Anal.[22] Calcd. for $C_{11}H_{14}N_6O_{12}P_3Ba_2 \cdot 6H_2O$: C, 14.94; H, 2.97; N, 7.92; total P, 10.51; phosphate P, 3.50; labile P, 0.0; mol. wt., 884; adenine:strong acid:weak acid, 1.0:3.0:1.0. Found: C, 14.90; H, 3.13; N, 8.23; total P, 10.56; phosphate P, 3.53; labile P, 0.0; equiv. wt., 892 (by ultraviolet measurements; λ_{max} 259 mμ, λ_{min} 227 mμ at pH 7); titration data, adenine:strong acid:weak acid, 0.97:3.0:1.0 (pK_A's 4.2, 8.5).[20]

Paper chromatography using solutions of the free acid (prepared by treatment of aqueous suspensions of the barium salt with Dowex-50(H) resin) gave single clean spots (solvent system A, R_f 0.26, R_{ATP} 1.20; solvent system C, R_f 0.81, R_{ATP} 0.97; solvent system D, R_f 0.39, R_{ATP} 0.82). The product gave a positive reaction when the chromatograms were sprayed with periodate–benzidine spray.

Hydrolysis of the product (as the free acid prepared from the barium salt with use of Dowex-50(H) resin, *ca.* 10 mg. per ml.) with 2.5 *N* NaOH for 30 min. at 100° caused degradation to AMP which was detected by paper chromatography (solvent system A, R_f 0.46; solvent system D, R_f 0.30).

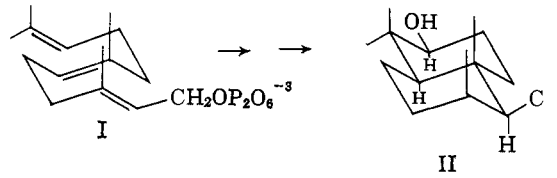
(22) Analyses for C, H, and N were conducted by the Midwest Microlab, Inc., of Indianapolis, Ind.

COMMUNICATIONS TO THE EDITOR

The Biogenetically Patterned *in vitro* Oxidation–Cyclization of Farnesyl Acetate

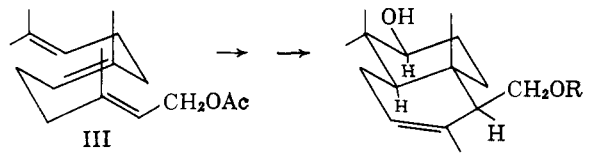
Sir:

By virtue of incisive tracer and isolation studies, it has been demonstrated that farnesyl pyrophosphate (I), derived from mevalonic acid *via* isopentenyl pyrophosphate, serves as a natural precursor of squalene, lanosterol, cholesterol, and, by implication, all of the many varieties of steroids, as well as sesqui-, di-, and



I II

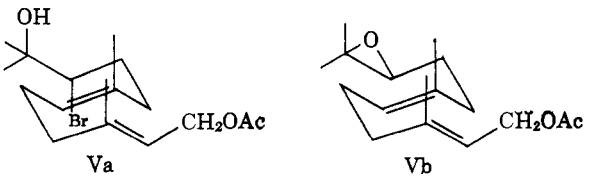
triterpenoids, which usually possess the characteristic part ring system and stereochemistry depicted in II.[1] We wish to report the nonenzymatic selective terminal oxidation of (*trans-trans*) farnesyl acetate (III) and



III IVa, R = Ac; IVb, R = H

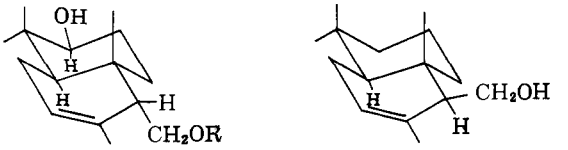
subsequent acid-catalyzed, stereo-directed cyclization to the bicyclic diol monoacetate (IVa), which duplicates, in respect to carbon framework, oxidation site, and stereochemistry at all of *four* asymmetric centers, the familiar 2-hydroxylated A–B ring system present in most polycyclic, di-, and triterpenoid systems.

Through the action of N-bromosuccinimide in aqueous glyme, *trans-trans*[2] farnesyl acetate was selectively—and exclusively, for all practical purposes—oxidized at the terminal nonallylic of the three trisubstituted double bonds,[3] giving rise to bromohydrin Va.[4] The latter, after chromatographic (silica gel) purification, was converted by means of base to epoxide Vb.[4] On treatment with boron trifluoride etherate in benzene,[5] the epoxide was transformed into a variety of



Va Vb

products, from which there could be isolated after extensive chromatographic purification a modest yield of bicyclic diol monoacetate, shown by vapor phase chromatography to consist of 85% stereoisomer IVa and 15% of the epimer VIa.[6] The constitution and stereochemistry of product VIa was proved by (1) chromic anhydride oxidation to the acetoxy ketone VIIa and



VIa, R = Ac
VIb, R = H

VIII

lithium aluminum hydride reduction to the same diol (VIb) (m.p. 150–151°) produced by hydrolysis of VIa, thus indicating the equatorial nature of the hydroxyl group, and (2) conversion, by means of Raney nickel desulfurization of VIIa ethylene dithio ketal, to *dl*-epidrimenol (m.p. 65.5–66.5°), an authentic sample of which was prepared by lithium aluminum hydride reduction of the methyl ester of the known corresponding acid (m.p. 138°).[7,8] In parallel experiments, the diol acetate IVa was (1) oxidized to ketone VIIb and reduced to authentic IVb (m.p. 113–114°) and (2) converted to monohydric alcohol identical with *dl*-drimenol (m.p. 61–62°).[7–9] When a mixture (65% *trans;* 35% *cis*) of farnesyl acetate was subjected to the oxidation–cyclization sequence described before, a mixture of 55% IVa and 45% VIa (by v.p.c.) was generated,[6] thus indicating that, under the specified conditions and to the extent that IVa and VIa are formed, geometry determines stereochemistry of product, at

(1) For reviews, see, *e.g.*, (a) F. Lynen and U. Henning, *Angew. Chem.*, **72**, 820 (1960); (b) L. Ruzicka, *Proc. Chem. Soc.*, 341 (1959).

(2) See R. Bates, *J. Org. Chem.*, **28**, 1086 (1963).

(3) *Cf.* the selective *in vitro* oxidation of the terminal double bonds in squalene: E. E. van Tamelen and T. J. Curphey, *Tetrahedron Letters*, **No. 3**, 121 (1962).

(4) This intermediate was not crystalline; but after suitable operations (chromatography on bromohydrin; short path distillaton of epoxide), analytically pure material was secured.

(5) For the acid-catalyzed cyclization of 2,6-dimethyl-5,6-epoxyheptene-1, see D. J. Goldsmith, *J. Am. Chem. Soc.*, **84**, 3913 (1962).

(6) Vapor phase chromatography data secured on acetoxy ketone VIIa,b (*vide infra*).

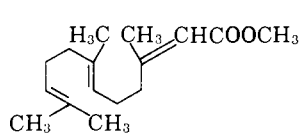
(7) P. A. Stadler, A. Eschenmoser, H. Schinz, and G. Stork, *Helv. Chim. Acta*, **40**, 2191 (1957).

(8) Comparison of bicyclic diol thus obtained with authentic material rests on identical v.p.c., infrared spectral, m.p. (and m.m.p.) behavior (as diol *per se*, or as suitable derivatives).

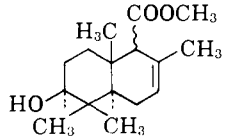
(9) We are indebted to Professor Dr. A. Eschenmoser (ETH) for an authentic sample.

least at the site under discussion. However, when epoxide derived from *trans-trans* farnesyl acetate was cyclized by means of 85% phosphoric acid, there resulted approximately the same epimeric mixture (85% VIa; 15% IVa) as secured by cyclization of epoxide from the same geometrical isomer mixture referred to before.[10]

The generality of the oxidization–cyclization sequence is suggested by preliminary experiments with methyl farnesate (IX), which, on successive treatment under appropriate conditions with (1) NBS–water–glyme and (2) phosphoric acid, is transformed into noncrystalline bicyclic hydroxy ester X, probably a mixture of carbomethoxyl epimers. The nature of this product was

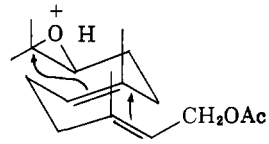


IX



X

demonstrated by lithium aluminum hydride reduction to bicyclic diol from which there was isolated material of m.p. 149.5–150°, identical (infrared and m.m.p.) with diol VIb secured from farnesyl acetate as described before. Whether the formation of diol monoacetate IVa, VIa, and/or hydroxy ester X proceeds by way of a concerted pathway XI, similar to that seem-

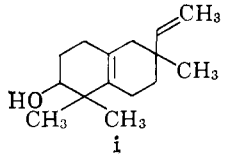


XI

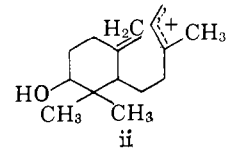
ingly operative *in vivo*,[11] or through a stepwise route, is a distinction we hope to make on the basis of future studies.[12] The application of this over-all synthetic approach to other, naturally occurring systems is under investigation in this Laboratory.

Acknowledgment.—These studies were aided by a grant (AI 05102-02 MCHB) from the National Institutes of Health.

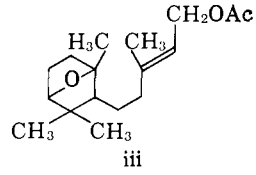
(10) Among the other products of this cyclization reaction, there is found a substance which, on the basis of its elemental analyses and infrared and n.m.r. spectral properties, appears to possess structure i. The characteristic moiety (which, interestingly enough, appears in various tricyclic diterpenes, *e.g.*



i



ii



iii

rimuene, rosenonolactone, as well as pimaric and isopimaric acids) could arise by interaction of an exocyclic methylene group in a monocyclic intermediate, as in ii, followed by proton loss to yield i. From the BF_3 etherate–benzene experiment there results still a different product, which appears, on the basis of similar evidence, to possess structure iii (*cf.* ref. 5).

(11) T. T. Tchen and K. Bloch, *J. Am. Chem. Soc.*, **78**, 1516 (1956); *J. Biol. Chem.*, **226**, 931 (1957).

(12) Full spectral and analytical data will be presented in a full publication.

(13) National Institutes of Health Predoctoral Fellow.

(14) National Science Foundation Predoctoral Fellow.

STANFORD UNIVERSITY
DEPARTMENT OF CHEMISTRY
STANFORD, CALIFORNIA
UNIVERSITY OF WISCONSIN
DEPARTMENT OF CHEMISTRY
MADISON, WISCONSIN

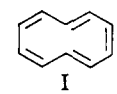
EUGENE E. VAN TAMELEN
ANGELO STORNI
EDWARD J. HESSLER[13]
MARTIN SCHWARTZ[14]

RECEIVED AUGUST 5, 1963

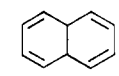
The 9,10-Dihydronaphthalene–Cyclodecapentaene Valence Bond Isomer System[1]

Sir:

Occupying a central position in the field of aromatic theory, the simplest $4n + 2$ π-electron homolog of benzene, cyclodeca-1,3,5,7,9-pentaene (I), has been often discussed,[2] but remains still only a hypothetical structure. As an original aim, we approached prepara-



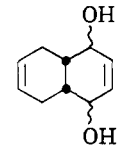
I



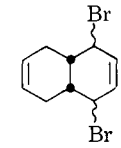
II

tion of the parent structure by way of the valence bond isomer 9,10-dihydronaphthalene (II), which, in the reasonable assumption that the barrier for conversion would be relatively low,[2e] should be tantamount to direct synthetic assault on the ten-membered cycle. In this Communication, we report production of *cis*-9,10-dihydronaphthalene and its apparent stability relative to the cyclodecapentaene.

The (*cis*) quinone–butadiene Diels–Alder adduct was subjected to the action of aluminum isopropoxide–isopropyl alcohol with the result that there was formed in good yield a mixture of stereoisomeric dienediols III. From the mixture there was isolated after column chromatography (Florisil) homogeneous material (m.p.

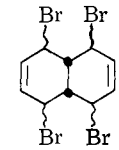


III

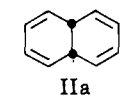


IV

165.5°) which consumed two moles of hydrogen under catalysis to give a saturated diol (m.p. 154–155°).[3,4] By means of 48% hydrobromic acid–petroleum ether mixture, the unsaturated diol III was transformed into a dibromide mixture; by direct crystallization, dibromide IV of m.p. 82–83° was secured.[4-6] In preparation for dehalogenation to the desired hydrocarbon, the dienedibromide IV was allylically brominated by means of N-bromosuccinimide in the presence of benzoyl peroxide; the desired, oily dienetetrabromide (V)[4,5] was separated from other halogenated materials[7] by chromatography over Florisil. The penultimate intermediate was converted to *cis*-9,10-



V



IIa

(1) Presented at the Eighteenth National Organic Symposium, Columbus, Ohio, June 16–20, 1963.

(2) (a) K. Mislow, *J. Chem. Phys.*, **20**, 1489 (1952); (b) W. Baker, in "Perspectives in Organic Chemistry," A. Todd, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p. 39; (c) V. Prelog, *ibid.*, p. 127; (d) W. Baker and J. F. W. McOmie, "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience Publishers, Inc., New York, N. Y., 1959, p. 477; (e) E. Vogel, *Angew. Chem. Intern. Ed. Engl.*, **2**, 1 (1963).

(3) Elemental analyses, carried out on all new substances described, were satisfactory.

(4) Stereochemistry of halogen and hydroxyl was not determined.

(5) The p.m.r. spectrum was in agreement with the assigned structure.

(6) In addition, a smaller amount of 1,2-dibromide, m.p. 65–67°, was isolated.[5]

(7) Crystalline hexabromide ($C_{10}H_{10}Br_6$), m.p. 181–182°, emerged as an easily isolable product.