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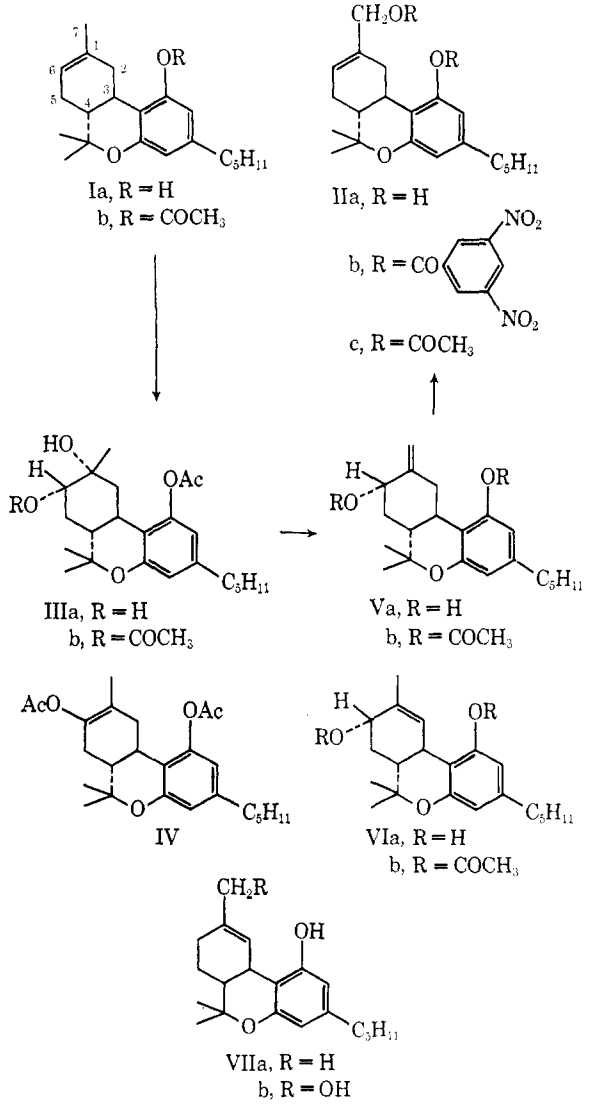
Identification through Synthesis of an Active $\Delta^{1(6)}$-Tetrahydrocannabinol Metabolite

Sir:

We recently reported[1] the isolation and partial elucidation of the structure of a $\Delta^{1(6)}$-tetrahydrocannabinol ($\Delta^{1(6)}$-THC) metabolite obtained from the urine of rabbits injected with $\Delta^{1(6)}$-THC (Ia) tritiated at C-2. On the basis of mass spectral analysis and certain chemical transformations, we deduced that the metabolite is a hydroxylated derivative of Ia. The new hydroxyl group was shown to be allylic, and we tentatively suggested structure IIa. The metabolite was only obtained in minute amounts which were not sufficient for a nuclear magnetic resonance determination; hence the problem was approached through synthesis. We report now that we have completed the preparation of IIa and have shown that it is identical with the metabolite.



Reaction of $\Delta^{1(6)}$-THC acetate (Ib)[2] with osmium tetroxide gave 1α,6α-dihydroxyhexahydrocannabinol acetate (IIIa) in 72% yield: mp 75–76°; $[\alpha]D$ −121° (EtOH); δ (CCl_4) 1.10, 1.27, 1.38 (three methyl groups), 2.32 (acetoxyl methyl group), 3.50 (quartet, $J_{5\alpha,6\beta}$ = 11 Hz, $J_{5\beta,6\beta}$ = 4.5 Hz; C-6 proton), 6.35, 6.50 (two aromatic protons). On acetylation (acetic anhydride–pyridine) the diacetate IIIb is obtained (95%) as an oil, $[\alpha]D$ −107° (EtOH). Dehydration of IIIb with thionyl chloride in pyridine yielded a mixture of three compounds: the enol acetate IV (31%; $[\alpha]D$ −67° (EtOH); δ (CCl_4) 1.12, 1.36 (two methyl groups), 1.54 (one vinylic methyl group), 2.08, 2.21 (two acetoxyl methyl groups), 6.24, 6.41 (two aromatic protons), no peaks between 2.95 and 6.24; $\nu_{max}^{CCl_4}$ 1770 cm^{-1}) and the allylic acetates Vb and VIb. The last two compounds were not separated[3] but were converted with lithium aluminum hydride directly to a mixture which on chromatography gave pure Va (28% from IIIb; $[\alpha]D$ −36° (EtOH); δ ($CDCl_3$) 1.07, 1.40 (two methyl groups), 3.87 (C-3 proton), 4.18 (br quartet, $J_{5\alpha,6\beta}$ = 11 Hz, $J_{5\beta,6\beta}$ = 6 Hz; C-6 proton), 4.97 (d, two C-7 protons), 6.07, 6.20 (two aromatic protons); $\nu_{max}^{CCl_4}$ 909 cm^{-1} (terminal methylene group)) and VIa (21%; $[\alpha]D$ −115° (EtOH); δ ($CDCl_3$) 1.10 and 1.40 (two methyl groups), 1.81 (vinylic methyl group), 4.15–4.60 (br, C-6 proton), 6.20, 6.28 (two aromatic protons), and 6.60 (C-2 vinylic proton)).

Treatment of Va with boron trifluoride etherate in methylene chloride caused an allylic rearrangement forming IIa (10%; $[\alpha]D$ −255° (EtOH); δ ($CDCl_3$) 0.98, 1.35 (two methyl groups), 4.06 (br s, two C-7 protons), 5.7 (C-6 proton), 6.08, 6.21 (two aromatic protons)), 7-OH-$\Delta^{1(6)}$-THC bis-3,5-dinitrobenzoate (IIb) (mp 140–142°; δ ($CDCl_3$) 1.20, 1.40 (two methyl groups), 4.65 (two C-7 protons), 5.88 (one olefinic proton), 6.53, 6.65 (two aromatic protons)), 7-OH-$\Delta^{1(6)}$-THC diacetate (IIc) (δ ($CDCl_3$) 1.12, 1.38 (two methyl groups), 2.07, 2.30 (two acetoxyl methyl groups), 4.48 (two C-7 protons), 5.77 (one olefinic proton), 6.42, 6.57 (two aromatic protons)).

Direct comparisons of IIc with the acetylated tritiated metabolite[4] were made by thin layer (tlc) and gas chromatography (glpc) and by mass spectral analysis under identical conditions. More than 90% of the radioactivity was found to migrate with the synthetic material (IIc) on tlc using 80% hexane–20% acetone as the eluent; similar results were obtained when a second chromatogram using 48% benzene–48% hexane–4% methanol was run. Identical retention times were observed on glpc (separately and as a mixture)

(1) S. H. Burstein, F. Menezes, E. Williamson, and R. Mechoulam, *Nature*, **225**, 87 (1970).

(2) Review: R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Org. Naturst.*, **25**, 175 (1967).

(3) When separation was attempted Vb could be obtained in low yield: mp 88–89°; $[\alpha]D$ −66° (EtOH); δ (CCl_4) 1.06, 1.36 (two methyl groups), 2.07, 2.25 (two acetoxyl methyl groups), 4.77 (two terminal methylene protons, br s), 5.15 (C-6 proton, quartet, $J_{5\alpha,6\beta}$ = 11 Hz, $J_{5\beta,6\beta}$ = 6 Hz), 6.25, 6.40 (two aromatic protons); $\nu_{max}^{CCl_4}$ 908 cm^{-1} (terminal methylene group).

(4) The material used for these comparisons was obtained by incubation of Ia with a homogenate of rabbit liver; the details will be reported later in a full paper. The *in vivo* and *in vitro* metabolites were shown to be chromatographically identical.

of IIc and the metabolite diacetate under two sets of conditions (2% XE-60 at 210°; 5% SE-30 at 245°). The mass spectra of both substances showed strong peaks at 414 (M), 372 (M − 42), and 312 (M − 102) with the same relative intensities. The fragmentation peaks are consistent with the loss of aromatic acetate as ketene followed by the loss of aliphatic acetate as acetic acid.

We assume that the C-6 hydroxyl (or acetoxyl) group in III, V, and VI is α on the basis of the splitting pattern of the axial (or pseudoaxial) C-6 proton which appears as a quartet, with large $J_{5\alpha,6\beta}$ and medium $J_{5\beta,6\beta}$ values. Dreiding models show that the axial C-6 proton forms dihedral angles of ~170–180° and ~50–60° with the C-5 protons. This is compatible with the J values observed. If the C-6 proton were equatorial the splitting would be expected to be considerably smaller (the dihedral angles between a C-6 equatorial proton and the C-5 protons are ~50–70°).[5] As osmium tetroxide leads to *cis*-glycols the C-1 hydroxyl group in IIIa is also α.

Synthetic 7-OH-$\Delta^{1(6)}$-THC (IIa) when administered to monkeys[6] is active at approximately the same dose level as $\Delta^{1(6)}$-THC (Ia). A full report will be submitted elsewhere by Drs. H. Edery and Y. Grunfeld.

Interestingly, an analogous metabolic pathway has been reported for Δ^1-THC (VIIa) in which VIIb was found to be the major product.[7] This "common" pathway coupled with published data on the half-life of the drug in the peripheral circulation[8] and the activity of IIa strongly suggests that the metabolites are responsible for the psychotomimetic properties of *Cannabis*.[9]

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(5) Chemical evidence supporting the α assignment of the hydroxyl groups will be presented in the full paper. The stereochemical argument is, however, irrelevant to the structure of the metabolite (IIa) in which the C-6 chiral center is eliminated. *Cf.* L. M. Jackman and S. Sternhell, "Applications of NMR Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 290.

(6) Y. Grunfeld and H. Edery, *Psychopharmacologia*, **14**, 200 (1969).

(7) This work was presented in part by R. M. at the 2nd International Symposium on Toxicology (Tel Aviv, Feb 21, 1970). During the discussion following the lecture Dr. M. E. Wall of Research Triangle Institute, Research Triangle Park, North Carolina, and Professor F. Sandberg of Kungl. Farmaceutiska Institutet, Stockholm, announced independently that VIIb has been isolated and identified as the major metabolite of VIIa (M. E. Wall, D. R. Brine, G. A. Brine, C. G. Pitt, R. I. Freudenthal, and H. D. Christensen, *J. Amer. Chem. Soc.*, **92**, 3466 (1970); I. M. Nilsson, S. Agurell, J. L. G. Nilsson, A. Ohlsson, F. Sandberg, and M. Wahlqvist, submitted for publication).

(8) S. Agurell, I. M. Nilsson, A. Ohlsson, and F. Sandberg, *Biochem. Pharmacol.*, in press.

(9) NOTE ADDED IN PROOF. Based soley on pharmacological data, Grunfeld and Edery have previously suggested that metabolites of the tetrahydrocannabinols may be active (see ref 6).

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Slow Solvolysis of 4-Tricyclyl Trifluoromethanesulfonate. Interaction of the Face of a Cyclopropane Ring with Positively Charged Carbon

Sir:

Interaction of a positively charged species and a cyclopropane ring is often an exothermic process. This is reflected most dramatically in the rapid solvolysis rates of cyclopropylcarbinyl derivatives[1] and in the rapid reaction of cyclopropanes with electrophiles.[2] It has long been thought, however, that the favorability of this interaction is greatly dependent upon the geometry of orientation of the ring and electrophile. In cyclopropylcarbinyl cases, favorable and unfavorable geometries for interaction of charged centers with an edge of the ring have been investigated by employing nmr techniques[3] and rate studies on appropriately substituted or relatively rigid systems.[4] Studies on bimolecular cyclopropane–electrophile reactions have been less definitive, but appear to be more easily rationalized in most cases by assuming the intermediacy of edge- rather than face-protonated cyclopropanes.[5] Recent theoretical work supports this point of view.[6]

We now wish to report some theoretical and experimental results concerning the energy of a 4-tricyclyl cation (**7**) which indicate that interaction of a positive charge with the center of a cyclopropane ring results in little or no stabilization, and provide a quantitative estimate of the energetics of the interaction.

4-Hydroxytricyclene (**2**) was prepared from 4-tricyclenecarboxylic acid (**1**)[7] by the route outlined in Scheme I, and converted to the *p*-bromobenzenesulfonate (brosylate) derivative (**3**) using standard methods. Although 1-apocamphyl brosylate (**9**, prepared from 1-apocamphanol[8a] (**8**)) underwent solvolysis in 70% (by weight) aqueous dioxane buffered with triethylamine at 200° ($k_{200} = (4.44 \pm 0.19) \times 10^{-5}$ sec^{-1}), **3** showed no reaction at this temperature. *Brosylate* **3** *was in fact stable to the solvolytic conditions up to unusually high temperatures, finally undergoing slow reaction at 295°.*

In order to obtain a quantitative estimate of the reactivity difference between **3** and **9**, we synthesized

(1) (a) J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951); (b) C. G. Bergstrom and S. Siegel, *ibid.*, **74**, 145, 254 (1952); (c) H. Hart and J. M. Sandri, *ibid.*, **81**, 320 (1959); (d) E. F. Cox, M. C. Caserio, M. S. Silver, and J. D. Roberts, *ibid.*, **83**, 2719 (1961); (e) S. A. Sherrod and R. G. Bergman, *ibid.*, **91**, 2115 (1969); (f) M. Hanack and T. Bassler, *ibid.*, **91**, 2117 (1969).

(2) (a) R. L. Baird and A. A. Aboderin, *Tetrahedron Lett.*, 235 (1963); *J. Amer. Chem. Soc.*, **86**, 252 (1964); (b) R. T. LaLonde and J. J. Batelka, *Tetrahedron Lett.*, 445 (1964); (c) R. T. LaLonde and L. S. Forney, *J. Amer. Chem. Soc.*, **85**, 3767 (1963); (d) R. T. LaLonde and M. A. Tobias, *ibid.*, **85**, 3771 (1963); **86**, 4068 (1964); (e) E. J. Corey and R. F. Atkinson, *J. Org. Chem.*, **29**, 3703 (1964); (f) C. H. DePuy, H. L. Jones, and D. H. Gibson, *J. Amer. Chem. Soc.*, **90**, 1830 (1968); (g) G. A. Olah and J. Lukas, *ibid.*, **90**, 933 (1968).

(3) (a) C. U. Pittman, Jr., and G. A. Olah, *ibid.*, **87**, 2998 (1965); (b) C. D. Poulter and S. Winstein, *ibid.*, **91**, 3649 (1969).

(4) (a) P. von R. Schleyer and V. Buss, *ibid.*, **91**, 5880 (1969); (b) J. C. Martin and B. R. Ree, *ibid.*, **91**, 5882 (1969); (c) P. von R. Schleyer and G. W. Van Dine, *ibid.*, **88**, 2321 (1966), and references cited there.

(5) For a summary of the evidence, *cf.* C. J. Collins, *Chem. Rev.*, **69**, 541 (1969).

(6) (a) R. Sustmann, J. E. Williams, M. J. S. Dewar, L. C. Allen, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 5350 (1969); (b) J. D. Petke and J. L. Whitten, *ibid.*, **90**, 3338 (1968).

(7) H. L. Hoyer, *Chem. Ber.*, **87**, 1849 (1954).

(8) (a) M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *J. Amer. Chem. Soc.*, **80**, 6393 (1958); (b) C. G. Swain and C. R. Morgan, *J. Org. Chem.*, **29**, 2097 (1964).