

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 acetoxy) group in III, V, and VI is  $\alpha$  on the basis of the splitting pattern of the axial (or pseudoaxial) C-6 proton which appears as a quartet, with large  $J_{\alpha,\beta}$  and medium  $J_{\beta,\beta}$  values. Dreiding models show that the axial C-6 proton forms dihedral angles of  $\sim 170$ – $180^\circ$  and  $\sim 50$ – $60^\circ$  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  $\sim 50$ – $70^\circ$ ).<sup>5</sup> As osmium tetroxide leads to *cis*-glycols the C-1 hydroxyl group in IIIa is also  $\alpha$ .

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

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

**Acknowledgment.** The work in both Jerusalem and Shrewsbury was supported by grants (MH-13180 and MH-16051) of the National Institute of Mental Health, to whom we are grateful. We thank Professor H. Ederly and Dr. Y. Grunfeld of the Institute for Biological Research, Nes Ziona, Israel, for the monkey tests, and Miss Ilana Ramati for her skillful technical help.

(5) Chemical evidence supporting the  $\alpha$  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. Ederly, *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 solely on pharmacological data, Grunfeld and Ederly have previously suggested that metabolites of the tetrahydrocannabinols may be active (see ref 6).

Z. Ben-Zvi, R. Mechoulam

Laboratory of Natural Products  
Hebrew University School of Pharmacy, Jerusalem, Israel

Sumner Burstein

Worcester Foundation for Experimental Biology  
Shrewsbury, Massachusetts 01545

Received March 10, 1970

## Slow Solvolysis of 4-Tricycyl 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 cyclopropylcarbonyl derivatives<sup>1</sup> and in the rapid reaction of cyclopropanes with electrophiles.<sup>2</sup> 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 cyclopropylcarbonyl cases, favorable and unfavorable geometries for interaction of charged centers with an edge of the ring have been investigated by employing nmr techniques<sup>3</sup> and rate studies on appropriately substituted or relatively rigid systems.<sup>4</sup> 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.<sup>5</sup> Recent theoretical work supports this point of view.<sup>6</sup>

We now wish to report some theoretical and experimental results concerning the energy of a 4-tricycyl 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-Hydroxytricycylene (2) was prepared from 4-tricyclicenecarboxylic acid (1)<sup>7</sup> by the route outlined in Scheme I, and converted to the *p*-bromobenzene-sulfonate (brosylate) derivative (3) using standard methods. Although 1-apocamphyl brosylate (9, prepared from 1-apocamphanol<sup>8a</sup> (8)) underwent solvolysis in 70% (by weight) aqueous dioxane buffered with triethylamine at 200° ( $k_{200} = (4.44 \pm 0.19) \times 10^{-5} \text{ sec}^{-1}$ ), 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).

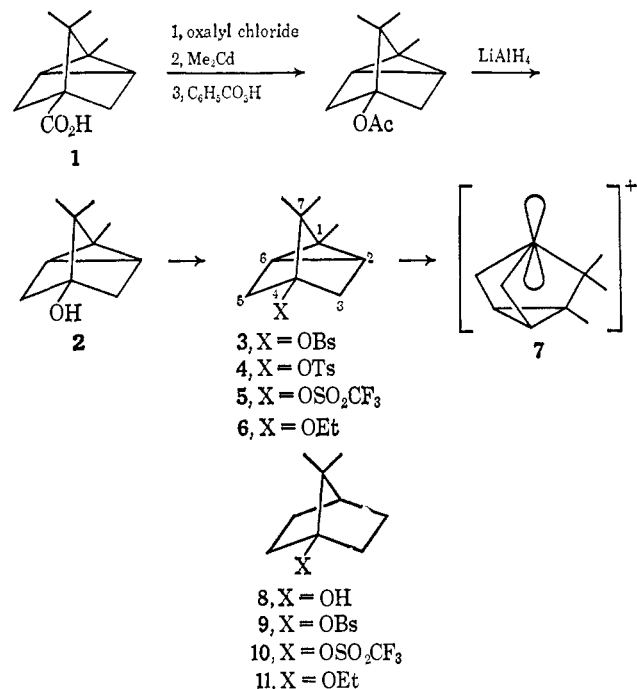
Table I. Calculated and Experimental<sup>a</sup> Data for the Bridgehead Ionization of Some Bi- and Tricyclic Substrates

Substrate	<i>T</i> , °C	10 <sup>6</sup> <i>k</i> , sec <sup>-1</sup>	<i>k</i> <sub>rel</sub> , 25°	Product ratio <sup>j</sup> (ROH:ROEt)	Calcd <sup>c</sup> Δ <i>H</i> , kcal/mol	Calcd <sup>d</sup> <i>k</i> <sub>rel</sub>
4-Nortricyclyl					30.44	
4-Tricyclyl	246.0 ± 0.1	14.6 ± 0.2				
	232.8 ± 0.1	7.35 ± 0.18	(1.0) <sup>b,e</sup>	72:28	31.26	1.0
	221.1 ± 0.1	3.74 ± 0.05				
1-Apocamphyl	108.5 ± 0.1	46.5 ± 2.0				
	99.0 ± 0.1	17.8 ± 0.1	(2.84 × 10 <sup>4</sup> ) <sup>b,h</sup>	63:37	25.39 <sup>e</sup>	1.34 × 10 <sup>3</sup>
	89.0 ± 0.1	6.02 ± 0.06				
1-Methyl-4-tricyclo-[2.2.2]octyl	50.4 ± 0.1	52.8 ± 0.7				
	41.0 ± 0.1	14.8 ± 0.3	(5.45 × 10 <sup>7</sup> ) <sup>b,i</sup>	69:31	19.07	3.12 × 10 <sup>6</sup>
	31.3 ± 0.1	4.16 ± 0.07				
1-Bicyclo-[2.2.2]octyl			(3.11 × 10 <sup>9</sup> ) <sup>j</sup>		12.93	5.8 × 10 <sup>9</sup>

<sup>a</sup> Measured rates refer to trifluoromethanesulfonates (0.02 *M*) in 60% (by weight) aqueous ethanol containing 0.06 *M* triethylamine buffer. <sup>b</sup> Extrapolated from higher temperatures. <sup>c</sup> Strain energy difference between the hydrocarbon and carbonium ion, calculated by the method of ref 12. <sup>d</sup> Calculated using an energy vs. log relative rate plot similar to Figure 2 in ref 12. <sup>e</sup> Value calculated for norbornyl (ref 12) plus 1 kcal/mol to approximate effect due to two methyls. The close similarity in energies for tricyclyl and nortricyclyl indicates that methyl substitution has only a small effect on the rates. <sup>f</sup> Estimated; see footnote 13. <sup>g</sup> Δ*H*<sup>‡</sup> = 26.8 ± 1.1 kcal/mol; Δ*S*<sup>‡</sup> = -25.4 ± 2.1 eu. <sup>h</sup> Δ*H*<sup>‡</sup> = 28.9 ± 0.3 kcal/mol; Δ*S*<sup>‡</sup> = 1.62 ± 0.98 eu. <sup>i</sup> Δ*H*<sup>‡</sup> = 25.4 ± 0.9 kcal/mol; Δ*S*<sup>‡</sup> = +4.8 ± 2.8 eu. All rate constants and activation parameters were determined by least-mean-squares analysis of the data employing a program written for the IBM 360/50 computer. <sup>j</sup> The products of each solvolysis were isolated by preparative vpc. The vpc retention times and infrared spectra of the purified alcohols were compared with those from which the triflates were made. The ethyl ethers were compared in the same way with independently synthesized samples made by treating **8** with triethyloxonium tetrafluoroborate in methylene chloride, and by alkylating the lithium alkoxides of **2** and **12** with ethyl iodide in DMSO. In all cases products were found to be formed without rearrangement.

the corresponding trifluoromethanesulfonate (triflate) derivatives (**5** and **10**). The triflate leaving group has in a number of cases<sup>9</sup> been shown to be on the av-

## Scheme I

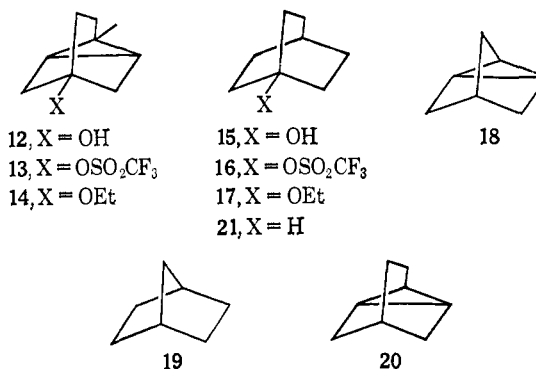


erage 10<sup>4.8</sup> times as reactive as *p*-toluenesulfonate (tosylate). The triflates **5** and **10** were prepared by reaction of alcohols **2** and **8** with trifluoromethanesulfonic anhydride;<sup>10</sup> good first-order rate and Ar-

(9) (a) R. L. Hansen, *J. Org. Chem.*, **30**, 4322 (1965); (b) A. Streitwieser, Jr., C. C. Wilkins, and E. Kiehlmann, *J. Amer. Chem. Soc.*, **90**, 1598 (1968); (c) P. J. Stang and R. Summerville, *ibid.*, **91**, 4600 (1969); (d) T. M. Su, W. F. Sliwinski, and P. von R. Schleyer, *ibid.*, **91**, 5386 (1969).

(10) T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.*, 4069 (1957). We are indebted to Dr. R. L. Hansen of the Minnesota Mining and Manufacturing Co. for a gift of trifluoromethanesulfonic acid.

renius data<sup>11</sup> were obtained for both derivatives (Table I). Though apocamphyl triflate (**10**) solvolyzed in the neighborhood of 100°, temperatures near 250° were necessary to cause **5** to react at the same rate. Extrapolating the data to an intermediate temperature (160°), the rate difference between **5** and **10** is 7.39 × 10<sup>4</sup>. At 25°, it extrapolates to 2.84 × 10<sup>4</sup>. Employing the tosylate factor of **10**<sup>4,8</sup>, we can estimate that at 25° 4-tricyclyl tosylate must undergo solvolysis with a rate constant of 4.77 × 10<sup>-18</sup> sec<sup>-1</sup> (half-life = 4.6 × 10<sup>9</sup> years), in 60% aqueous ethanol.



Using the semiempirical approach of Gleicher and Schleyer,<sup>12</sup> we have calculated the C-4 ionization strain energies for tricyclene, nortricyclene (**18**), and norbornane (**19**), and used these values to predict solvolysis rates (Table I). The predicted rates are in quite good agreement with our observations. The calculations indicate that the deceleration of **5** results mainly

(11) Kinetics had to be carried out in buffered, aqueous ethanolic solution due to the ease of acid-catalyzed opening of the tricyclic ring in more severe solvolytic media. An ultraviolet spectrophotometric technique<sup>8b</sup> was employed to follow the rate of ionization of **9**, but for triflates **5** and **10**, the rates were followed by vpc (vs. an internal standard) since the triflates can, with some effort, be efficiently gas chromatographed.

(12) G. J. Gleicher and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 582 (1967).

from the compression in C-C-C angles at carbons 3, 5, and 7 produced on partial flattening at C-4, and from the distortion of angles at C-4 resulting from the inability of this carbon to reach full planarity.

A similar situation, though less extreme, is obtained in the bi- and tricyclooctyl<sup>13a</sup> systems. Triflate **13** is more reactive than **10**, but less reactive<sup>13b</sup> by a factor of  $10^2$  than **16**. Once again, both trends are well accounted for by calculations<sup>12</sup> based only on strain effects (Table I).

It is clear from our observations that the proximity of the face of a three-membered ring provides little or no stabilization for a developing positive charge. We infer from this that the approach of an electrophile to the edge of a cyclopropane ring must be a great deal more favorable than approach to the face.

Consideration of the Walsh model<sup>14</sup> of cyclopropane offers an explanation for this edge-face reactivity difference. When interacting with the face, the empty orbital of an electrophile must mix with the three  $sp^2$  orbitals pointed toward the center of the ring. Interaction with an edge occurs between the empty orbital and cyclopropane electrons in more pure p-like orbitals. Even though the electron density in the center of the ring is probably relatively high,<sup>14</sup> the lower energy of  $sp^2$  orbitals (ionization potential  $\cong 14.7$  eV<sup>15</sup>) will make them much more reluctant than p orbitals (ionization potential  $\cong 11.4$  eV<sup>15b</sup>) to transfer electron density to the incoming electrophile.<sup>16</sup>

**Acknowledgments.** We are grateful to the National Institutes of Health (Grant No. GM16231-01) for partial support of this work, to Professor S. Julia for a sample of alcohol **12**, to Drs. W. C. Ripka and J. C. Kauer for samples of 1,4-dichloro- and 1,4-dibromobicyclo[2.2.2]octanes, and to Professor P. von R. Schleyer for informing us of related work being carried out in his laboratory.

(13) (a) S. Julia and G. Guerey, *Bull. Soc. Chim. Fr.*, 3002 (1965). (b) The rate for **16** was estimated by determining an approximate triflate-bromide rate ratio from the solvolysis rates of 1-norbornyl bromide<sup>13c</sup> and 1-apocamphyl triflate (**10**), and then applying this factor to the known<sup>13c</sup> solvolysis rate of 1-bicyclo[2.2.2]octyl bromide. Corrections for differing  $\gamma$  values were made when necessary. (c) M. Finkelstein, Ph.D. Dissertation, Yale University, New Haven, Conn., 1955.

(14) Cf. A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949).

(15) (a) Approximated as one-third of the sum of the ionization potentials<sup>15b</sup> of a carbon 2s orbital and two carbon 2p orbitals; (b) R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963).

(16) We are carrying out EHT and CNDO-II calculations on the 1-nortricyclyl cation which will be described in a full paper. Preliminary results, however, of the EHT calculations indicate that very little charge is transferred to the cyclopropane ring carbons of the cation, in accord with our experimental results.

(17) (a) National Science Foundation Predoctoral Fellow, 1967-present; (b) Fellow of the Alfred P. Sloan Foundation, 1970-1972; (c) Fellow of the Alfred P. Sloan Foundation, 1969-1971.

Shelby A. Sherrod,<sup>17a</sup> Robert G. Bergman<sup>17b</sup>

Contribution No. 4010, Gates and Crellin  
Laboratories of Chemistry  
Pasadena, California 91109

Gerald Jay Gleicher<sup>17c</sup>

Department of Chemistry, Oregon State University  
Corvallis, Oregon 97331

David G. Morris

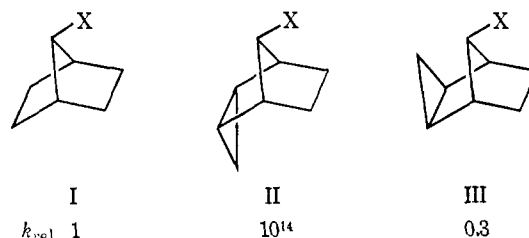
Chemistry Department, University of Glasgow  
Glasgow, Scotland

Received January 29, 1970

## Solvolytic Reactivity of 4-Nortricyclyl Triflate. A Carbonium Ion Analog of a Face-Protonated Cyclopropane

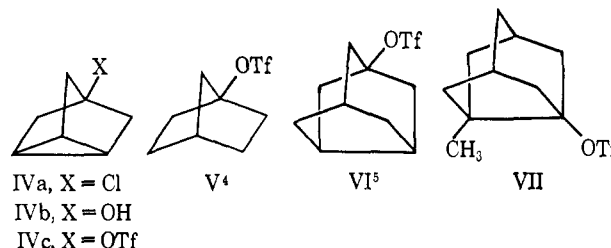
Sir:

In favorable cases, participation by a neighboring cyclopropane ring can rival that by a double bond.<sup>1</sup> The orientation is very important. Thus, II, in which edge participation is possible, shows a remarkable rate enhancement over I, which enhancement is completely absent in III.<sup>1a,c</sup>



These observations are qualitatively consistent with theoretical calculations on protonated cyclopropane<sup>2</sup> and protonated nortricyclene.<sup>3</sup> Considerably greater proton binding energy is found for the edge-protonated form than for the corresponding face-protonated isomer. Significant stabilization is nevertheless indicated for face protonation.

In an attempt to obtain further information concerning the extent of participation by the face of remote cyclopropane in solvolysis reactions, we have now studied the solvolytic reactivity of 4-tricyclo[2.2.1.0<sup>2,6</sup>]-heptyl trifluoromethanesulfonate (4-nortricyclyl triflate, IVc) and compared its reactivity with that of three other bridgehead triflates, V-VII.



The 4-nortricyclyl system (IV) uniquely permits the generation of an electron-deficient center in a position fixed directly and centrally above the cyclopropane ring.<sup>6</sup> Participation by the cyclopropane ring should result in an enhanced reactivity relative to that predicted on the basis of steric effects alone.

We have employed computer-conformational analysis to quantitatively evaluate the significance of such

(1) (a) H. Tanida, T. Tsuji, and T. Iris, *J. Amer. Chem. Soc.*, **89**, 1953 (1967); M. A. Battiste, C. L. Deyrup, R. E. Pincock, and J. Haywood-Farmer, *ibid.*, **89**, 1954 (1967); (b) M. J. S. Dewar and J. M. Harris, *ibid.*, **90**, 4468 (1968), and references cited therein; Y. E. Rhodes and T. Takino, *ibid.*, **90**, 4469 (1968); (c) G. D. Sargent, R. L. Taylor, and W. H. Demisch, *Tetrahedron Lett.*, 2275 (1968); (d) R. Muneyuki, T. Yano, and H. Tanida, *J. Amer. Chem. Soc.*, **91**, 2408 (1969); (e) J. Haywood-Farmer, R. E. Pincock, and J. I. Wells, *Tetrahedron*, **22**, 2007 (1966).

(2) R. Sustmann, J. E. Williams, M. J. S. Dewar, L. C. Allen, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 5350 (1969), and references cited therein.

(3) G. Klopman, *ibid.*, **91**, 89 (1969).

(4) 1-Norbornanol: D. B. Denney and R. R. DiLeone, *ibid.*, **84**, 4737 (1962).

(5) 1-Noradamantanol: J. S. Wishnok, P. v. R. Schleyer, A. Nickon, G. Pandit, and R. Williams, to be published.

(6) The distance between the 4 position and the plane of the cyclopropane ring is found to be 2.1 Å; cf. J. F. Chiang, C. F. Wilcox, Jr., and S. H. Bauer, *Tetrahedron*, **25**, 369 (1969).