In summary the transition-state representations most readily reconciled with the experimental observations are Ia for the uncatalyzed ammonolysis reaction and IIb for the catalyzed. The main factors taken into account in reaching these conclusions are (1) the fractional charge on the attacking nucleophile and (2) the extent to which carbon–oxygen bond breaking contributes to the over-all free energy of activation. Increased developing negative charge on the nucleophile and stabilization of the leaving group either by electron withdrawal or by general acid catalysis both lead to larger values of ρ for acyl substituents.

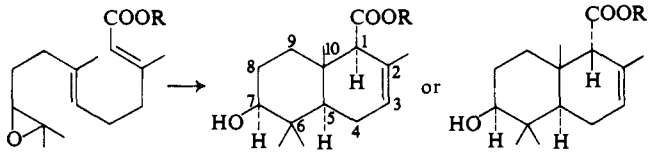
Communications to the Editor

Terpene Terminal Epoxides. Mechanistic Aspects of Conversion to the Bicyclic Level

Sir:

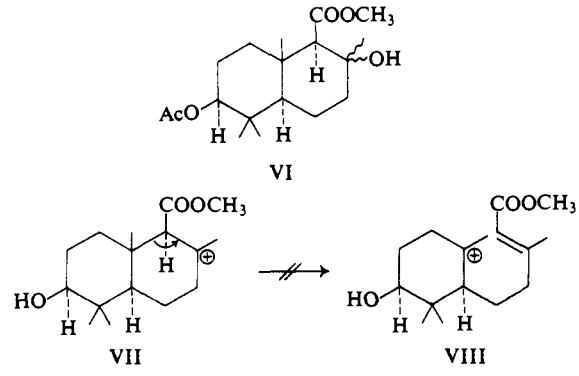
In order to assess the requirements for enzyme control in the biosynthesis of lanosterol (I) from squalene 2,3-oxide (II), it is informative to compare and contrast the results of enzymic and nonenzymic reactions of this epoxide or suitable models.[1,2] For these reasons and also to understand more completely the purely organic aspects of such cyclizations, we have taken up physical organic studies which pertain to the mechanism of A,B ring formation.

Previous work[3] has revealed that, depending upon reaction conditions, cyclization of *trans,trans*-10,11-oxidofarnesic ester (III) produces predominantly either the C-1,C-10 *trans dl*-bicyclic hydroxy ester IV or the corresponding



III IV V

cis isomer V, the latter being of particular interest because this stereochemical arrangement at a comparable pair of chiral centers is deemed necessary for isomerization of tetracyclic intermediate in the bioconversion II → I.[4] That such behavior is general is indicated by the similar specificity exhibited by 10,11-oxidofarnesyl acetates,[3c] and by $\Delta^{2,6}$-*cis,trans*-farnesyl ether.[3b] Of value in this connection are the following new observations. Both $\Delta^{2,6}$-*trans,trans*- and $\Delta^{2,6}$-*trans,cis*-farnesic esters are geometrically stable under the reaction conditions (cold phosphoric acid) used for cyclization of epoxide III. Isomer IV is at least 80% unchanged under these conditions, which induce conversion of epoxide III to bicyclic hydroxy ester comprising as much as 62% of V. Isomer V is largely recovered from the reaction medium (boron trifluoride etherate in benzene) which serves to convert starting epoxide to a mixture rich (75–90%) in isomer IV. A mixture of tertiary alcohols VI (obtained by hydration of ester IV),[5] on being subjected to reaction conditions used for cyclization of epoxide III to hydroxy ester V (presumably the more stable of the IV–V pair),[6] dehydrated—presumably *via* carbonium ion VII—to give exclusively the hydroxy ester isomer IV. On the basis of the foregoing, it seems certain that neither starting material nor product undergoes stereochemical change under cyclization conditions. Also, it appears likely that bicyclic carbonium ion VII does *not* suffer bond cleavage to monocyclic carbonium ion VIII which then recloses to the



VI VII VIII

more stable bicyclic type (V), and thus carbonium ion VII is not an intermediate in the over-all phosphoric acid promoted cyclization of epoxide III to bicyclic ester V. In light of these aspects of epoxide cyclizations, it seems likely that the stereochemical outcome at C-1/C-10 in IV and V is determined by the *solvent-dependent conformation of reacting epoxide.*

When *trans,trans*-epoxy ester III was cyclized in trideuteriophosphoric acid under the usual conditions, no deuterium incorporation into product V was observed (mass spectral determination). This result rules out monocyclic, dienoid intermediates which require repro-

(1) For a review of earlier investigations along these lines see E. E. van Tamelen, *Accounts Chem. Res.*, **1**, 111 (1968).

(2) For example, by such means we have been able to demonstrate biochemical overriding of normal chemical tendencies in the construction of a six-membered C-ring: E. E. van Tamelen, J. Willett, M. Schwartz, and R. Nadeau, *J. Am. Chem. Soc.*, **88**, 5937 (1966). See also K. B. Sharpless and E. E. van Tamelen, *ibid.*, **91**, 1848 (1969).

(3) (a) E. E. van Tamelen, M. Schwartz, and A. Storni, *Chem. Commun.*, **13**, 409 (1966); (b) E. E. van Tamelen and R. C. Coates, *ibid.*, **13** (1966); (c) E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *J. Am. Chem. Soc.*, **85**, 3295 (1963); (d) J. P. McCormick, unpublished observations.

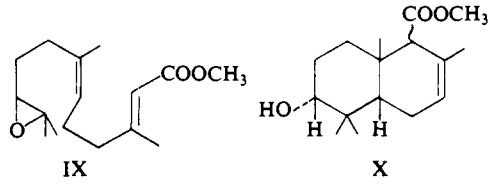
(4) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

(5) Conversion of bicyclic ester IV to VI was accomplished by treatment with mercuric acetate, followed by reductive cleavage of the intermediary acetoxy mercury compound with $NaBH_4$. Assignment of structure VI rests upon consonant ir, uv, nmr, and mass spectral data, as well as satisfactory elemental analysis.

(6) Because of steric interaction of the pseudoequatorial ester function with both the neighboring olefinic methyl and axial angular methyl, the substituent is considered to be more stable in the pseudo-axial conformation.

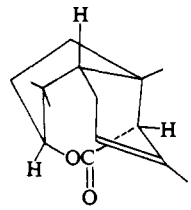
tonation, but can be interpreted in terms of either (a) a completely synchronized cyclization, or (b) a pathway involving an intermediary monocyclic carbonium ion (VIII).

In order to learn more about the intimate stereochemical aspects of the cyclization course, comparable ring closure attempts were made on the *trans,cis*-epoxy ester IX. Under the influence of boron trifluoride etherate in benzene at room temperature, this epoxy ester was converted into a mixture of products, including rearranged acyclic keto ester (~45%), monocyclic hydroxy ester (~10%), and bridged bicyclic ether[3] (~10%) (all yields by vpc). In addition there was formed in small (~3%) yield the bicyclic hydroxy ester X, which, as a component of the original cyclization mixture, was easily transformed by methanolic potassium hydroxide into the



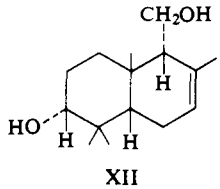
IX

X

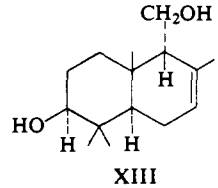


XI

tricyclic lactone XI, mp 107.5–108°. Neither the lactone nor *trans* bicyclic esters IV–V could be detected as components of the original cyclization mixture. The structure (and therefore stereochemistry) of the lactone was suggested by: ir (carbonyl at 5.83 μ), nmr (three-proton resonances at δ 0.92, 0.95, and 1.03 (singlets) and 1.75 (doublet of doublets), one-proton resonances at 2.27 (doublet), 3.78 (broad singlet), and 5.42 (multiplet)), and mass spectroscopy (high-resolution molecular ion at 234.1602 ($C_{15}H_{22}O_2$), base at *m/e* 105, large peak at *m/e* 190). Confirmation of structure was realized by the study of bicyclic diol XII, provided by lithium aluminum hydride reduction of the lactone. The diol of established structure XIII (obtained by hydride reduction of hydroxy ester V)[3] and the stereoisomeric XII possessed complex mass



XII



XIII

spectra identical with regard to the appearance (but not intensity) of individual peaks. The yield of carbobicyclic material from IX is low; although to the extent that any is formed, the ring closure of epoxide seems to be stereoselective in the production of *cis*-fused product. This result is in harmony with the concept of cyclization which (1) wholly concerted proceeds with preservation of stereochemical relationships, or (2) involves conformationally "frozen" monocyclic carbonium ions, one type (from IX) giving rise to *cis* product and another type (from III) destined for *trans* fusion.[7]

In regard to formation of the A,B(C) ring system of lanosterol (I), it appears that the biochemical cyclization of squalene oxide is strongly based on organic chemical foundations and that no uncommon enzymic assistance may be needed (1) to produce the temporary 9,10-*cis* stereochemistry considered necessary for further, stereospecific isomerization to I,[4] and (2) to realize stereospecific cyclization without proton exchange from the medium, as observed.[8] Obviously, in A,B ring formation, enzyme action is mandatory (1) to ensure essentially quantitative operation of the squalene oxide cyclization elements which possess purely organic parallels, as outlined, and (2) to block other reaction outlets for starting epoxide, such as isomerization to acyclic ketone and generation of various monocarbocyclic species, as described above and elsewhere.[1,3]

Acknowledgment. The authors are indebted to the National Science Foundation for grant (GP 1937) support.

(7) For the stereoselective cyclization of *trans*- and *cis*-5,9-decadienyl *p*-nitrobenzenesulfonates, see W. S. Johnson, D. M. Bailey, R. Owyang, R. A. Bell, B. Jacques, and J. Crandall, *J. Am. Chem. Soc.*, **86**, 1959 (1964); W. S. Johnson and J. Crandall, *ibid.*, **86**, 2085 (1964).
(8) T. T. Tchen and K. Bloch, *ibid.*, **78**, 1516 (1956).
(9) National Science Foundation Fellow, 1965–present.

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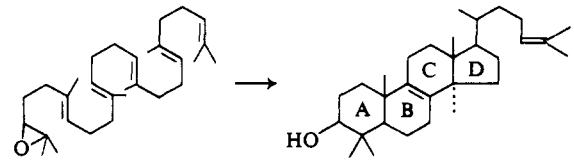
Terpene Terminal Epoxides. Skeletal Rearrangement Accompanying Bicyclization of Squalene 2, 3-Oxide

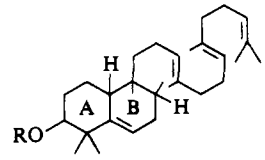
Sir:

By comparing enzymic and nonenzymic reactivity of a given substrate, it becomes possible to identify qualitatively the role of an enzyme in directing synthetic behavior beyond that normal in the organic chemical sense (see accompanying communication). As part of a program concerned with the bioorganic chemistry of terpenoid terminal epoxides,[1] we describe herein the direct nonenzymic conversion of squalene 2,3-oxide to bicyclic, rearranged product III. Although arrested by the cyclase



I

II



III, R = H
IV, R = $Si(CH_3)_3$
V, R = $SO_2C_6H_4$-*p*-CH_3
IX, R = $COCH_3$

(1) E. E. van Tamelen, *Accounts Chem. Res.*, **1**, 111 (1968).