results should be careful, because the present studies were conducted only on incubation with an intact fungus. In Scheme I we speculate on one of the possible mechanisms to explain the cis opening, which proceeds presumably in two steps. First the *S*-(−)-epoxide may be trans opened by a backside attack of a nucleophillic center of an enzyme to form an intermediate complex IX, which is then solvolyzed, also enzymatically, in an SN2 type reaction into the *S*-(−)-glycol.

In connection with the less dominant attack (8–11%) on $C_{11}$, optical purity of the glycollic metabolites was examined by nmr using chiral lanthanide shift reagent.[7] IIIa, showing $[\alpha]_D$ −14.1° (*c* 0.7, MeOH), was found to consist of 86.5% of *S*(−) and 13.5% of *R*(+) enantiomer.[8] This partial racemization is probably accounted for by the above minor route of hydration.[9]

The enzymatic hydration of racemic epoxides into a single stereoisomer has been reported on several compounds,[10] in every case occurring as a trans opening. The present studies suggested the operation of two different pathways, trans and cis opening, in the fungal hydration of racemic epoxyfarnesol, the latter pathway being quite novel. Further refined study on the level of the enzyme *in vitro* will be necessary to elucidate the precise mechanism of this interesting hydration.

(7) H. L. Goering, J. N. Eikenberry, and G. S. Koemer, *J. Amer. Chem. Soc.*, **93**, 5913 (1971).

(8) Enantiomeric composition of IIIa (0.23 *M*) was determined in $CCl_4$ in the presence of 0.07 *M* tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III). Under these conditions, some of the signals of the *S* enantiomer shift downfield more than those of *R* enantiomer. The signals used for the determination were those for $C_{10}$-methine ($\Delta\Delta\delta$ 0.3 ppm) and either one of $C_{11}$-methyls ($\Delta\Delta\delta$ 0.09 ppm).

(9) Nonenzymatic hydration of an epoxide during the incubation was prevented by powdered calcium carbonate added into the medium. In the controlled experiment with heat-inactivated fungus, the substrate did not produce a glycollic compound (II).

(10) (a) D. M. Jerina, J. W. Daly, B. Witkop, P. Z. Nirenberg, and S. Udenfriend, *J. Amer. Chem. Soc.*, **90**, 6525 (1968); (b) T. Tanabe, S. Kanehira, K. Kiyinaga, and S. Hara, 2nd Symposium on Drug Metabolism and Action, K. Kakemi, Ed., Hirokawa Publishing Co., Tokyo 1970, p 59; (c) W. G. Niehaus, Jr., A. Kisic, A. Torkelson, D. J. Bednarczyk, and G. J. Schroepfer, Jr., *J. Biol. Chem.*, **245**, 3802 (1970).

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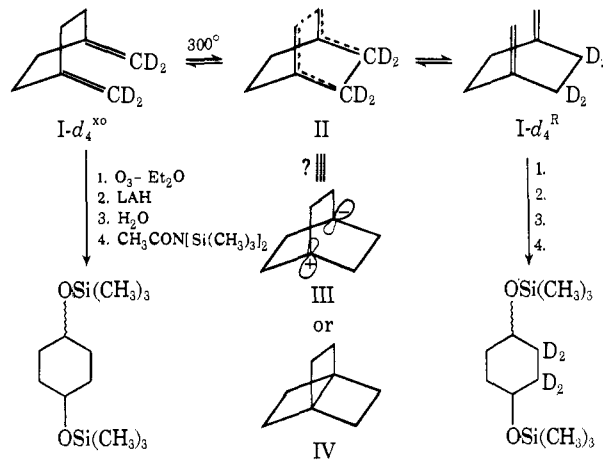
## Hydrocarbon Thermal Degenerate Rearrangements. VI. A Boat Cope Transition State in the Self-Interconversion of 1,4-Dimethylenecyclohexane

*Sir:*

Concern over the energetics of the high temperature Cope rearrangement in comparison with the "chair" process[1] prompts us to report the energetics of the necessarily boat-like 3,3-sigmatropic rearrangement of 1,4-dimethylenecyclohexane (I) the transition state of which, II, has the added feature of resembling [2.2.2]propellane.[2]

Lithium aluminum deuteride reduction of 1,4-dicarbomethoxycyclohexane followed by tosylation, iodide displacement, and *tert*-butoxide–*tert*-butyl alcohol elimination gave 1,4-bis(dideuteriomethylene)cyclohexane (*I*-$d_4^{xo}$).




Pyrolysis of this material in a well-conditioned bulb at 333° for 35 min (100 μl in a 2-l. vessel with 40 Torr of $N_2$) gave only I[3] with 30% of total protium on the exomethylene position. Ozonolysis of recovered I in $Et_2O$ at −78° followed by lithium aluminum hydride reduction gave a cyclohexane-1,4-diol which was converted to the bis(trimethylsilyl) ether whose mass spectrum (in the M − 15 region) revealed the presence of $d_0$, $d_2$, and $d_4$ materials in the ratio, 1:<0.02:0.46. Thus the rearrangement is best interpreted as a 3,3-sigmatropic shift as depicted above.

The temperatures necessary to affect the Cope rearrangement were 50–75° higher than that for reaction of 1,5-hexadiene *via* the chair process[1] and provided impetus for determination of the activation parameters. Examination of the kinetics over a temperature range of 42° (to ±0.3°) gave $\Delta S^{\ddagger} = -13.8 \pm 2$ eu and $\Delta H^{\ddagger} = 39.0 \pm 1.0$ kcal/mol for the conversion of I-$d_4^{xo}$ to I-$d_4^{R}$ ($K_{eq} = 2.1$ at 300°).[4]

As a result of the partial, but elegant, stereochemical labeling studies of Doering and Roth,[5] the lowest energy Cope process has been accepted as that involving the chair transition state; a higher energy (5.7 kcal/mol) process also occurred with stereochemistry consistent with a boat-like transition state. Indeed, Dewar has calculated, by the MINDO technique, this energy difference but has poorly reproduced the absolute heats of formation of individual species.[6] Other symmetry allowed[7] transition states of the antara–antara variety have been recognized by ourselves[8] and Goldstein,[9] namely the "helix" or twist and the "plane" with $C_2h$ symmetry. The observed partial stereochemistry of the low energy pathway can be explained by either the chair or helix;[8] however, an important, but occasionally overlooked[8] study by Hill[10] clearly reveals the chair to

(1) (a) W. von E. Doering, V. G. Toscano, and G. H. Beasley, *Tetrahedron*, **27**, 5299 (1971); (b) M. J. Goldstein and M. S. Benzon, *J. Amer. Chem. Soc.*, **94**, 7147 (1972).

(2) P. E. Eaton and G. H. Temme III, *J. Amer. Chem. Soc.*, **95**, 7508 (1973).

(3) Without prior conditioning with dimethyldichlorosilane, *p*-xylene was a major product.

(4) (a) For comparison, Humski, *et al.*,[4b] reported $K_{eq}$ for conversion of 1,1,6,6-tetradeuterio-1,5-hexadiene to 3,3,4,4-tetradeuterio-1,5-hexadiene as 1.23 at 200°. (b) K. Humski, R. Malojčić, S. Borčić, and D. E. Sunko, *J. Amer. Chem. Soc.*, **92**, 6534 (1970), and references contained therein.

(5) W. von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

(6) A. Brown, M. J. S. Dewar, and W. Schoeller, *J. Amer. Chem. Soc.*, **92**, 5517 (1970).

(7) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(8) J. J. Gajewski, *Mech. Mol. Migr.*, **4**, 1 (1972).

(9) M. J. Goldstein and M. J. Benzon, *J. Amer. Chem. Soc.*, **94**, 7149 (1972).

(10) R. K. Hill and N. W. Gilman, *Chem. Commun.*, 619 (1967).

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 $\Delta H_f$ 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 ($\Delta H_f$ = −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.

(11) (a) J. A. Berson and P. B. Dervan, *J. Amer. Chem. Soc.*, **94**, 7597 (1972); (b) C. Ullenius, P. W. Ford, and J. E. Baldwin, *ibid.*, **94**, 5910 (1972).

(12) J. L. Franklin, *Ind. Eng. Chem.*, **41**, 1070 (1949); *J. Chem. Phys.*, **21**, 2029 (1953).

(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).

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(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.