for this reaction which should yield an interesting comparison of relative nucleophilicities of cycloheptatrienylidene and 4,9-methano[11]annulenylidene.

**Acknowledgment.** The authors are indebted for support of this work received from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation.

(16) University of Florida postdoctoral fellow, 1971–1972.

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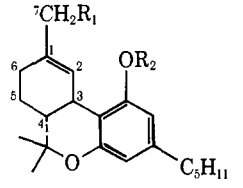
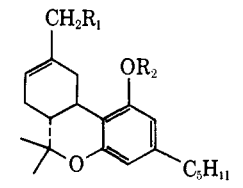
## Hashish.[1] Synthesis of 7-Hydroxy-$\Delta^1$-tetrahydrocannabinol (THC). An Important Active Metabolite of $\Delta^1$-THC in Man[2]

*Sir:*

Knowledge of the metabolic pathways of $\Delta^1$-THC (**1a**) is of great importance in understanding its physiological activity. Recent studies in humans[3] and animals[4,5] have established that 7-OH-$\Delta^1$-THC (**1b**) is an important active metabolite of $\Delta^1$-THC. Similarly, $\Delta^{1(6)}$-THC (**2a**) is metabolized to the biologically active **2b**.[6,7] Thus, an urgent need exists for the ready availability of **1b** for further biological and toxicological investigations.



**1a**, $R_1 = R_2 = H$
**b**, $R_1 = OH$; $R_2 = H$
**c**, $R_1 = OCOCH_3$; $R_2 = COCH_3$



**2a**, $R_1 = R_2 = H$
**b**, $R_1 = OH$; $R_2 = H$
**c**, $R_1 = OCOCH_3$; $R_2 = COCH_3$

The main problem in the synthesis of *trans*-THC derivatives containing the $\Delta^1$ double bond is that they are thermodynamically less stable than the corresponding compounds with the $\Delta^{1(6)}$ unsaturation.[8] Hence, during chemical reactions derivatives containing the $\Delta^{1(6)}$ double bond generally predominate. Whereas, numerous syntheses of **2b** have appeared,[6,7,9] including one from this laboratory,[10] thus far only one practical although low yield synthesis of **1b** has been published.[11,12]

We wish to report in this communication the practical synthesis of 7-OH-$\Delta^1$-THC (**1b**) from (−)-$\Delta^{1(7)}$-THC (**3a**, Scheme I) utilizing high-pressure liquid chromatography. This is the first successful application of high-pressure liquid chromatographic (lc) techniques in the cannabinoid field.

The conversion of (−)-$\Delta^{1(7)}$-THC (**3a**)[9,13] to its acetate (**3b**) was carried out in nearly quantitative yield.[10] Treatment of the acetate (**3b**) with *m*-chloroperbenzoic acid in chloroform gave the epoxide **4**: $\delta(CCl_4)$ 0.90, 1.08, 1.35 ($CH_3$ groups) 2.12 (acetate $CH_3$), 2.53 (s, 2 H, C-7 methylene), 6.20, 6.40 (2 H, aromatic). Without further purification the epoxide was hydrolyzed with a 0.3 *N* solution of potassium hydroxide in 85% aqueous DMSO[14] at 100° for 8 hr. Basic conditions were chosen for the epoxide opening to avoid formation of $\Delta^{1(6)}$ dehydration products. The crude triol **6a** was acetylated in pyridine to form the diacetate alcohol **6b**: $\delta(CDCl_3)$ 0.87, 1.07, 1.35 ($CH_3$ groups), 2.26 (phenolic acetate $CH_3$), 2.06 (C-7 acetoxy $CH_3$), 3.94 (AB, $J$ = 11 Hz, 2 H, C-7 protons), 6.36, 6.53 (2 H, aromatic). Treatment of **6b** with thionyl chloride in pyridine at 0° for 16 hr furnished a mixture of the two metabolites as their diacetates **1c** and **2c** (ratio of 1:2).[15] The metabolite diacetate **1c** was separated from the mixture[16] by liquid chromatography as described below. It was then hydrolyzed with a 2:1 mixture of methanol/1 *N* sodium hydroxide solution at room temperature to give **1b**: nmr (100 MHz) $\delta(CCl_4)$ 0.86, 1.04, 1.36 ($CH_3$ groups), 3.86 (s, C-7, hydroxymethyl), 5.89, 6.02 (2 H, aromatic), 6.51 (br, 1 H, vinylic); mass spectrum (70 eV) *m/e* 330 ($M^{\cdot+}$), 315, 312, 299 (base peak), 297, 271, 231, 193 (consistent with published data).[4] The identity was further established by comparison with an authentic sample[17] on glc and lc. The overall yield of isolated **1b** from **3a** is 13%.

Alternatively, **6b** was obtained from **3b** by hydroxylation of the exocyclic double bond with osmium tetroxide in ether followed by acetylation.[9] This material

(1) Part IX. For part VIII see B. A. Zitko, J. F. Howes, R. K. Razdan, B. C. Dalzell, H. C. Dalzell, J. C. Sheehan, H. G. Pars, W. L. Dewey, and L. S. Harris, *Science*, 177, 442 (1972).

(2) This work was presented in part by R. K. Razdan at the Symposium on the Chemistry and Biological Activity of Cannabis, Stockholm, Oct 26–28, 1971.

(3) L. Lemberger, J. Axelrod, and I. J. Kopin, *Ann. N. Y. Acad. Sci.*, 191, 142 (1971), and earlier references given in this paper; L. Lemberger, R. E. Crabtree, and H. M. Rowe, *Science*, 177, 62 (1972); L. Lemberger, J. L. Weiss, A. M. Watanobe, I. M. Galanter, R. J. Wyatt, and P. V. Cardon, *N. Engl. J. Med.*, 286, 685 (1972); M. Perez-Reyez, M. C. Timmons, M. A. Lipton, K. H. Davis, and M. E. Wall, *Science*, 177, 633 (1972); M. E. Wall, D. R. Brine, C. G. Pitt, and M. Perez-Reyez *J. Amer. Chem. Soc.*, 94, 8579 (1972).

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(5) I. M. Nilsson, S. Agurell, J. L. G. Nilsson, A. Ohlsson, F. Sandberg, and W. Wahlquist, *Science*, 168, 1228 (1971); S. Agurell, I. M. Nilsson, A. Ohlsson, and F. Sandberg, *Biochem. Pharmacol.*, 19, 1333 (1970).

(6) Z. Ben-Zvi, R. Mechoulam, and S. H. Burstein, *Tetrahedron Lett.*, 4495 (1970), and earlier references given in this paper.

(7) R. L. Foltz, A. F. Fentiman, Jr., E. C. Leighty, J. L. Walter, H. R. Drews, W. E. Schwarz, T. F. Page, and E. B. Truitt, *Science*, 168, 844 (1970).

(8) Review: R. K. Razdan in "Progress in Organic Chemistry," Vol. 8, W. Carruthers and J. K. Sutherland, Ed., Butterworths, London, 1973.

(9) J. L. G. Nilsson, I. M. Nilsson, S. Agurell, B. Akermark, and I. Lagerlund, *Acta Chem. Scand.*, 25, 768 (1971).

(10) K. K. Weinhardt, R. K. Razdan, and H. C. Dalzell, *Tetrahedron Lett.*, 4827 (1971).

(11) C. G. Pitt, F. Hauser, R. L. Hawks, S. Sathe, and M. E. Wall, *J. Amer. Chem. Soc.*, 94, 8578 (1972).

(12) The formation of minute quantities of **1b** is mentioned during selenium dioxide oxidation of $\Delta^1$-THC acetate.[6] The problem of obtaining the material completely free of toxic selenium combined with the miniscule yield renders this method unsuitable for practical purposes.

(13) J. W. Wildes, N. H. Martin, C. G. Pitt, and M. E. Wall, *J. Org. Chem.*, 36, 72 (1971); R. K. Razdan, A. J. Puttick, B. A. Zitko, and G. R. Handrick, *Experientia*, 28, 121 (1972). (—)-$\Delta^{1(7)}$-THC (**3a**) has become available in large quantities as an impurity during the large scale conversion of $\Delta^{1(6)}$-THC to $\Delta^1$-THC. We have been supplied with 200 g of **3a** (85% pure by glc) by the National Institutes of Mental Health and as far as we are aware more material is available.

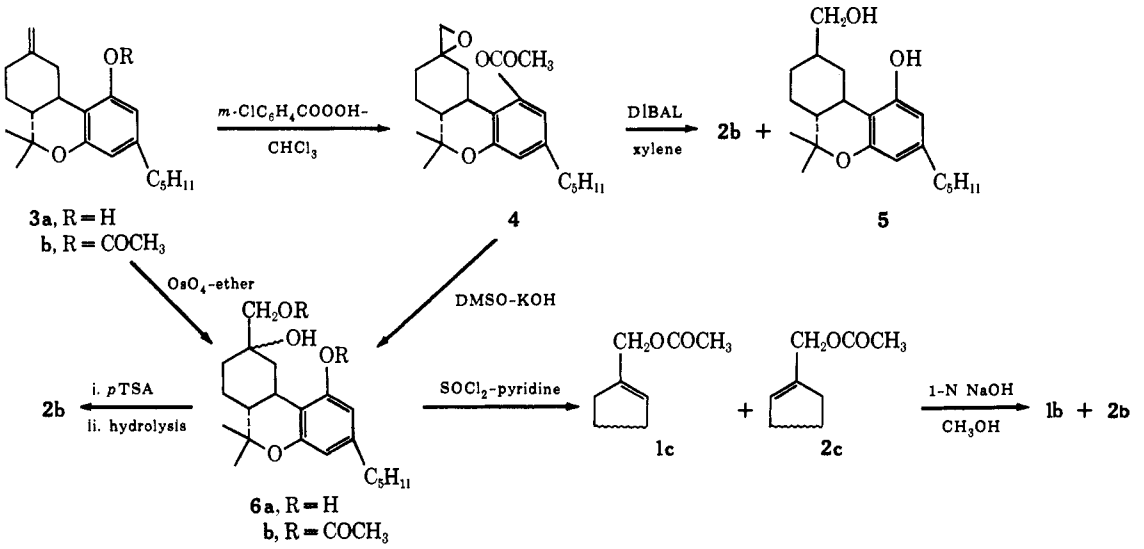
(14) G. Berti, B. Macchia, and F. Macchia, *Tetrahedron Lett.*, 3421 (1965).

(15) The relative amounts of **1c** and **2c** were determined by hydrolysis to **1b** and **2b** and glc analysis of a silylated sample using a Varian Aerograph Model 1400 equipped with a 6 ft × 1/8 in.-s.s. column packed with 2% OV-17 on 100–200 mesh Gas Chrom Q and a flame ionization detector. Retention time (248°) **1b**, 4 min 36 sec; **2b**, 4 min 54 sec.

(16) The mixture showed a single spot on tlc in various solvent systems even after multiple developments.

(17) Kindly supplied by Dr. C. G. Pitt, Research Triangle Institute, N. C.

**Scheme I**




showed slight differences in the acetate region of the nmr and when it was treated with thionyl chloride in pyridine the resulting mixture contained **1c** and **2c** in a ratio of 1:6.[15,18]

Separation of the diacetates **1c** and **2c** was achieved using high-pressure liquid chromatography (lc) on a Waters Associates ALC-202 chromatograph equipped with a Model 6000 solvent delivery system. Various solvent systems were investigated on an 8 ft × 1/8 in. column of Corasil II. With 99.5% 1,2-dichloroethane–0.5% acetonitrile the capacity factor ($k'$) was 2.08 for the $\Delta^1$-diacetate **1c** and 2.52 for $\Delta^{1(6)}$ isomer **2c** giving a separation factor ($\alpha$) of 1.21. Under these conditions, near base line resolution was obtained at low loading. Preparative separation was carried out with the same solvent system on an 8 ft × 3/8 in. column of Porasil C ($k'_{1c} = 1.64$, $k'_{2c} = 2.00$, $\alpha = 1.22$). In a typical separation 240 mg of crude diacetate mixture containing approximately 18% of **1c** by glc analysis was placed on the column, impurity peaks were collected, and the peaks due to diacetates **1c** and **2c** were recycled into the column. After 2 recycles (2.5 hr) the $\Delta^1$-diacetate **1c** (30 mg) was collected. This material is greater than 95% pure by glc analysis. Similar results have been obtained with sample sizes up to 800 mg.

The metabolites **1b** and **2b** can also be separated[16] by lc. On an 8 ft × 1/8 in. column of Corasil II eluting with heptane–dichloromethane–acetonitrile (90:17.5:7.5), the elution parameters were $k'_{1b} = 4.9$, $k'_{2b} = 5.4$, $\alpha = 1.10$. Preparative separation has been carried out with this solvent system on an 8 ft × 3/8 in. column of Corasil II. This separation is more difficult than that of the diacetates **1c** and **2c** requiring eight recycles (6.5 hr) to obtain satisfactory separation of a 240-mg sample of crude **1b** and **2b**.

Additionally, two convenient syntheses of 7-OH-$\Delta^{1(6)}$-THC (**2b**) are provided by intermediates in Scheme I. Diacetate alcohol **6b** was dehydrated with *p*-toluenesulfonic acid,[9] followed by hydrolysis, to give **2b** in 75% overall yield from **3a** (*via* epoxide **4**). This route appears to be the method of choice for the preparation of **2b** as a comparison of this procedure with the osmium tetroxide route (overall yield 25%)[9] shows that the former gives cleaner products and is much simpler. Treatment of **4** with diisobutylaluminum hydride (DIBAL)[19] in xylene at 120° gave metabolite **2b** in 65% yield (based on glc analysis) together with 22% of 7-hydroxyhexahydrocannabinol (**5**) as identified by its mass spectral data *m/e* (70 eV) 332($M\cdot^+$), 289, 276, 231, 193. Another product was found in this reaction mixture which showed the same retention time on glc as the metabolite **1b**. However, this material was shown by high-pressure lc and nmr not to be **1b**. It has been tentatively identified as the epimer of **5** at $C_1$. This finding illustrates the value of high-pressure lc as an analytical tool.

**Acknowledgment.** This work was carried out with the support of Contract No. HSM-42-72-230, National Institute of Mental Health, NIH, and HEW. We wish to thank Mr. J. Waters of Waters Associates for helpful suggestions in carrying out the lc separation work and Dr. G. Dudek of Harvard University for recording the Fourier transform nmr spectra.

(18) We attribute this change to differences in the stereochemistry of the hydroxyl group at C-1. The possibility that one isomer eliminates stereoselectively to give **1c** is at present under investigation.

(19) W. Kirchhof, *Chem. Ber.*, **93**, 2712 (1960).

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## Phosphorylation of Amides. Evidence for Participation in Catalysis

*Sir:*

Amide groups are known to serve as intramolecular nucleophilic catalysts for reactions at neighboring acyl carbon atoms.[1] However, no similar case of par-

(1) C. K. Sauers, C. L. Gould, and E. S. Ioannou, *J. Amer. Chem. Soc.*, **94**, 8156 (1972), and references therein.