).
8. Satisfactory analyses were obtained for all new compounds.
9. It is interesting to note that under the conditions used for the conversion of 3b to 4, $\Delta^{1(6)}$-THC acetate was recovered unchanged whereas 2a was brominated in the aromatic ring.

10. An analytically pure sample was obtained by chromatography on Florisil with hexane.
11. No attempt was made to optimize the yield.
12. The material obtained after work up did not require further purification for practical purposes. Z. Ben-Zvi, R. Mechoulam and S. Burstein, J. Am. Chem. Soc., **92**, 3468 (1970) reported the rotation $[\alpha]_D$-255° (EtOH), however, our rotation was obtained on a chromatographed sample.
13. Kindly supplied by Professor L. S. Harris, University of North Carolina, N. C.