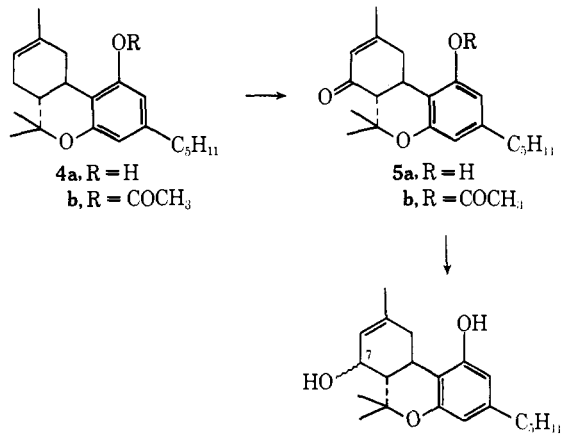

tained was chromatographed on Florisil. Δ^8-THC-7-one acetate (**5b**) was obtained in 20% yield as an oil: $[\alpha]^{EtOH}D$ −301°; δ_{max}^{EtOH} 223 mμ (ε 12,700), 281 (shoulder) (ε 2100), 285 (ε 2140); δ ($CDCl_3$) 1.16, 1.42, 1.65, 1.95 (CH_3 groups), 2.16 (acetate methyl), 3.05 (C-10α H), 5.80 (C-8 H), 6.36, 6.51 (aromatic H); ν_{CCl_4} 1680, 1780 cm^{-1}.

Anal. Found for ($C_{23}H_{30}O_4$): C, 74.05; H, 8.11.

These data are in agreement with those presented for the metabolite and support the suggested structure.

Lithium aluminum hydride reduction of 630 mg of **5b** gave a mixture from which on preparative tlc two products were obtained. One of these was shown to be (10a*R*,6a*S*,7*S*)-Δ^8-THC-7β-ol (**6a**): 116 mg; mp 117°; $[\alpha]^{EtOH}D$ −240°; λ_{max}^{EtOH} 274 (ε 1250), 286 (ε 1300); δ (CD_3COCD_3) 0.91, 1.16, 1.57, 1.71 (CH_3 groups), 3.52 (C-10α H), 4.13 (br d, J = 9 Hz, C-7 H, axial), 5.35 (s, C-8 H), 6.11, 6.27 (aromatic H); mol wt (mass spectrum) 330. *Anal.* Found for ($C_{21}H_{30}O_3$): C, 76.48; H, 9.10.

The second compound was identified as (10a*R*,6a*S*,-7*R*)-Δ^8-THC-7α-ol (**6b**): 104 mg; mp 154°; $[\alpha]^{EtOH}D$ −345°; λ_{max}^{EtOH} 274 mμ (ε 1215), 281 (ε 1260); δ (CD_3-$COCD_3$) 0.91, 1.27, 1.46, 1.70 (CH_3 groups), 3.25 (C-10α H), 4.30 (br, C-7 H, equatorial), 5.60 (d, J = 4.5 Hz, C-8 H), 6.10, 6.25 (aromatic H); mol wt (mass spectrum) 330. *Anal.* Found for ($C_{21}H_{30}O_3$): C, 75.72; H, 8.75.

The above assignments of stereochemistry at C-7 in **6a** and **6b** are based on the differences of chemical shifts and splitting patterns of the C-7 and C-8 protons.[10]

The psychopharmacological activity of the above synthetic metabolites (or their acetates[11]) was assessed by the behavior and somatic changes elicited in adult rhesus monkeys when administered by intravenous injection as described previously.[12,13] The epoxy acetate **3b** showed no activity at 0.1 mg/kg; however, at 0.5 mg/kg it caused stupor, ataxia, suppression of motor activity, full ptosis, and a typical crouched posture kept for up to 3 hr. The second Δ^9-THC metabolite, Δ^9-THC-8-one acetate (**2b**), showed no activity up to 5 mg/kg. The three Δ^8-THC metabolites showed activity in the above test, though at different dose levels. Δ^8-THC-7-one acetate (**5b**) at 0.5 mg/kg and Δ^8-THC-7α-ol (**6b**), mp 154°, at 0.25 mg/kg caused significant tranquility; **5b** at 1 mg/kg and **6b** at 0.5–1 mg/kg caused the same symptoms as described above for the epoxy acetate (**3b**) (at 0.5 mg/kg). The 7β-hydroxy isomer **6a** (mp 117°) was six–eight times less active than the 7α-hydroxy isomer **6b**: at 1 mg/kg it caused no observable changes in the monkey; at 2 mg/kg it caused drowsiness, decreased motor activity, occasional partial ptosis, and an occasional head drop.

The plethora of metabolites[14] of Δ^9- and Δ^8-THC isolated from *in vivo* or *in vitro* studies with different animal species or animal organ homogenates makes it imperative to determine the *human* metabolic pathways *in vivo* before any conclusions as regards the molecular basis of marijuana activity in humans can be made. However, the fact that many of the THC metabolites so far isolated are active in psychobiological tests in animals (including monkeys)[14d,e,h] and in humans[14b] supports the tentative suggestions[4,13,15] that the effects of Cannabis are caused (in part at least) by metabolites.

Acknowledgment. The research in Jerusalem was supported by a grant (MH-13180) from NIMH.

(10) *Cf.* S. H. Burstein and H. J. Ringold, *J. Amer. Chem. Soc.*, **86**, 4952 (1964); S. H. Burstein and H. J. Ringold, *ibid.*, **89**, 4722 (1967).

(11) The acetates of active cannabinoids show the same activity as the parent cannabinoid but the onset of activity may be delayed.[12]

(12) H. Edery, Y. Grunfeld, Z. Ben-Zvi, and R. Mechoulam, *Ann. N. Y. Acad. Sci.*, **191**, 40 (1971).

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

(14) (a) Review: S. H. Burstein in "Marihuana. Chemistry, Metabolism, Pharmacology and Clinical Effects," R. Mechoulam, Ed., Academic Press, New York, N. Y., in press; (b) L. Lemberger, R. E. Crabtree, and H. M. Rowe, *Science*, **177**, 62 (1972); (c) S. H. Burstein, J. Rosenfeld, and T. Wittstruck *ibid.*, **176**, 422 (1972); (d) Z. Ben-Zvi, R. Mechoulam, H. Edery, and G. Porath, *ibid.*, **174**, 951 (1971); (e) M. E. Wall, *Ann. N. Y. Acad. Sci.*, **191**, 23 (1971); (f) K. Nakazawa and E. Costa, *Nature (London)*, **234**, 48 (1971); (g) J. L. G. Nilsson, S. Agurell, B. Akermark, and I. Lagerlund, *Acta Chem. Scand.*, **25**, 768 (1971); (h) Z. Ben-Zvi, R. Mechoulam, and S. Burstein, *J. Amer. Chem. Soc.*, **92**, 3468 (1970).

(15) L. Lemberger, J. L. Weiss, A. M. Watanabe, I. M. Galanter, R. J. Wyatt, and P. V. Cardon, *N. Engl. J. Med.*, **286**, 685 (1972).

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Evidence Against the Involvement of 0,0-Diradical Intermediates in the Pyrolysis of Five-Membered Ring Azo Compounds

Sir:

We wish to report a study which provides strong evidence against the intervention of "π-cyclopropanes" (or "0,0 diradicals") in the thermal decomposition of five-membered ring azo compounds.[1,2]

exo-4-Methyl-2,3-diazabicyclo[3.2.0]hept-2-ene (**1e**) and its endo isomer (**1n**) were prepared[3] by the addition

(1) R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 1475 (1968).

(2) (a) R. J. Crawford and A. Mishra, *ibid.*, **88**, 3963 (1966); (b) A. Mishra and R. J. Crawford, *Can. J. Chem.*, 47, 1515 (1969).

(3) Stereochemistries of **1e** and **1n** were assigned (as in related systems, see ref 8 and references therein) by proton nmr coupling constants. Compound **1e**, the major isomer, displayed a 1.5-Hz coupling between protons on carbons 4 and 5, indicating a trans relationship, while the coupling for **1n** was 7.0 Hz, indicating a cis eclipsed configuration.

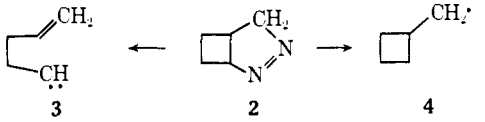
Table I. Products Formed on Gas-Phase Thermal Decomposition[a] of *exo*- and *endo*-4-Methyl-2,3-diazabicyclo[3.2.0]hept-2-enes(**1e** and **1n**)

Substrate	Temp, °C	Products, %[b] 9t	9c	10t	10c	5e	5n	14[c]	15[d]	16[e]	Unident[f]	Ratio 5e/5n
1n	256	0	12.4	0	0.8	54.5	31.7	0.4	0.2	0	5.0	1.7
	313	0	12.7	0.1	1.1	53.5	26.8	3.5	1.8	0.5	0.5	2.0
	352	0	12.6	0.1	1.3	52.0	26.1	3.7	1.9	2.3	0.6	2.0
	395	0	12.2	0.1	1.5	45.1	24.1	4.5	2.6	9.9	0.7	1.9
	438	0	12.4	0.1	1.6	30.6	14.1	5.6	4.2	31.4	1.5	2.2
1e	233	57.0	0	2.4	0.1	8.0	31.9	0.5	0.2	0	4.0	0.25
	250	56.5	0	2.9	0.1	8.2	31.3	0.4	0.6	0	1.5	0.3
	302	52.5	0	4.0	0.3	20.2	19.1	2.4	1.3	0.2	0.4	1.0
	354	46.1	0	4.1	0.3	24.3	19.1	3.1	1.8	1.1	0.4	1.3
	400	45.4	0	4.2	0.4	24.1	16.4	3.7	2.0	3.8	0.4	1.5
	460	41.2	0	4.2	0.4	20.8	10.1	4.4	2.3	16.6	1.4	2.1

[a] Decomposition effected by flow pyrolysis of a mixture of toluene and substrate on the injection port of a gas chromatograph. Control experiments in conventional reactors (empty and packed) demonstrated the independence of product distribution and surface/volume ratio. [b] Determined by digital integration of at least two gc pyrolysis runs (separate columns). Reproducibility good to ±0.2%. A zero entry indicates ≤0.1%. Percentages are normalized to 100% not including unidentified products. For structures of products, see Scheme II; in the cases of **9** and **10**, the suffix **c** refers to the stereoisomer having the alkyl groups on the disubstitued double bond in a cis relationship and the suffix **t** indicates the corresponding trans isomer. [c] 2-Ethylbutadiene. [d] Ethylidenecyclobutane. [e] 1-Methylcyclopentene. [f] Unidentified materials (mostly low molecular weight) reported as per cent of total identified products.

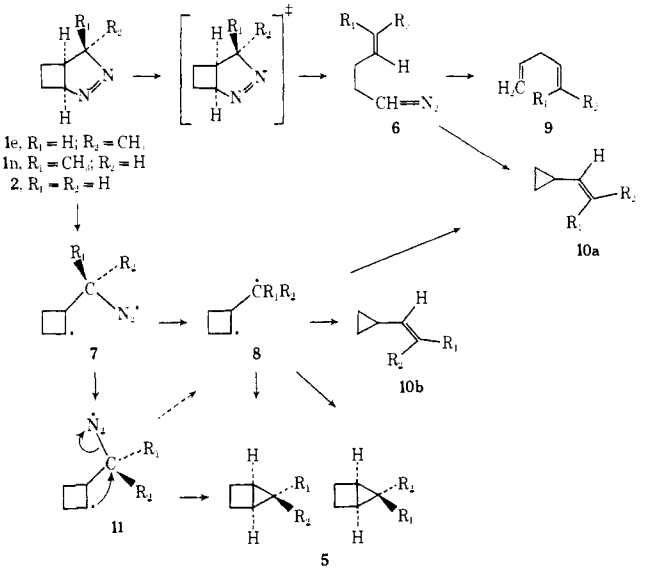
of diazoethane to cyclobutene. The azo compounds were obtained >99% pure by preparative gas–liquid chromatography on glass columns (3/8 in. × 10 ft UCW98 on Chromosorb P operated at 100°). Thermal decomposition of **1e** and **1n** is exceedingly complex, each compound leading to different amounts of nine products on pyrolysis. We recently reported[4] that in the case of the parent molecule **2** and its 6,7-dimethyl analog, the complexity of the product distribution is due to two parallel pathways for decomposition: the first leading to 1,4-dienes and olefinic cyclopropanes *via* carbene **3**, and the second leading to bicyclopentanes and cyclobutyl products *via* the expected diradical **4** (Scheme I). We were not able to determine in the previous study[4] whether **3** arose directly from **2** *via* retro-1,3-dipolar reaction or was formed by ring cleavage in **4**.

Scheme I



The products formed on thermal decomposition of **1e** and **1n** again reflect the operation of the carbene and diradical mechanisms, but provide important stereochemical information about each pathway. The product distributions at a number of temperatures in the range 233–460° are recorded in Table I. The substituted diene product **9** (*cf.* Scheme II) formed from the carbene pathway completely retains the stereochemistry of the starting azo compound (Table I). This suggests that the carbene is formed from **1** *via* retro-1,3-dipolar addition, rather than by ring cleavage in diradical **8** (Scheme II), which might have been expected to produce more stereochemical randomization in the diene. The substituted vinylcyclopropane product **10**, however, is formed with some randomization of stereochemistry, although the products are stable to the reaction conditions. A portion of this product therefore apparently arises from the diradical route, perhaps *via* ring contraction in **8**. At the higher temperatures, stereoequilibration of the 5-methylbicyclopentanes[5,6] **5e** and **5n** obscures the kinetic ratio of these products. The product bicyclopentanes were isolated and pyrolyzed separately. Both equilibrated to a 2.5:1

Scheme II



(4) (a) D. H. White, P. B. Condit, and R. G. Bergman, *J. Amer. Chem. Soc.*, **94**, 1348 (1972); (b) R. A. Keppel and R. G. Bergman, *ibid.*, 94, 1350 (1972).

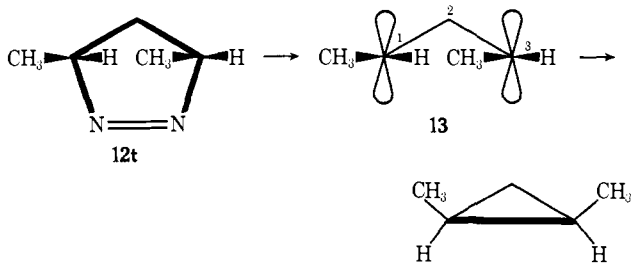
(5) For the thermal isomerization of a related system, see J. P. Chesick, *ibid.*, **84**, 3250 (1962).

(6) (a) Stereochemistries of the 5-methylbicyclopentanes were assigned by noise-decoupled ^{13}C magnetic resonance spectroscopy. Compound **5e** absorbed at 23.0 and 15.2 ppm downfield from TMS in an approximate ratio of 5:1. The latter peak was assigned to methyl since it formed a quartet when analyzed by off-resonance decoupling. The methyl carbon in **5n** showed an upfield shift of 9.2 ppm compared to **5e**, and the other absorptions were shifted 5–8 ppm upfield, which is an even greater steric compression shift than that observed for methyl and its strained neighbors in *endo*-2-methylnorbornane[6b] and other compounds.[6c] In addition, the compound assigned structure **5n** reacted with *N*-phenyltriazolinedione to give a single adduct formed by addition of the triazolinedione across the strained central bond of the bicyclopentane. Examination of the lanthanide-shifted proton nmr spectrum of this adduct demonstrated that the methyl group at C-7 was oriented syn to the nitrogen atoms, as expected.[7a] (b) J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 7107 (1970); (c) M. Cristl, H. J. Reich, and J. D. Roberts, *ibid.*, **93**, 3463 (1971), and references therein.

(7) (a) W. R. Roth and M. Martin, *Tetrahedron Lett.*, 4695 (1967). (b) We use the term "single inversion" to indicate inversion of stereochemistry at one of the C–N carbons in the decomposition reaction; "double inversion" indicates inversion of stereochemistry at both C–N carbons.

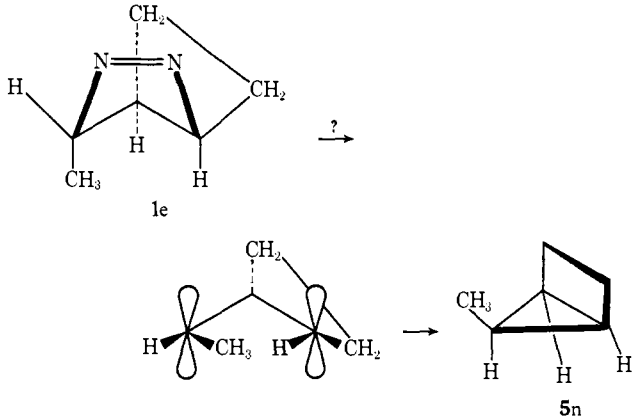
mixture and began converting to 1-methylcyclopentene above 400° but were equilibrated less than 1% at 250°. Thus the **5e**/**5n** ratios observed at low temperatures (less than 5% conversion of pyrazolines to products) are true kinetic ratios and the stereochemistry is *predominantly singly inverted*.[7b]

The ratio of **5e** to **5n** is similar to those obtained from *cis*- and *trans*-3,5-dimethylpyrazolines[2] (**12c** and **12t**) and *endo*- and *exo*-4-methyl-2,3-diazabicyclo[3.3.0]oct-2-enes.[8] The predominant single inversion of stereochemistry observed in the decomposition of **12c** and **12t**



12t **13**

was accounted for[2] by postulating the intermediacy of a π-cyclopropane or 0,0 diradical intermediate (*e.g.*, **13**) which has been predicted on the basis of approximate molecular orbital calculations to undergo ring closure in a conrotatory sense.[1] However, if **13** is responsible for the single-inversion product formed from **12**, its formation must require an energy only slightly lower than that of some other, less stereoselective process because some double retention and double inversion products are also formed.[2b] Raising the energy of **13**—for example, by connecting C_2 and C_3 with a short carbon chain—should allow this secondary process to become predominant. As can be seen from the data reported here, however, connecting C_2 and C_3 by *even a two-carbon bridge* (which inspection of model shows should severely strain the 0,0 intermediate) produces essentially no change in the propensity of these pyrazolines to undergo decomposition with inversion of configuration.



1e **5n**

The complete absence of any strain effect on the stereochemistry of pyrazoline decomposition makes it seem very unlikely that the single inverting part of this stereochemistry is controlled by conrotation of a 0,0 intermediate. We once again suggest that Roth's hypothesis,[9] involving sequential C–N cleavage and backside displacement of N_2 in a nitrogen-containing intermediate (**11**, Scheme II), is a viable alternative.[10] Besides accounting well for our observations, this hypothesis is also consistent with recent kinetic data on the decomposition of acyclic azo compounds,[11] with *ab initio* calculations[12] which question on theoretical grounds the existence of a predominantly conrotating trimethylene diradical intermediate, and with earlier experimental work which suggested that 0,0 diradicals were probably not involved in the isomerization of 1,2-dialkylcyclopropanes.[13]

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(8) (a) P. B. Condit and R. G. Bergman, *Chem. Commun.*, 4 (1971); (b) see also M. P. Schneider and R. J. Crawford, *Can. J. Chem.*, **48**, 628 (1970).

(9) (a) W. R. Roth and M. Martin, *Justus Liebigs Ann. Chem.*, **702**, 1 (1967); see also (b) E. L. Allred and R. L. Smith, *J. Amer. Chem. Soc.*, **89**, 7133 (1967); (c) the Roth hypothesis[7a,9a] also provides a reasonable alternative to the so-called "recoil" mechanism,[9b] which has recently been questioned on theoretical grounds; *cf.* F. S. Collins, J. K. George, and C. Trindle, *ibid.*, **94**, 3732 (1972).

(10) (a) We believe that R_1R_2C–N cleavage in **1** is concurrent with or followed closely by C_4–C_5 cleavage, leading only to **6**. This mode therefore leads to no methylbicyclopentanes and does not complicate the stereochemistry of formation of these products. However, our mechanism requires that cleavage of the R_1R_2C–N bond be at least competitive with cleavage of the cyclobutyl C–N bond in **1e** and **1n**. Whether this is consistent with observations in acyclic systems is difficult to determine. For example, 1,1′-dicyanoazocyclobutane decomposes in solution 36 times slower than does the corresponding strain-free dicyclohexyl compound.[10b] Because cyano-substituted systems probably decompose by a concerted mechanism in which both C–N bonds break simultaneously,[10c] the six/four ring size effect to be expected in one-bond cleavage would be $(36)^{1/2}$ or 6. However, this rate difference is totally entropy controlled; the activation energy for the four-ring compound is actually *lower* than that for the six.[10b] These considerations, combined with the demonstrably profound effect of chain branching on the rate of azo compound decompositions,[10d] make it seem quite reasonable that both C–N cleavage reactions illustrated in Scheme II take place at similar rates. (b) C. G. Overberger, H. Biletch, A. B. Finestone, J. Lilker, and J. Herbert, *J. Amer. Chem. Soc.*, **75**, 2078 (1953); (c) S. Seltzer and S. G. Mylonakis, *ibid.*, **89**, 6584 (1967), and earlier papers; (d) C. G. Overberger, W. F. Hale, M. B. Berenbaum, and A. B. Finestone, *ibid.*, **76**, 6185 (1954).

(11) K. Takagi and R. J. Crawford, *ibid.*, **93**, 5910 (1971).

(12) (a) K. Q. Siu, W. M. St. John, and E. F. Hayes, *ibid.*, **92**, 7249 (1970); (b) J. A. Horsley, Y. Hean, C. Moser, L. Salem, R. M. Stevens, and J. S. Wright, *ibid.*, **94**, 282 (1972); (c) P. J. Hay, W. J. Hunt, and W. A. Goddard, *ibid.*, **94**, 638 (1972).

(13) (a) W. L. Carter and R. G. Bergman, *J. Amer. Chem. Soc.*, **90**, 7344 (1968); R. G. Berman and W. L. Carter, *ibid.*, **91**, 7411 (1969).

(14) National Science Foundation Predoctoral Fellow, 1967–1971.

(15) Alfred P. Sloan Foundation Fellow, 1970–1972; Camille and Henry Dreyfus Foundation Teacher-Scholar Grant Awardee, 1970–1975.

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The Readily Reversible Nucleophilic Reaction of Imidazole with β-(2-Hydroxy-3,5-dinitrophenyl)ethanesulfonic Acid Sultone

Sir:

The study of the hydrolytic reactivity of aromatic five-membered cyclic sulfonates has yielded important information concerning not only the influence of ring structure on reactivity, but also the mechanism of action of serine proteases.[1] The sulfonylation of the

(1) E. T. Kaiser, *Accounts Chem. Res.*, 3, 145 (1970).