Tetrahedron Letters No. 49, 4369 - 4372, 1975. Pergamon Press. Printed in Great Britain.

HASHISH[1]: SYNTHESIS OF dl-$\Delta^{1,6}$-CIS-TETRAHYDROCANNABINOL (THC)

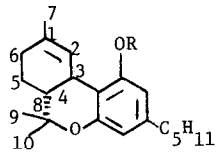
David B. Uliss, Raj K. Razdan*, Haldean C. Dalzell, G. Richard Handrick
Sheehan Institute for Research, Cambridge, Mass., 02138

(Received in USA 19 August 1975; received in UK for publication 28 October 1975)

It is well documented[2] that the main physiologically active principle of marijuana or hashish is (-)-Δ^1-3,4-trans-THC (1a). On treatment with acid catalysts, it is isomerized to the thermodynamically more stable $\Delta^{1,6}$-trans-THC (2a) which also occurs naturally in a few varieties of Cannabis sativa L., and is similar to trans-Δ^1-THC in physiological potency. Of the corresponding compounds with a 3,4-cis-ring fusion only Δ^1-3,4-cis-THC (3a) is known.[3,4] It is much less potent than the trans isomer and has not yet been found in the plant.[2] On acid catalysis it is converted to $\Delta^{4,8}$-iso-THC (4)[5] which was at one time erroneously regarded as the $\Delta^{1,6}$-3,4-cis-THC (6a).[3] This cis isomer is heretofore unknown and claims regarding its synthesis have not been substantiated.[2,3,6]

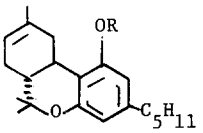
In this communication, we describe three unambiguous syntheses of authentic dl-$\Delta^{1,6}$-cis-THC (6a) and compare the mobility of the double bond in both the cis and the trans isomers of Δ^1- and $\Delta^{1,6}$-THC. In the first synthesis we have utilized the stereospecific intramolecular epoxide cleavage by phenolate anion which we reported earlier.[1a]

Thus 3b (Scheme) on oxidation with m-chloroperbenzoic acid in CH_2Cl_2 at 0° gave epoxide 7; δ (CCl_4) 6.40 (s,2,aromatics), 3.00 (m,2,C_2-H,C_3-H), 2.28 (s,3,acetate), 1.30 (s,3,C_1-CH_3), 1.23, 1.20 (2s,6,$C_8(CH_3)_2$), 0.90 (t,3,ω-CH_3), in 80% yield. Under basic hydrolytic conditions the epoxide was cleaved, as expected, by the phenolate anion to furnish the benzofuran 8 in 90% yield: δ (CCl_4) 6.00 (s,2,aromatics), 4.73 (d,1,J=9Hz,C_2-H), 3.65 (dd,1,$J_{2,3}$=9Hz,$J_{3,4}$=6Hz,C_3-H), 1.34, 1.30 (2s,6,C_8-$(CH_3)_2$), 0.90 (t,3,ω-CH_3), 0.83 (s,3,C_1-CH_3). The configuration shown for epoxide 7 is based on the attack of the peracid from the less hindered side and on the subsequent facile trans intramolecular opening of the epoxide to give a 2,3-cis ring junction in compound 8.[1a,7] This assignment is supported by the coupling constant of the hydrogens at C_2 and C_3 (9Hz).[8] The result of the epoxide opening is unusual in that the oxygen functions in the product are diequatorial. The reacton probably proceeds by the normal anti periplanar opening to give initially a boat C ring which then assumes the more stable chair conformation. This conclusion is supported by the C_1-CH_3 absorption at δ 0.83, a high field position caused by the methyl group being in the shielding cone of the benzene ring. Furthermore the assignment of the



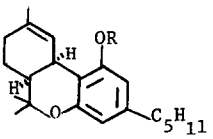
1a, R = H

1b, R = $COCH_3$



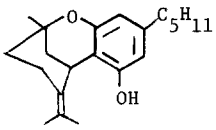
2a, R = H

2b, R = $COCH_3$

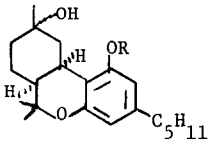


3a, R = H

3b, R = $COCH_3$

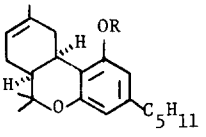


4



5a, R = H

5b, R = $COCH_3$



6a, R = H

6b, R = $COCH_3$

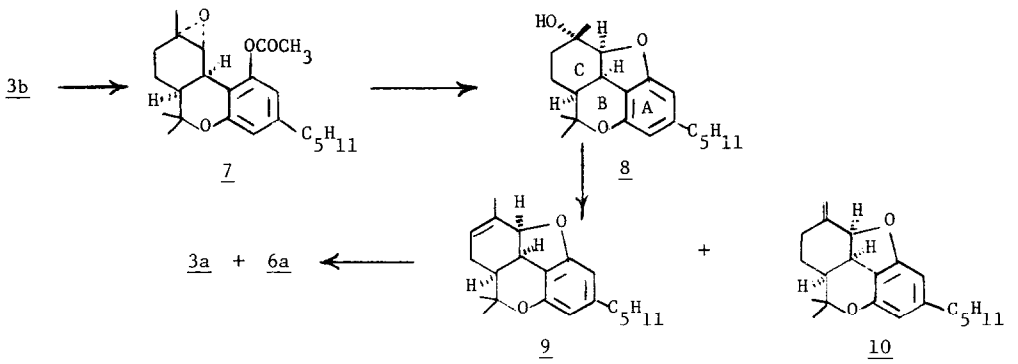
C_1 hydroxyl group as equatorial[8,9] is supported by dehydration results (see below) in which both the exo (10) and the endo (9) elimination products were obtained.

Dehydration of 8 (HMPA, 240°, 0.25 hr) gave a mixture of 9 and 10 (approx. 3:2 by nmr) which was used in the subsequent reaction without purification. Treatment with K/NH_3 liq. for 1.5 hr afforded a mixture (7:3 by glc after silylation) of Δ^1- and $\Delta^{1,6}$-cis-THC (3a and 6a, 90% from 8). It was acetylated (acetic anhydride, pyridine at 0°) to give a mixture of acetates which was separated using high pressure liquid chromatography[10] into 3b[5b] and $\Delta^{1,6}$-cis-THC acetate (6b): δ (CCl_4) 6.48, 6.33 (AB,2,J=2Hz), 5.38 (br,1,C_6-H), 3.05 (br,1,C_3-H) 2.23 (s,3,acetate), 1.65 (s,3,C_1-CH_3), 1.35, 1.25 (2s,6,C_8-$(CH_3)_2$), 0.92 (t,3,ω-CH_3). Hydrolysis of 6b with a 2:1 mixture of methanol/1N sodium hydroxide at room temperature furnished $\Delta^{1,6}$-cis-THC (6a): δ (CCl_4) 6.12, 5.93 (AB,2,J=2Hz,aromatics), 5.30 (br,1,olefinic), 3.13 (br,1,C_3-H), 1.63 (s,3,C_1-CH_3), 1.33, 1.25 (2s,6,C_8-$(CH_3)_2$), 0.88 (t,3,ω-CH_3); mass spectrum (70 eV) m/e (%) 314(22), 299(7), 271(10), 258(6), 246(21), 231(100). The positions of the C_8 α-CH_3 at δ 1.25 and the vinylic proton at δ 5.30, as well as the conversion of the acetate 6b to Δ^1-cis-THC acetate (3b) (see below) confirm the structure. Furthermore on treatment with p-toluenesulfonic acid (p-TSA) in boiling benzene, 6a gave $\Delta^{4,8}$-iso-THC (4) as the major product. Δ^1-cis-THC undergoes the same transformation on acid catalysis.[5,11]

In a second synthesis of Δ^1-cis-THC acetylation of the known cis-tertiary alcohol 5a[4] (acetic anhydride, pyridine at 0° for 2 hr, quantitative) gave compound 5b (appropriate nmr). Treatment of 5b with thionyl chloride in pyridine at 0° for 0.5 hr furnished in quantitative yield a mixture of 3b and 6b (3:2 by glc) which was separated and hydrolyzed as described above to yield 6a.

It was found that Δ^1-cis-THC acetate (3b) under acid catalysis (p-TSA in boiling benzene) provided substantial quantities of the thermodynamically less stable $\Delta^{1,6}$-cis-THC acetate (6b) at equilibrium (ratio of 77:23 respectively). This is contrary to results reported in the literature[5] and constitutes, on hydrolysis, the third synthesis of 6a.

SCHEME



The equilibrium constants and free energy differences (ΔG) of the double bond isomers in the cis and the trans THC's are given in Table 1. The double bond equilibria in these systems are qualitatively similar to those in the cis and the trans octalins.[12] There are quantitative differences, however, such as the greater extent to which the $\Delta^{1,6}$-position is favored in the trans-THC's. This difference may be due to the steric repulsion between either the phenolic OH and the C_2-H,[5a] or the C_3-H and the C_8 axial-CH_3 group,[13] or to both interactions. The role that steric factors play in these equilibria is presently under investigation.

Compound 6a showed no CNS activity in mice up to 25 mg/kg iv.

TABLE 1

Reaction[a]	$K(\frac{k_1}{k_{-1}})$	ΔG (Kcal/mole)
3b $\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}$ 6b	0.30	0.85
1b $\rightleftharpoons$ 2b	13.3	-1.82
1a $\rightleftharpoons$ 2a	13.3	-1.82

(a) Equilibrations of the isomers were effected as .01 molar solutions in refluxing benzene using p-TSA as catalyst; analyzed by glc as the silates (3% OV-17, 240-250°).

Acknowledgement. This work was carried out with the support of NIDA (Grant No. DA-00574-01). We are grateful to Professor John C. Sheehan for helpful discussion and Dr. J. F. Howes for biological testing.

REFERENCES

1. Part XV. For parts XII to XIV, see (a) D. B. Uliss, R. K. Razdan, H. C. Dalzell, J. Amer. Chem. Soc., 96, 7372 (1974); (b) R. K. Razdan, H. G. Pars, W. R. Thompson, F. E. Granchelli, Tetrahedron Lett., 4315 (1974); (c) R. K. Razdan, G. R. Handrick, H. C. Dalzell, Experientia, 31, 16 (1975) respectively.

2. Review: (a) R. K. Razdan in "Progress in Organic Chemistry", Vol. 8, W. Carruthers and J. K. Sutherland, Ed., Butterworths, London, 1973. (b) "Marijuana, Chemistry, Pharmacology, Metabolism, and Clinical Effects", R. Mechoulam, Ed., Academic Press, New York, N. Y. 1973.

3. E. C. Taylor, K. Lenard, Y. Shvo, J. Amer. Chem. Soc., 88, 367 (1966).

4. K. E. Fahrenholtz, M. Lurie and R. W. Kierstead, ibid., 89, 5934 (1967).

5. Y. Gaoni and R. Mechoulam, (a) ibid., 88, 5673 (1966); (b) Isr. J. Chem., 6, 679 (1968).

6. T. B. Vree, D. D. Breimer, C.A.M. Van Ginneken, J. M. Van Rossum, and N.M.M. Nibbering, J. Chromat., 79, 81 (1973); The discussion regarding $\Delta^{1,6}$-cis-THC should be ignored.

7. An examination of Dreiding models shows that in the molecule with the alternative epoxide configuration, the intramolecular attack of the phenolate anion will be possible only with a cis opening of the epoxide.

8. A. Shani and R. Mechoulam, Tetrahedron, 30, 2437 (1974).

9. D. H. R. Barton, A. da S. Campos-Neves and R. C. Cookson, J. Chem. Soc., 3500 (1956).

10. A Waters Associates ALC-202 chromatograph equipped with a Model 6000 solvent delivery system was used. Preparative separation was carried out on a 7 ft x 3/8 in. column packed with Porasil C. With 3.0% ether-hexane as solvent, the capacity factor (K') was .72 for the Δ^1 isomer and .88 for the $\Delta^{1,6}$ isomer, giving a separation factor (α) of 1.22. With a 300 mg-charge, baseline separation was achieved after 5 recycles yielding 100 mg of 6b.

11. R. K. Razdan and B. A. Zitko, Tetrahedron Lett., 4947 (1969).

12. P. Oberhansli and M. C. Whiting, J. Chem. Soc. (B), 467 (1969) and references cited therein.

13. E. J. Corey and R. A. Sneen, J. Amer. Chem. Soc., 77, 2505 (1955).