be the favored pathway. The stereochemistry of the high energy pathway can be explained by either a boat or plane transition state but these have yet to be distinguished except by inference in the 1,2-dialkenylcyclobutane[11a] and cyclopropane[11b] systems and by the present study.

The 3,3-rearrangement of I can only occur *via* a boat-like transition state, all others being impossibly strained, yet its activation free energy is only 6 kcal/mol higher (46.7 *vs.* 40.8 kcal/mol) than that for reaction of 1,5-hexadiene *via* the chair transition state and virtually the same as that for the higher energy process which can either be boat or plane.[1b] This, therefore, reveals the accessibility of the boat transition state in the high energy process. On closer inspection, however, it is interesting that the rearrangement of I does not have still a higher activation free energy than the acyclic boat process since more angle strain must be built into the transition state for the reaction of I. It is surprising that the entropy of activation of I is almost the same as that of the acyclic chair process (−13.8 eu) since the former freezes no C–C bond rotations (only rocking motions) at the transition state, while the latter must freeze three rotations. It is further surprising that the activation entropy of the high energy acyclic[1b] process is only slightly negative (−3 ± 3.6 eu) since it too must freeze three C–C bond rotations.

A final, important, aspect of the rearrangement of I is the resemblance of the transition state to [2.2.2]propellane—a speculation given viability by Goldstein's observation of similar heats of formation for the transition states involved in the high temperature (boat) acyclic rearrangement and in the inversion and cleavage of bicyclo[2.2.0]hexane.[1b] To determine if [2.2.2]propellane was accessible in the rearrangement some thermochemical estimates were made. The heat of formation of I was calculated[12] to be +14.1 kcal/mol at room temperature giving +53 kcal/mol for the ΔH_f of the transition state of the reaction of I. The heat of formation for bicyclooctane-1,4-diyl can be estimated to be +52 kcal/mol by removing (algebraically) the two bridgehead hydrogens from bicyclo[2.2.2]octane (ΔH_f = −24.09 kcal/mol)[13] and assuming that these are ordinary tertiary C–H bonds (BDE = 91 kcal/mol) and ignoring changes in heat capacity with temperature. Thus it would appear possible that the propellane, IV, is accessible provided that it is more stable than the 1,4-diyl.

MO calculations by Hoffmann[14] and Newton[15] indicate that the diyl is stabilized in its antisymmetric form, III, by through bond coupling and further that the bona fide propellane, IV, is higher in energy than III and is separated from the antisymmetric diyl by a substantially higher energy barrier. Hoffmann has pointed to the conservation of orbital symmetry in the conversion of the antisymmetric biradical to I. Consideration of the energetics and orbital symmetry, therefore, suggests that the antisymmetric biradical III can be involved in the degenerate rearrangement of I. Whether or not IV is formed depends on its stability relative to the diyl and to the activation barrier converting IV to the diyl. Eaton has found a substantial barrier (22 kcal/mol) for conversion of a [2.2.2]propellane derivative to a 1,4-dimethylenecyclohexane derivative indicating that IV would have to be substantially more stable than the non-interacting diyl to be accessible in the rearrangement of I. To answer this question thermochemical measurement would be most helpful.[16]

Acknowledgment. We thank the Alfred P. Sloan Foundation and the National Science Foundation for support.

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(13) P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Amer. Chem. Soc.*, **92**, 2377 (1970).

(14) W. D. Stohrer and R. Hoffmann, *J. Amer. Chem. Soc.*, **94**, 779 (1972).

(15) M. D. Newton and J. M. Schulman, *J. Amer. Chem. Soc.*, **94**, 4391 (1972).

(16) (a) Very recently Wiberg[16b] and Dannenberg[16c] have provided inferential evidence for the synthesis of the parent [2.2.2]propellane, the latter being a Hg sensitized photolysis of I. (b) K. B. Wiberg, G. A. Epling, and M. Jason, *J. Amer. Chem. Soc.*, **96**, 912 (1974). (c) J. J. Dannenberg, T. M. Prociv, and C. Hutt, *ibid.*, **96**, 913 (1974).

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Novel Maytansinoids. Structural Interrelations and Requirements for Antileukemic Activity[1–3]

Sir:

The potent antileukemic activity of maytansine (**1**)[4] and related maytanside esters[5,6] stimulated interest in the chemical and biological properties of related compounds. This interest has been heightened by the recent finding that maytansine also shows significant inhibitory activity against the Lewis lung carcinoma and B-16 melanocarcinoma solid murine tumor systems,[7] and the agent is under toxicological investigation in preparation for clinical trials. We report herein the isolation, structural elucidation, and chemical interrelation of four new maytansinoids from *Maytenus buchananii* (Loes.) R. Wilczek. Maytanvaline (**4**) is a highly active antileukemic maytanside ester.[8] Maysine (**5**), normaysine (**6**), and maysenine (**7**), the first reported maytansides, lack antileukemic activity and show *ca.*

(1) Tumor Inhibitors. 96. Part 95: S. M. Kupchan, A. L. Dessertine, B. T. Blaylock, and R. F. Bryan, *J. Org. Chem.*, in press.

(2) Supported by grants from the National Cancer Institute (CA-11718) and American Cancer Society (CI-102J) and a contract with the Division of Cancer Treatment, National Cancer Institute (N01-CM-12099).

(3) It is proposed that "maytansinoid" be used as a generic term for all ansa macrolide derivatives structurally related to maytansine and "maytanside" as the term for those maytansinoids which contain the macrocyclic ring system but lack the ester moiety.

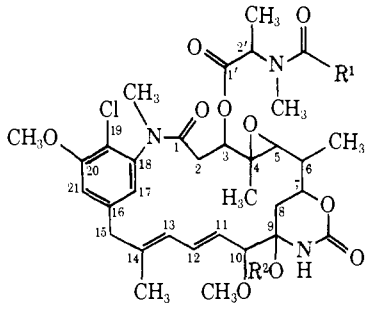
(4) S. M. Kupchan, Y. Komoda, W. A. Court, G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Haltiwanger, and R. F. Bryan, *J. Amer. Chem. Soc.*, **94**, 1354 (1972).

(5) S. M. Kupchan, Y. Komoda, G. J. Thomas, and H. P. J. Hintz, *J. Chem. Soc., Chem. Commun.*, 1065 (1972).

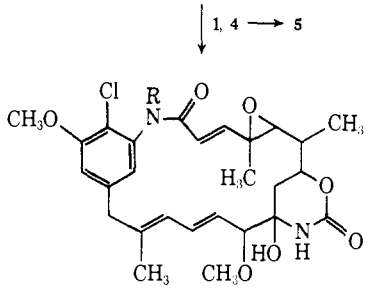
(6) M. C. Wani, H. L. Taylor, and M. E. Wall, *J. Chem. Soc., Chem. Commun.*, 390 (1973).

(7) Tumor inhibitory activity and cytotoxicity were assayed under the auspices of the National Cancer Institute, by the procedures described by R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, **3**, 1 (1972)].

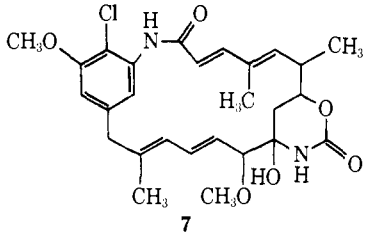
(8) Maytanvaline (4) showed significant antileukemic activity against the P-388 lymphocytic leukemia over a 50–100-fold dosage range at the microgram per kilogram level and cytotoxicity (ED_{50}) against KB cell culture at 10^{-5}–10^{-6} μg/ml. Maysine (**5**), normaysine (**6**), maysenine (**7**), and maytansine ethyl ether (**2**) showed cytotoxicity at 1–10^{-2} μg/ml and no antileukemic activity.



1, $R^1 = CH_3$; $R^2 = H$
2, $R^1 = CH_3$; $R^2 = CH_2CH_3$
3, $R^1 = CH_3$; $R^2 = CH_2CH_2CH_2Br$
4, $R^1 = CH_2CH(CH_3)_2$; $R^2 = H$



5, R = CH_3
6, R = H



7

1/10,000 the cytotoxicity of maytanside esters such as maytanvaline (**4**). The potent biological activity of maytanvaline (**4**) confirms and extends the earlier observations[4-6] that variations in the nature of the ester group affixed at C-3 are not accompanied by marked changes in antileukemic activity. In contrast, the strikingly diminished biological activity of the newly discovered maytansides reveals the key importance of the ester moiety for the biological activity of the antileukemic maytansinoids.

The alcoholic extract of wood and bark collected in Kenya in 1972 was fractionated by the procedure outlined earlier,[4,5] to yield a highly enriched concentrate. Repeated preparative tlc and column chromatography gave maytanvaline (**4**, 3.5 × 10^{-6}%): $C_{37}H_{52}ClN_3O_{10}$; mp 175–176.5°; $[\alpha]^{26}D$ − 135° (*c* 0.950, $CHCl_3$); uv (EtOH) 233 (ε 2.91 × 10^4), 243 (sh, ε 2.64 × 10^4), 254 (ε 2.68 × 10^4), 281 (ε 5.30 × 10^3), 288 nm (5.36 × 10^3); ir (KBr) 5.72, 5.80, 6.02, 6.34, 8.48, 9.27 μ; maysine (**5**, 5 × 10^{-6}%): $C_{28}H_{35}ClN_2O_7$; mp 137–141°; $[\alpha]^{30}D$ −173° (*c* 0.023, EtOH); uv (EtOH) 226 (ε 2.91 × 10^4), 241 (sh, ε 2.33 × 10^4), 252 (sh, ε 1.75 × 10^4), 280 (ε 4.28 × 10^3), 289 nm (sh, ε 3.90 × 10^3); ir (KBr) 5.85, 6.01, 6.14, 6.34, 9.19 μ; normaysine (**6**, 7 × 10^{-6}%): $C_{27}H_{33}ClN_2O_7$; mp 187–188°; $[\alpha]^{30}D$ −217° (*c* 0.051, EtOH); uv (EtOH) 229 (ε 4.45 × 10^4), 242 (sh, ε 3.64 × 10^4), 252 (sh, ε 2.73 × 10^4), 280 (sh, ε 5.77 × 10^3), 290 nm (sh, ε 5.20 × 10^3); ir (KBr) 5.92, 6.12, 6.30, 9.24 μ; and maysenine (**7**, 2.6 × 10^{-6}%): $C_{27}H_{33}ClN_2O_6$; mp 184–185°; $[\alpha]^{30}D$ −57° (*c* 0.056, EtOH); uv (EtOH) 234 (sh, ε 4.40 × 10^4), 243 (ε 5.34 × 10^4), 252 (sh, ε 4.14 × 10^4), 271 (ε 2.35 × 10^4), 300 nm (sh, 9.47 × 10^3); ir (KBr) 5.87, 6.01, 6.21, 6.31, 9.26 μ.

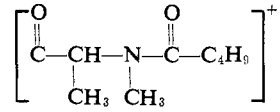
The nmr and mass spectral characteristics (Table I)

Table I[a]

	$M^+ - (a)$	$M^+ - (a + b)$	$485 - (CH_3)$	$485 - (Cl)$
1	630	485	470	450
4	672	485	470	450
			$M^+ - (a + CH_3)$	$M^+ - (a + Cl)$
5	485		470	450
6	471		456	436
7	455		440	420

[a] (a) = H_2O + HNCO; (b) = $R^1 \cdot CO \cdot NCH_3 \cdot CHCH_3 \cdot COOH$.

of maytanvaline (**4**) indicated that it possesses the same ansa macrolide ring system as maytansine (**1**) but a new ester grouping. The mass spectral data suggested a molecular weight of 170 for the ester fragment, consistent with structure A. The nmr spec-



A

trum ($CDCl_3$) of **4** differed from that of **1** solely in the signals corresponding to the R^1 group. Hydrolysis of **4** with Na_2CO_3 in 50% aqueous MeOH at room temperature yielded maysine (**5**) and *N*-isovaleryl-*N*-methyl-L-alanine, characterized as its methyl ester by comparison with a synthetic sample[9] (mass spectrum *m/e* 202.1434 (M^+) (calcd, 202.1438); ir (neat) 3.36, 3.48, 5.72, 6.07 μ; nmr ($CDCl_3$) τ 9.05 (d, $2CH_3$, J = 6.0 Hz), 8.64 (d, $CHCH_3$, J = 7.6 Hz), 7.84 (m, CH_2CH), 7.83 (d, CH_2CH, J = 2.0 Hz), 7.23, 7.11 (0.5 H, 2.5 H, NCH_3), 6.38 (s, $COOCH_3$), 4.84 (q, $CHCH_3$, J = 7.6 Hz)).

The mass spectra of **5**, **6**, and **7** indicated that these compounds have ansa macrolide structures similar to those of **1** and **4** but lack the ester function. The relationship between **5** and **1** was supported by the nmr spectrum of **5**, which showed the presence of a trans α,β-unsaturated amide (τ 4.35 (1 H, d, J = 16 Hz), 3.63 (1 H, d, J = 16 Hz)). Alkaline hydrolysis of **1**, as for **4**, yielded maysine (**5**) and *N*-acetyl-*N*-methyl-L-alanine, characterized as its methyl ester.[10]

The mass spectrum of normaysine (**6**) indicated that the structures of **5** and **6** differ only in the nature of the nitrogen substitution and that **6** is the *N*-desmethyl homolog of **5**. Accordingly, the nmr spectrum of **6** showed a signal corresponding to the proton on C-1-nitrogen (τ 2.62 (1 H, br s), exchangeable with D_2O) and lacked the N-CH_3 signal of **5**.

The mass spectrum of maysenine (**7**) showed that **7** is a

(9) *N*-Isovaleryl-*N*-methyl-L-alanine methyl ester was prepared by acylation of *N*-methyl-L-alanine methyl ester with isovaleryl chloride; *cf.* H. Krebs and W. Schumacher, *Chem. Ber.*, **99**, 1341 (1966).

(10) J. R. Coggins and N. L. Benoiton, *Can. J. Chem.*, **49**, 1968 (1971).

desoxy derivative of **6**. The nmr spectrum of **7** showed signals for a vinyl methyl group (τ 8.44 (3 H, br s)) and vinyl proton (τ 4.50 (1 H, br d, J = 10 Hz)) instead of the signals for the 4-methyl and 5-H protons of the 4,5-epoxide system of **6** and a downfield shift of the C-2 and C-3 protons relative to **6**. The structure of **7** was supported also by the bathochromic shift of its uv and ir carbonyl absorption peaks in comparison with those of **6**. Chemical interrelation was effected by reductive elimination of the epoxide of **6** with chromous chloride in acetic acid to give maysenine (**7**).[11]

The X-ray crystallographic structural elucidation of maytansine bromopropyl ether (**3**) revealed that the two longer sides of the 19-membered ring are roughly parallel and separated by about 5.4 Å, so that there is a hole in the center of the ring.[4,12] The two faces of the ring have a different character; the lower surface, opposite the ester residue, is predominantly hydrophobic, while the upper face is more hydrophilic. Furthermore, the ester residue is oriented in a manner which would hinder sterically the approach of reactants to the hydrophilic face. The ester function in the antileukemic maytansinoids may play a key role in the formation of highly selective molecular complexes with growth-regulatory biological macromolecules. Such molecular complex formation may be crucial for the subsequent selective alkylation of specific nucleophiles by, *e.g.*, the carbinolamide and epoxide functions.[13] In this connection, it is noteworthy that maytansine ethyl ether (**2**),[4] in which the reactive carbinolamide is no longer available as a potential alkylating function, shows no antileukemic activity. Structural studies of additional active principles are in progress, to elucidate further the requirements for biological activity among the antileukemic maytansinoids.

(11) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954).
(12) R. F. Bryan, C. J. Gilmore, and R. C. Haltiwanger, *J. Chem. Soc., Perkin Trans. 2*, 897 (1973).
(13) *Cf.* S. M. Kupchan, *Intra-Sci. Chem. Rep.*, **8**, 57 (1973).
(14) NIH Postdoctoral Fellow, 1972–1974.

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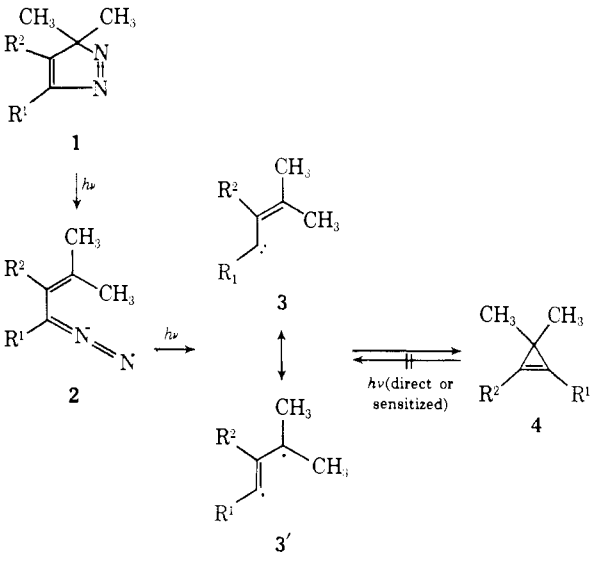
Electronic Excited States of Small Ring Compounds: Cyclopropene, Vinylcarbene, and Vinylmethylene[1]

Sir:

The mechanism(s) for the interconversion, and the relative energies of, three-membered rings and the corresponding heterolytic and homolytic bond-cleaved species continues to be of both theoretical and experimental interest.[2] In this communication we report the esr spectral characterization of the triplets, vinylmethylenes, **3a** and **3b**, formally derived from the cyclopropenes (**4a, b**).[3] These species were obtained by irradiating the vinyl azo compounds (**2a, b**).



a, $R^1 = R^2 = C_6H_5$
b, $R^1 = C_6H_5$; $R^2 = CO_2CH_3$
c, $R^1 = CO_2CH_3$; $R^2 = C_6H_5$

The 3*H*-pyrazoles (**1a–c**) have been reported previously.[2a,4] Treatment of methyl phenylpropiolate with diazoisopropane gives the isomeric adducts **1b** (mp 41°) and **1c** (mp 84°). The structure assigned to the major product (**1b**:**1c**, 2.5:1) was based on expectation of polar factors directing the cycloaddition. Since this reasoning is not compelling, we sought additional proof for these structures. Irradiation[5a] of the 3*H*-pyrazoles (**1a–c**) in benzene solution, brings about formation of the vinyl azo compounds (**2a–c**) in good yield. These vinyl azo compounds are stable for hours in benzene solution at room temperature. The spectral evidence, summarized in Table I, shows the pertinent uv and ir

Table I. Spectral Properties of the Vinyl Azo Compounds

Vinyl azo compound	Ir (CCl_4), cm^{-1}	Uv (C_6H_6), nm (ϵ)	Nmr (CCl_4) $\delta(CH_3)$	Nmr (CCl_4) $\delta(CO_2CH_3)$
2a	2040	512 (80)	1.87, 1.92	
2b	2043	510 (75)	1.93, 2.27	3.58
2c	2083	420 (115)	1.82, 1.92	3.68

absorption bands of **2a** and **b** are similar to one another and are significantly different from **2c**; this provides additional support for structures **1b** and **c**. Irradiation[5b] of benzene solutions of the vinyl azo compound **2a–c**, at room temperature, leads to good yields of the cyclopropenes **4a** and **b**.[2a,4]

(1) Contribution No. 99 from the Photochemistry Unit.
(2) For cyclopropene, for example: experimental (a) J. A. Pincock, R. Morchat, and D. R. Arnold, *J. Amer. Chem. Soc.*, **95**, 7536 (1973); (b) E. J. York, W. Dittmar, J. R. Stevenson, and R. G. Bergman, *ibid.*, **95**, 5680 (1973); (c) W. J. Baron, M. E. Hendrick, and M. Jones, Jr., *ibid.*, **95**, 6286 (1973); (d) M. F-Neumann and C. Buchecker, *Tetrahedron Lett.*, 2875 (1973); (e) L. Schrader and W. Hartmann, *ibid.*, 3995 (1973); (f) R. S. Streeper and P. S. Gardner, *ibid.*, 767 (1973); (g) O. L. Chapman, J. Pacansky, and R. Roth, unpublished results; theoretical, (h) R. Hoffmann, G. D. Leiss, and G. W. Van Dine, *J. Amer. Chem. Soc.*, **90**, 1485 (1968); (i) L. Salem and C. Rowland, *Angew. Chem., Int. Ed. Engl.*, **11**, 92 (1972); (j) L. Salem and W. D. Stohrer, unpublished results.

(3) Closs has reported the esr detection of a triplet vinylmethylene for a "phenyl-substituted" case; however, no details have appeared. G. L. Closs, W. A. Boll, H. Heyn, and V. Dev, *J. Amer. Chem. Soc.*, **90**, 173 (1968); see footnote *b*, Table II.
(4) M. F-Neumann and C. Buchecker, *Tetrahedron Lett.*, 15 (1969).
(5) (a) 2 cm, 1.0 *M* $CuSO_4 \cdot 7H_2O$ and 0.1 *M* $NiSO_4 \cdot 6H_2O$ in 5% H_2SO_4 and 1 cm, 0.4 *M* $SnCl_2 \cdot 2H_2O$ in 10% HCl. (b) 1 cm, 4×10^{-3} *M* $BiCl_3$ in 10% HCl. (c) Corning filter CS 7-51 or CS 7-59.