records well with theoretical expectation for a partial change in hybridization of the C2 carbon from sp² to sp³ in the transition state for disrotatory closure to 2. The near identity of the other three values in the upper right quadrant of Table I suggests that valence tautomerism is likewise rate limiting in these examples.

The deuterium isotope effects which are evidenced in the cycloaddition of MA to 1a and 1b are substantially larger and arise because of reduced dienophlic reactivity which causes the \( k_2 \) (DP) and \( k_{-1} \) terms to approach each other in magnitude. The same progression toward case II behavior is witnessed in the DCMI reactions with 1c and 1d but for a different reason. In these examples, the diminished concentration gradient of 2c and 2d (relative to the methyl and phenyl derivatives) arising from an increase in \( k_{-1} \) is the responsible factor.

The enormous \( k_{1c}/k_D \) values for the 1c- and 1d-MA examples, utterly unprecedented in their magnitude, can be understood if the kinetic profile has progressed well into the case I manifold (eq 2). Under these circumstances, a multiplicative isotope effect (\( k_1^{1c}/k_1^{-1}D^{1c}/k_1^{1c}/k_1^{-1} \)) obtains. Consequently, limiting case I behavior is merely a preequilibrium situation where 2H and 2D are of necessity in complete equilibrium with each other. Accordingly, these large isotope effects reflect the full difference in heats of formation of the isomeric species 2H and 2D. One should recognize that \( k_3 \) could be the source of a small fraction of this isotope effect and that it tends to amplify matters in the observed direction. As concerns eq 2, the assumption has been made that the \( k_{1c}^{1H} \) and \( k_{1c}^{1D} \) terms are essentially identical (thus cancelling) and therefore noncontributory to the isotopic fractionation due to the low level of discrimination anticipated for capture of 2H and 2D by dienophile. To our knowledge, however, experiments designed to assess this specific question remain to be addressed and our assumption must be viewed as presently untested.

To the extent that the isotope effect in case I is indeed wholly derived from an equilibrium isotope effect, then these are unusually large values which reflect the equilibrium isotope effect difference for tetrahedral vs. trigonal deuterium. Notwithstanding, the observed \( K_{eq} \) (Table I) are in essential agreement with the best estimates available from consideration of appropriate vibrational frequencies, although this level of magnitude has never been attained in Sn1 solvolysis reactions.

Thus we have demonstrated that the kinetic deuterium isotope effect at the transition state of a cycloaddition reaction which is preceded by electrocyclic rearrangement is substantially less than that which constitutes equilibrium. The study takes advantage of the correlatability of a predictable mechanistic trend (kinetic order) with a relatively unpredictable but mechanistically sensitive probe (secondary deuterium isotope effects). This method may serve as a simple experimental device to derive useful conclusions concerning the kinetic order of these cycloadditions without resorting to tedious dilatometric rate measurements.

Acknowledgment. The generous financial support of the National Science Foundation made possible this study. The authors thank Professors R. A. Caldwell and W. R. Dolbier, Jr., for stimulating discussion and Ronald K. Russell for assistance in recording of several 100-MHz spectra.

References and Notes

(4) Highly reactive N-phenyltriazolininediones (PTAD) frequently attains case III behavior. However, unlike 2r reactants of lesser reactivity which select only the 7-substituted bicyclo[4.2.0]octatetraene, PTAD combines with a greater number of valence tautomers and adds directly to the monocyclic tetratriene in certain cases. We have independently established by competition methods that DCMI lies between TCNE and PTAD in its reactivity as a dienophile toward 2.
(5) In the case of DCMI, this general mode of positional regioselectivity has also been observed for R = \( COCH_3 \) and Br.
(6) Very careful measurement of signal intensities in the labeled 1c-MA adduct (\( H_2+H_2 \)) vs. \( 2H \) yields, respectively, corresponding to 34.4% a (sp²) and 28.3% a (sp²), character at these sites. (M. L. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N.Y., 1969, p 345. It follows from these data that the extent of hybridization perturbation in C2-H during conversion of 1 to 2 is minimal by comparison.
(7) Use of the model, Streitzweig has calculated that the maximum \( \omega \)-effect arising from changes in the bonding force constants during sp² → sp³ hybridization at the transition state to be 1.40. A. Streitzweig, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, J. Amer. Chem. Soc., 80, 2326 (1958).

Stereospecific Intramolecular Epoxide Cleavage by Phenolate Anion. Synthesis of Novel and Biologically Active Cannabinoids

Sir:

As part of a program initiated to further our understanding of the chemical and biological activity of Hashish constituents, 1 we wish to report a stereospecific intramolecular epoxide cleavage by phenolate anion leading to the dihydrobenzofuran, 2 dihydrobenzopyran, and tetrahydrobenzoxepin ring systems. Utilizing this transformation we have effected: (a) the first stereochemically unambiguous synthesis of cannabinol (3) (5), (b) the preparation of a new biologically potent derivative of \( \Delta^2 \)-tetrahydrocannabinol (THC) (6); and (c) the synthesis of a novel tetracyclic cannabinoid (10) (Scheme I).

Cannabidiol diacetate (1), prepared from (−)-cannabidiol (5) (pyridine, acetic anhydride, room temperature, quantitative), gave a mixture of epoxides 2, 3, and 4 when allowed to react at room temperature with \( n \)-chloroperbenzoic acid in chloroform. Gradient elution from Florisil with an ether-petroleum ether solvent system furnished pure diepoxide 4 (40% isolated yield) (δ (CCl₄): 6.73 (s, 2, aromatics), 3.05 (d, 1, J = 11 Hz, \( C_2H_3 \)), 2.73 (s, 1, \( C_2H_2 \), 2 Hz band width at half-height), 2.30 (s, 3, acetate), 2.23 (s, 3, acetate), 2.00, 1.67 (AB, 2 / = 5 Hz, \( -H, -H \)), 1.30 (s, \( C_3H_3 \)), 1.10 (s, 3, \( \omega-C_3H_3 \)), 0.88 (t, 3, \( \omega-C_3H_3 \)) and a mixture of 2 and 3 (40% isolated yield, in a ratio of 4:1) which shows similar absorptions at 3.10 (d, 1, \( J = 11 Hz, C_2H_3 \)), and 2.80 (s, 1, \( C_2H_2 \), 2 Hz band width at half-height). The lack of observable coupling between the \( C_2 \) and \( C_3 \)-protons, the presence of significant steric hindrance on the \( \beta \)-face, and the ease of opening these epoxides (below) make the assignment of an \( \alpha \)-configuration to the endocyclic epoxides in 2 and 4 secure.

Journal of the American Chemical Society / 96:23 / November 13, 1974
The mixture of epoxides 2 and 3, in the presence of 2% NaOH in MeOH-H₂O (1:1) at room temperature afforded cannabinoids 5 and 6 via ester hydrolysis and phenolate anion attack at the oxirane. Separation by preparative tlc on silica gel using an ether-petroleum ether (1:1) solvent system gave pure 5 and 6 in 75% isolated yield in a ratio of 4:1. The nmr of 5 (δ (CCl₄) 6.15 (s, 2, aromatics), 5.50 (br, 1, OH), 4.90 (br, 2, vinylics), 3.92 (d, 1, J = 6 Hz, C₂-H), 3.23 (m, 1, C₃-H), 2.10 (br, 1, OH), 1.78 (s, 3, C₈-CH₃), 1.38 (s, 3, C₁–CH₃), 0.88 (t, 3, w-CH₃)) as well as the mass spectrum and glc retention time are virtually identical with those reported for cannabielsoin obtained by decarboxylation of cannabielsoic acid. Acetylation of 5 provided a monoacetate (7): δ (CCl₄) 6.43, 6.33 (AB, 2, J = 2 Hz, aromatics), 4.63 (br, 1, vinylic), 4.58 (br, 1, vinylic), 3.95 (d, 1, J = 5 Hz, C₂-H), 3.13 (m, 1, C₃-H), 2.23 (br, 1, OH), 2.13 (s, 3, acetate), 1.72 (s, 3, C₈-CH₃), 1.33 (s, 3, C₁–CH₃), 0.88 (t, 3, w-CH₃). Dehydration of 5 (pyridine, SOCl₂, room temperature, 80%) gave 8: δ (CCl₄) 6.13 (s, 2, aromatics), 5.72 (br, 1, C₆-H, vinylic), 5.40 (s, 1, OH), 5.03 (br, 2, C₉–2H, vinylic), 4.60 (d, 1, J = 8 Hz, C₂-H), 3.17 (dd, J₂,₃ = 8 Hz, J₃,₄ = 12 Hz, C₃–H), 1.87 (s, 3, C₈–CH₃), 1.80 (s, 3, C₉–CH₃), 0.88 (t, 3, w-CH₃); mass spectrum (70 eV) m/e 312 (M⁺), 297, 257, 244, 231, and 193. The transformation of 2 to 5 involves an intramolecular trans diaxial cleavage of the α-epoxide at its less hindered site which fixes the stereochemistry of the fused furan ring at C₂ and C₃ as cis and the configuration of the C₁-hydroxyl group as α (axial). In view of this we wish to revise the reported stereochemistry of cannabielsoin at C₁ so as to conform to structure 5.

In epoxide 3 generation of the phenolate anion resulted in...
cleavage of the oxirane at the more hindered site to form dihydrobenzopyran 6; mp 146–147°C; [a]D -166° (c 0.97, EtOH); δ (CDCl₃) 6.37 (br, 1, vinylic), 6.20, 6.08 (AB, 2, J = 2 Hz, aromatics), 4.90 (br, 1, OH), 3.65 (s, 2, CH₂OH, 3 Hz band width at half-height), 3.23 (m, 1, Cβ-H), 2.05 (br, 1, OH), 1.67 (br, 3, CH₃, vinylic), 1.00 (s, 3, Cβ-CH₃), 0.90 (t, 3, ω-CH₃); mass spectrum (70 eV) m/e 330 (M⁺), 299 ([M - CH₂OH]+, base peak), 231 and 193.

Acetylation of 6 resulted in the facile formation of a diacetate (9) δ (CDCl₃) 4.68, 3.60 (AB, 2, J = 2 Hz, aromatics), 5.95 (br, 1, vinylic), 4.15 (s, 2, CH₂-OAc, 3 Hz band width at half-height), 3.03 (m, 1, Cβ-H), 2.20 (s, 3, acetate), 2.03 (s, 3, acetate), 1.66 (br, 3, Cβ-CH₃, vinylic), 1.06 (s, 3, Cβ-CH₃), 0.88 (t, 3, ω-methyl); mass spectrum (70 eV) m/e 414 (M⁺), 371, 355, 295, and 231), which caused the expected downfield shift of the methylene adjacent to the asymmetric Cβ. Although this methylene appears as a singlet, the nonequivalence of its protons can be demonstrated using benzene-d₆ as solvent: δ (CDCl₃) 4.17, 4.32 (AB, 2, J = 12 Hz). The assignment of the β-configuration to the Cβ-hydroxymethyl substituent in 6 is based on the presence of a methyl signal at δ 1.00 and the absence of the lower field signal (δ 1.35–1.41) exhibited by the Cβ-methyl group in various THC derivatives. Since no β-methyl isomers were isolated, the precursor epoxide 3 probably consisted of a single isomer indicating stereoselectivity during epoxidation of the 8,9-double bond. This selectivity would be expected in the formation of diepoxide 4.

When 4 was treated with aqueous NaOH in MeOH the compound isolated in 60% yield showed: δ (CDCl₃) 6.22 (2, s, 2, aromatics), 4.34 (d, 1, J = 9 Hz, Cβ-H), 4.04, 3.38 (AB, 2, J = 13 Hz, CH₂-O), 3.3 (m, 1, Cα-H), 2.17 (br, 2, 2, OH), 1.30 (s, 3, CH₃), 1.22 (s, 3, CH₃), 0.88 (t, 3, ω-CH₃); mass spectrum (70 eV) m/e 346 (M⁺), 290, 285, 218, and 214. The same material (by glc) could be obtained from 7 via epoxidation and alkaline hydrolysis. Although two exchangeable protons are apparent in the nmr, silylation would not be expected in the formation of diepoxide 4.

The selectivity of these cyclizations indicates that in the intramolecular base-induced cleavage of epoxides ring size is more important than substitution. While both ring size and steric factors favor furan ring formation in 5, ring size prevails in the cyclization of 3, in spite of an adverse substitution pattern, to give a pyran (6) rather than an oxepin. Formation of the oxepin ring in 10 probably occurs only after initial closure to the furan ring. Furan formation places severe steric constraints on the subsequent cyclization, thus effectively eliminating the possibility of pyran formation. These findings, together with the observation that both compounds 11 and 12 give dihydrobenzofurans under basic conditions, suggest that the entropy of ring formation is the major factor in determining the product of an intramolecular epoxide cleavage.12

(--)-8a-Hydroxymethyl-Δ¹-THC (6) exhibited THC-like overt CNS symptomatology in rodents at 1 mg/kg iv (equivalent to that of Δ¹-THC) and is of interest as a possible metabolite of Δ¹-THC. Cannabielsoin (5) and the tetra cyclic ether (10) showed no CNS activity up to 10 mg/kg iv.

Acknowledgment. This work was carried out with the support of NIDA (Grant No. DA-00574-01). We are grateful to Professors John C. Sheehan, Robert E. Lyle, and Sukh Dev for helpful discussions.

References and Notes


7. Trans diastil cleavage of the β-epoxide would not be possible.

8. After submission of this article details of earlier work24 by Shani and Mechoulam appeared (A. Shani and R. Mechoulam, Tetrahedron, 30, 4257 (1974)). The findings of these authors are in agreement with structure 5.


11. Stereospecificity has been observed3 in the epoxidation of the related (4S)-[2-propenyl]-1-cyclohexene-1-carboxylic acid methyl ester to the extent of a 3:2 ratio of (2R):(2S)-epoxypropyl compounds.