

chromic acid,⁸ dichlorodicyanoquinone dehydrogenation of ketones,⁹ etc.

Δ¹-3,4-*trans*-Tetrahydrocannabinol (Δ¹-THC) (I)¹⁰ is converted into cannabinol (II) in 90% yield on boiling with chloranil in benzene for 2 hr while Δ¹⁽⁶⁾-THC (III)¹¹ and Δ¹-3,4-*cis*-THC (VI)^{12a} remain almost unchanged under identical experimental conditions for up to 20 hr. The same applies also to cannabidiol (IV),¹³ which does not yield the corresponding biphenyl derivative, and to the chroman V,¹⁴ which is not converted into VIII.¹⁵

Braude, Linstead, and Jackman have shown that quinone dehydrogenation of hydroaromatic compounds is a two-step reaction proceeding through a cationic intermediate.¹⁶ On this basis we assume that the difference in reactivity between Δ¹-THC (I), Δ¹⁽⁶⁾-THC (III), and V is due to the absence of allylic activation on the benzylic hydrogens in III and V. The difference among I, IV, and VI is more subtle. In I, the

pseudo-axial C₃-H is essentially perpendicular to the planes of both the aromatic ring and the double bond, while in IV it is nearly perpendicular to the plane of the double bond only and is nearly parallel to the plane of the aromatic ring. These conformations have been deduced from nmr analysis.^{10,13} In I, the C₃-H, during abstraction as hydride, will remain in constant overlap with the π electrons of both unsaturated systems, thus lowering the energy of the transition state. In IV, overlap is possible with the π electrons of the double bond only. The same factors are probably involved in the nonreactivity of VI. The C₂-H in the preferred^{17a,c} conformation of VI is at a dihedral angle of *ca.* 35° with the C₃-H¹⁷ and hence σ-π overlap in the transition state is limited to the phenolic ring only, with which C₃-H forms an angle of *ca.* 80°.^{17a,c} The observed differences in reactivity are not due to steric hindrance. Cannabigerol (VII) is dehydrogenated with chloranil in benzene at a lower rate than is I,¹⁸ though in any reasonable conformation at least one of the two allylic-benzylic hydrogens in VII is subject to less hindrance than the C₃-H in I. The lower rate is probably due to the tendency of the double bond to be slightly out of the plane of the aromatic ring.^{17a} This leads to less overlap with the leaving hydride during the dehydrogenation.

The products of the dehydrogenation of VII are *dl*-cannabichromene (VIII)¹⁹ (in 45% yield) and the

(7) S. H. Burstein and H. J. Ringold, *J. Am. Chem. Soc.*, **86**, 4952 (1964).

(8) S. H. Burstein and H. J. Ringold, *ibid.*, **89**, 4722 (1967).

(9) H. J. Ringold and A. Turner, *Chem. Ind. (London)*, 211 (1962); H. J. Ringold, M. Gut, M. Hayano, and A. Turner, *Tetrahedron Letters*, 835 (1962).

(10) Y. Gaoni and R. Mechoulam, *J. Am. Chem. Soc.*, **86**, 1646 (1964).

(11) Y. Gaoni and R. Mechoulam, *Tetrahedron*, **22**, 1481 (1966); R. L. Hively, W. A. Mosher, and F. W. Hoffmann, *J. Am. Chem. Soc.*, **88**, 1832 (1966).

(12) (a) E. C. Taylor, K. Lenard, and Y. Shvo, *ibid.*, **88**, 367 (1966);

(b) Y. Gaoni and R. Mechoulam, *ibid.*, **88**, 5673 (1966).

(13) R. Mechoulam and Y. Shvo, *Tetrahedron*, **19**, 2073 (1963).

(14) Y. Gaoni and R. Mechoulam, *Proc. Chem. Soc.*, 82 (1964).

(15) In all cases 5–10% of unidentified products which seem to be due to phenolic oxidation were formed.

(16) L. M. Jackman, *Advan. Org. Chem.*, **2**, 329 (1960); E. A. Braude, L. M. Jackman, R. P. Linstead, and G. Lowe, *J. Chem. Soc.*, 3133 (1960); R. F. Brown and L. M. Jackman, *ibid.*, 3144 (1960), and earlier references therein.

(17) (a) By empirical measurements from Dreiding models. Cf. also (b) E. J. Corey and R. A. Sneed, *J. Am. Chem. Soc.*, **77**, 2505 (1955), for a vector analysis of cyclohexene, leading to $\theta = 37^\circ$ for the corresponding angle. (c) F. Johnson and S. K. Malhotra, *ibid.*, **87**, 5492 (1965).

(18) The period of half-life of I in this reaction is 30 min, while that of VII is 8 hr.

(19) (a) Y. Gaoni and R. Mechoulam, *Chem. Commun.*, 20 (1966); (b) U. Claussen, F. V. Spulak, and F. Korte, *Tetrahedron*, **22**, 1477

tetracyclic diether IX (in 15% yield). This represents the first total synthesis of cannabichromene (in its racemic form). *dl*-Cannabichromene thus obtained is, except for optical rotation, identical with the natural product:²⁰ it has the same infrared, nmr, and mass spectra, the same R_f (on thin layer chromatography), and the same retention time on vapor phase chromatography. It gives a 3,5-dinitrophenylurethan, mp 106–107°, which does not depress the melting point of the same derivative of natural cannabichromene, mp 106–107°.

Structure IX for the compound formed together with cannabichromene is put forward on the following grounds: (a) mol wt 314 (by mass spectrum); (b) four methyl groups (by nmr), one of which is the terminal methyl group on the side chain, while the others (at δ 0.94, 1.30, and 1.40) are in the region normally associated in this series with methyls on a saturated carbon atom or α to an oxygen atom, but not on a double bond; (c) no olefinic protons; two aromatic protons (at δ 6.13) which appear essentially as a singlet, indicating a similarity in the environment of the aromatic protons; (d) no hydroxylic bands in the infrared, strong etheric bands at 1060 and 1120 cm^{-1} ; (e) conversion into $\Delta^{4(8)}$ -isotetrahydrocannabinol (X)¹² on boiling with *p*-toluenesulfonic acid in benzene.

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(1966); (c) I. M. Campbell, C. H. Calzadilla, and N. J. McCorkindale, *Tetrahedron Letters*, 5107 (1966).

(20) Synthetic *dl*-cannabichromene shows no activity in the dog ataxia or monkey behavioral tests in doses up to 10 mg/kg. These observations are in accord with the negative results reported for natural cannabichromene in humans.²¹ The positive dog ataxia test previously observed by us^{19a} was probably due to impurities in the natural material, which was available in minute amounts.

(21) H. Isbel, C. W. Gorodetzky, D. Yasinsky, U. Claussen, F. von Spulak, and F. Korte, *Psychopharmacologia*, 11, 184 (1967).

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Stereospecifically Labeled $\Delta^{1(6)}$ -Tetrahydrocannabinol

Sir:

The widespread use of marijuana as a psychotomimetic agent has prompted us to undertake a study of the metabolism of the active principles of this drug. ($-$)- Δ^1 -Tetrahydrocannabinol [($-$)- Δ^1 -THC] (I) and its isomer ($-$)- $\Delta^{1(6)}$ -THC (II) are believed to be the compounds responsible for both the psychotomimetic and analgetic properties of *Cannabis* resin.¹ We therefore sought a method for introducing a radioisotope into

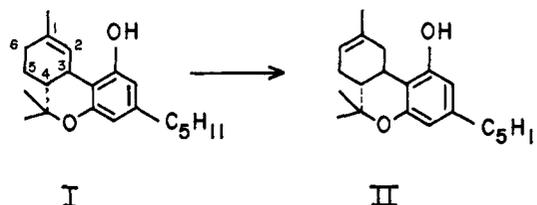
(1) R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Organ. Naturstoffe*, 25, 175 (1967).

either of these compounds to permit a metabolic study to be made.

Work done by our group² and others³ has shown that I can be readily isomerized to II in the presence of *p*-toluenesulfonic acid in nearly quantitative yield. It was thought that, if catalyst in which the acidic proton had been exchanged with tritium were used, the introduction of isotopic hydrogen at the 2 position could be accomplished.

In order to test the feasibility of this procedure, an isomerization with deuterium-exchanged *p*-toluenesulfonic acid was carried out. A sample of ($-$)- Δ^1 -THC (I, 18 mg) in which the phenolic hydrogen had been exchanged by exposure to excess 99.8% D_2O , was dissolved in dry benzene (50 ml), and deuterated acid (10 mg) was added. The mixture was refluxed for 2 hr, at which time the solution was extracted with 2% Na_2CO_3 solution and the product isolated from the neutral fraction as a red oil. Thin layer chromatography on silica gel in a hexane-acetone system (9:1) yielded 15 mg of ($-$)- $\Delta^{1(6)}$ -THC (II) as a pale yellow oil.

The nmr spectrum⁴ of the product showed that the isomerization had taken place under these conditions and that approximately one atom of deuterium had been introduced at position 2. Evidence for the isomerization was observed in the shift of the signal for the olefinic proton from 378 cps in I to 322 cps in II, as



reported previously.¹ The position and stereochemistry of the deuterium was demonstrated by the nature of the signal from the hydrogen at position 3. In the undeuterated compound this appeared as a broad doublet centered at 190 cps. The deuterated sample gave a quartet centered at 193 cps with coupling constants of about 16 and 4.5 cps. The larger coupling constant is assigned to the coupling between the C-3 and C-4 protons which are diaxial. The smaller constant is due to the coupling between C 3 and an equatorial proton at C-2. Therefore, there must be deuterium at the C-2 axial position. This is the expected orientation since the protonation of the double bonds usually proceeds by axial addition.⁵

The isomerization was repeated exactly as above except that tritiated water⁶ (specific activity 1.80 Ci/mole) was used instead of deuterated water. The product was again purified by thin layer chromatography and the radiochemical purity demonstrated by paper chromatography on a "Bush A" system. The specific activity of the ($-$)- $\Delta^{1(6)}$ -THC-2-axial-³H thus obtained was deter-

(2) Y. Gaoni and R. Mechoulam, *Tetrahedron*, 22, 1481 (1966).

(3) (a) E. C. Taylor, K. Lenard, and Y. Shvo, *J. Am. Chem. Soc.*, 88, 367 (1966); (b) R. Hively, W. A. Mosher, and F. Hoffman, *ibid.*, 88, 1832 (1966).

(4) The spectra were run on a Varian DP/DA-60 instrument in CCl_4 with $(\text{CH}_3)_4\text{Si}$ as an internal standard. The authors wish to thank Thomas Wittstruck of the Worcester Foundation for Experimental Biology for aid in interpretation of the spectra.

(5) For a recent example see S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, 87, 3228 (1965).

(6) Purchased from New England Nuclear Corp., Boston, Mass.