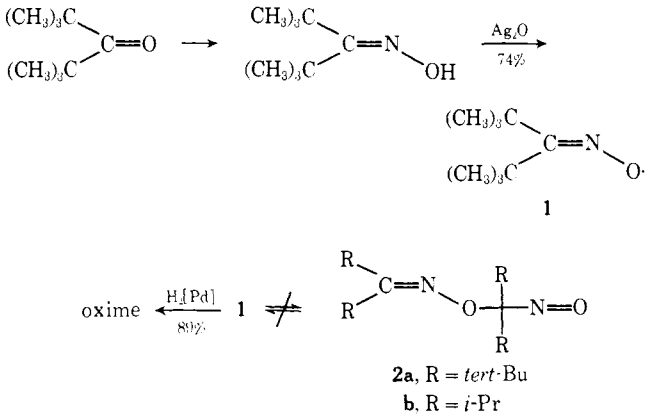
camphor. Two distillations at 25° by the bulb-to-bulb technique gave material that analyzed correctly (C, H, N) and which gave a value of 160 for the molecular weight (vapor pressure thermistor). Other properties were fp −21°, $n^{21}D$ 1.4452, and $d^{22°}$ 0.824; strong absorption at 1610 cm^{-1} (C=N and/or N=O); mass spectrum superimposable on that of parent oxime (parent ion *m/e* 157).[10]



The esr spectrum of **1** in benzene showed a triplet with a_N = 32.2 G. Each of the three peaks was further resolved into at least 24 lines with a_H = 0.4 G at 24–42°, decreasing to 16 lines at 60° and 14 lines at 75°. Syn–anti isomerization was described in the first report of iminoxy radicals,[11] but we feel the complexity of this splitting must be explained in part in terms of proton nonequivalence due to hindered rotation of the *tert*-butyl groups.

We could find no compelling evidence for dimerization of **1**. A plot of esr signal intensity *vs.* concentration is linear up to 0.3 *M* in cyclohexane at 25°.[12] An isopentane solution 0.21 *M* in **1** was cooled from 25 to −150°. The doubly integrated esr signal showed only an *increase* by a factor of 2.70. This is the same within error as the increase shown by a dilute DPPH solution under these conditions (2.84).[13] The color of pure **1** is not visibly changed at −196°.

The visible spectrum of **1** (0.02 *M* in cyclohexane) showed a weak maximum at 720 nm (ε 4.5). At high concentration this shifted to shorter wavelengths (λ_{max} 701 nm at 0.39 *M*). The solutions obey Beer's law only if the absorbance at λ_{max} is plotted against concentration. This shift is either a solvent effect or the result of dimerization (*cf.*[8] **2b**: λ_{max} 703 nm (ε 11)). The first explanation is more consistent with the esr results and is the preferred one.

Finally, the ir spectrum of **1** as a neat liquid shows only a weak shoulder at 1560 cm^{-1}, whereas a strong peak assigned to the N=O group appears at this frequency in **2b**.[8]

Di-*tert*-butyliminoxy is stable to air, diffuse light, concentrated HCl, and aqueous NaOH at 25°. The radical liberates iodine from acidified starch–iodide paper. Catalytic reduction affords the parent oxime in high yield. In the neat state at 25° the radical decomposes within a week,[14] and a new absorption at 1555 cm^{-1} appears after 4 days even at −20°. The stability increases with dilution, however. A *ca.* 0.02 *M* solution of **1** in benzene shows a 15% decrease in the esr signal after 5 hr at 50°, and 50% after 9 days at 25°, but is stable indefinitely when frozen at −20°.

Di-*tert*-butyliminoxy is the first isolated example of a large number of iminoxy radicals hitherto observed only in solution.[10,15–18] The behavior of this compound can be determined leisurely and in the absence of the reagents of formation. We hope that further study of this radical will shed light on the properties of less stable members of its class.

(10) We have observed analogous behavior with some hydroxylamines, which give mass spectra identical with those of the corresponding nitroxides.
(11) J. R. Thomas, *J. Amer. Chem. Soc.*, **86**, 1446 (1964).
(12) From the maximum error in the plot we calculate that K_{eq} must be greater than 10 *M*.
(13) Both values are somewhat larger than that predicted (2.42) from the Boltzmann equation over this temperature range.
(14) The nmr of a decomposed sample displayed eight singlets of different intensities between δ 1.1 and 1.6. The major product (~45%) is di-*tert*-butyl ketone.
(15) B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc. B*, 981 (1967), and preceding papers.
(16) M. Bethoux, H. Lemaire, and A. Rassat, *Bull. Soc. Chim. Fr.*, 1985 (1964).
(17) W. M. Fox and M. C. R. Symons, *J. Chem. Soc. A*, 1503 (1966), and preceding papers.
(18) L. Burlamacchi and E. Tiezzi, *Gazz. Chim. Ital.*, **99**, 1313 (1969).
(19) NRC Postdoctoral Fellow, 1969–1971.
(20) NRC Postdoctoral Fellow, 1971–1972.

J. L. Brokenshire,[19] G. D. Mendenhall,[20] K. U. Ingold*
National Research Council of Canada
Ottawa, Canada K1A OR9
Received July 6, 1971

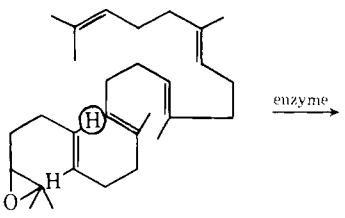
Formation of A/B *cis*- and *trans*-19-Norlanosterols by Enzymic Cyclization of 6′-Norsqualene 2,3-Oxide

Sir:

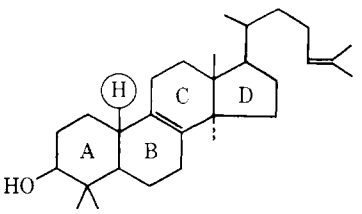
Replacement of an individual methyl by hydrogen at position 15,[1a] 10,[1b] or 6[2] in squalene 2,3-oxide does not preclude cyclization to a norlanosterol by lanosterol squalene 2,3-oxide cyclase. While such transformations are no longer novel, the enzymic formation of skeletal or stereoisomeric lanosterol analogs from squalene 2,3-oxide variants is noteworthy. We now report that 6′-norsqualene (I) cyclizes enzymically not only to the A/B *trans*-19-norlanosterol II, but also to the A/B cis isomer III.[3]

Radiolabeled *all-trans*-oxide I was obtained by overall reductive coupling of *trans,trans*-farnesyl bromide with stereoselectively prepared allylic bromide IV.[4]

(1) (a) E. E. van Tamelen, R. P. Hanzlik, K. B. Sharpless, R. B. Clayton, W. J. Richter, and A. L. Burlingame, *J. Amer. Chem. Soc.*, 90, 3284 (1968); (b) E. E. van Tamelen, R. P. Hanzlik, R. B. Clayton, and A. L. Burlingame, *ibid.*, **92**, 2137 (1970).
(2) That an individual methyl at C-6 is not essential for enzymic cyclization was mentioned, in a broader context, by E. E. van Tamelen and J. H. Freed, *ibid.*, **92**, 7206 (1970). Recently, E. J. Corey, A. Krief, and H. Yamamoto (*ibid.*, **93**, 1493 (1971)) reported the hog sterol cyclase catalyzed conversion of 6′-norsqualene 2,3-oxide to a single product, considered to be 19-norlanosterol on the strength of mass spectral analysis of the sterol, dihydrosterol, and its ene-7,11-dione. However, no stereochemical assignment or identification of product as either of the sterols II or III was possible on the basis of their published data.
(3) These epimers are believed to possess the lanosterol stereochemistry at centers other than C-10, since (1) the nmr spectral properties are very similar to those of lanosterol and its stereochemical analogs, and (2) various other squalene oxide modifications are enzymically converted to products proved to be in the lanosterol stereochemical class. See E. E. van Tamelen and J. H. Freed[2] and preceding papers in this series.
(4) Alkylation of the dianion of 3-butyn-1-ol[5a] with β-bromopropionaldehyde ethylene acetal afforded the heptynol i,[6] reduction of which with sodium–liquid ammonia provided the *trans*-heptenol ii (X = OH).[6] Treatment of the corresponding *p*-toluenesulfonate with anhydrous lithium bromide in acetone gave the *trans*-heptenyl bromide

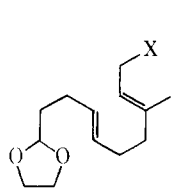


I

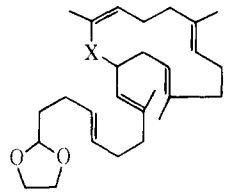


II, A/B trans
III, A/B cis

Alkylation in benzene (25°) of tri-*n*-butylphosphine with IV gave the oily quaternary phosphonium bromide V (one spot on tlc), which was converted (in THF, −75°) to the ylide by treatment with phenyllithium in ether and then by C-alkylation (≤15° with excess farnesyl bromide) to the new phosphonium salt VI (85%, one spot on tlc). On reduction with lithium ethylamine (−75°), VI afforded pentaenal acetal VII (70%, crude). Pure *all-trans*-VII,[6] a clear oil, was obtained *via* its thiourea clathrate and subsequent silver nitrate–silica gel column chromotography: nmr[8] δ 1.60 (12 H, broad singlet, 4 trans CH_3's), 1.68 (3 H, broad singlet, 1 cis CH_3), *ca.* 1.7 (2 H multiplet), 2.05 (18 H, multiplet), 3.90 (4 H multiplet), 4.85 (2 H, triplet, J = 4.5 Hz), 5.15 (4 H, multiplet), 5.23 (2 H, multiplet); mass spectrum parent ion, *m/e* 414.3493. The free aldehyde was generated quantitatively from VII by treatment with dilute $HClO_4$ in THF–H_2O, for 48 hr: nmr δ 1.60 (12 H, broad singlet), 1.68 (3 H, singlet), 2.0 (16 H, multiplet) 2.4 (4 H, multiplet), 5.15 (4 H, multiplet), 5.45 (2 H, multiplet), 9.75 (1 H, triplet, –CHO). The aldehyde[9] was tritiated by exchange with acidic ^3H_2O and then treated with diphenylsulfonium isopropylide[10] in THF (75°) to give the desired ^{3}H-*dl*-epoxide I (65%):[9] nmr[8] δ 1.18 and 1.22 (two 3 H singlets, oxirane CH_3's), *ca.* 1.6 (2 H, multiplet), 1.58 (12 H, broad singlet), 1.66 (3 H, broad singlet), 2.0 (18 H, multiplet), 2.52 (1 H, triplet, J = 6 Hz), 5.10 (4 H, multiplet, 5.40 (2 H, multiplet); mass spectrum parent ion, *m/e* 412.3702.

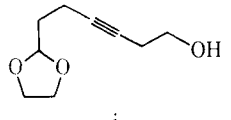


IV, X = Br
V, X = +P(*n*-C_4H_9)$_3$

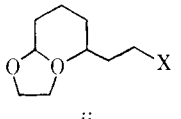


VI, X = +P(*n*-C_4H_9)$_3$
VII, X = H

ii (X = Br).[6] The Grignard reagent corresponding to the latter was converted by means of tri-*n*-butylphosphine copper(I) iodide to the homoallylcopper complex, which was added to methyl 2-butynoate in THF, giving *trans,trans*-diene ester ii [X = C(CH_3)=CHCOOCH_3][6] in



i



ii

31% yield from ii (X = Br) (isolated and purified by column chromatography): nmr *inter alia* δ 2.12 (3 H doublet, C-3 CH_3), 5.58 (1 H multiplet, C-2 hydrogen). Aluminum hydride reduction led to the corresponding alcohol [X = C(CH_3)=CHCH_2OH] (84%, pure by analytical glc): nmr *inter alia* δ 1.64 (3 H singlet, C-3 CH_3 on trans C=C). Lee halogenation with carbon tetrabromide and triphenylphosphine in CH_2Cl_2 gave the corresponding trans,trans C=C), which was used in the coupling procedure.[7]

Hydrogenation of A-Ac (Pt-EtOAc) to AH_2-Ac, followed by sequential LAH reduction and TMSCl–pyridine treatment, gave AH_2-TMSE. Glc retention time comparisons[12] (R_c: LH_2-TMSE, 2.28; AH_2-TMSE, 2.20) are consistent with the presence of one less CH_3 in A than in L, and of a saturated side chain in AH_2. The mass spectrum (gc-mass spectral, 20 eV) of AH_2-Ac displays the molecular ion at

By methods previously described,[11] 3.00–4.00 mg of ^{3}H-I (8.7 × 10^4 dpm/μg) was incubated with *ca.* 40–60 ml of rat liver cyclase solution for 45–60 min at 37°. Boiled enzyme preparations served as controls. After extraction with MeOH (recovery of radioactivity, ~90%), tlc on silica gel (ethyl acetate–hexane) separated unchanged epoxide from sterol products (4.2–9.5 × 10^6 dpm), which migrated (R_f = 0.27–0.40) similarly to lanosterol. Multiple development on tlc completely separated the steryl acetate into two components: A–Ac and B–Ac (9 and 90% of recovered radioactivity, respectively). The trimethyl silyl ethers (TMSE) on glc[12] gave *R* cholestane: A–TMSE, 3.01; B–TMSE, 2.62; lanosterol–TMSE, 3.39. Sterols A and B have been obtained with efficiencies as high as 10 and 30% (squalene 2,3-oxide → lanosterol = 100%), respectively, but in ratios which depend on incubation conditions. Structure II is assigned to product A on the basis of chemical and spectral properties which parallel those of lanosterol and previously obtained analogs.[1] Time-averaged 100-MHz pmr spectra ($CDCl_3$–TMS solution) of A and A–Ac were identical (δ ±0.01) with the corresponding spectra of lanosterol (L) and L–Ac,[1] except that: (1) the signal for the 19-CH_3 in L (δ 1.01) is missing in A and A–Ac, and (2) the chemical shifts of the 30,31-CH_3 pairs in L appear at δ 0.99 and 0.82, while those in A fall at 1.02 and 0.77, respectively. Since the Δδ for 30-CH_3 (−10 to −12.5) and 31-CH_3 (+7 to +7.5) on acetylation of L and other 4,4-dimethyltriterpenes and sterols is diagnostic for the A–B trans ring system,[13,14] the corresponding Δ values (−12 and +8) for acetylation of A indicate its A–B trans arrangement.

(5) (a) D. E. Ames, A. N. Covell, and T. G. Goodburn, *J. Chem. Soc.*, 5889 (1963); (b) G. Büchi and H. Wüest, *J. Org. Chem.*, **34**, 1122 (1969).

(6) Correct carbon–hydrogen analyses were exhibited by this substance.

(7) E. H. Axelrod, G. M. Milne, and E. E. van Tamelen, *J. Amer. Chem. Soc.*, **92**, 2139 (1970).

(8) 60-MHz spectrum measured on $CDCl_3$ solution, TMS standard.

(9) Corey, Krief, and Yamamoto[2] reported preparation of these substances by a different synthetic pathway.

(10) E. J. Corey and W. Oppolzer, *J. Amer. Chem. Soc.*, **86**, 1899 (1964); R. G. Nadeau and R. P. Hanzlik, *Methods Enzymol.*, **15**, 346 (1969).

(11) E. E. van Tamelen, K. B. Sharpless, R. Hanzlik, R. B. Clayton, A. L. Burlingame, and P. C. Wszolek, *J. Amer. Chem. Soc.*, **89**, 7150 (1967).

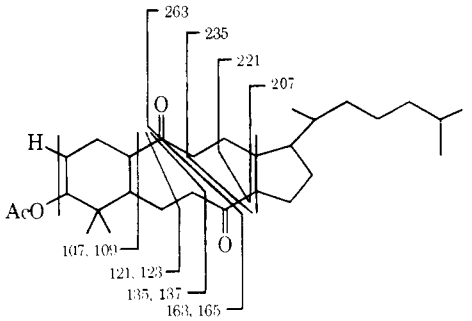
(12) 5% DEGS at 200°.

(13) A. I. Cohen, D. Rosenthal, G. W. Krakower, and J. Fried, *Tetrahedron*, **21**, 3171 (1965).

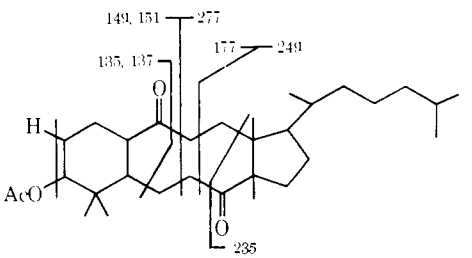
(14) F. Hemmert, B. Lacoume, J. Levisalles, and G. R. Pettit, *Bull. Soc. Chim. Fr.*, 976 (1966); F. Hemmert, A. Lablache-Combier, B. Lacoumbe, and J. Levisalles, *ibid.*, 982 (1966).

m/e 456, and closely resembles that of LH_2–Ac, but with corresponding peaks 14 mass units lower.

To establish the presence of the 10-H and the $\Delta^{(8,9)}$ double bond, AH_2–Ac was oxidized with RuO_4 to the secodiketone AH_2O_2–Ac (VIII), a product analogous to those similarly[1a] secured from LH_2–Ac and 18-nor-LH_2–Ac. A high resolution mass spectrum (70 eV) of AH_2O_2–Ac revealed the parent ion at *m/e* 488.3865 ($C_{31}H_{52}O_4$) with a base peak at *m/e* 95. The major fragmentations are shown in VIIIa and VIIIb. Transannular condensation of VIII to the desmethyl abeo

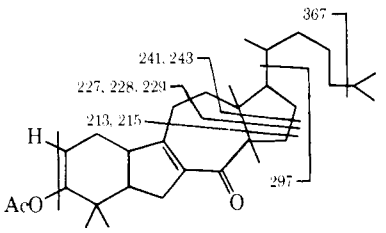


VIIIa

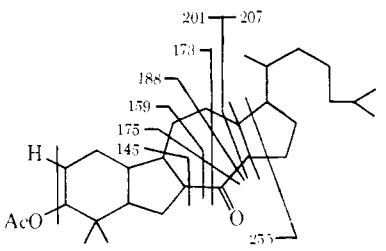


VIIIb

triterpenoid IX (R_c = 4.31) occurred in concentrated HCl–HOAc or during glc. Mass spectral fragmentations indicative of structures IXa and IXb confirm the assignment II to the original norsterol A.



IXa



IXb

The mass spectrum of BH_2-TMSE closely resembled that of AH_2–TMSE. The desmethyl abeo compound derived from the RuO_4 oxidation product of BH_2–Ac was identical in mass spectral and glc properties with that obtained from AH_2–Ac. Evidently the A and B structures must differ in their relative configurations at C-10, since in the derived secodiketone an enolizable proton at this site may epimerize during the trans annular condensation to the abeo compound IX.[15] Since nmr data call for an A–B trans juncture in A, we conclude that B is the corresponding A–B cis counterpart III. In corroboration, the pmr properties of *C*-methyls in the A series (*vide supra*) differ markedly from those in B. In keeping with trends previously observed for *cis*-decalins,[16] the chemical shifts in B (A–B cis) fall at distinctly lower fields than those in the A (A–B trans) cases; thus, in B–Ac, nonallylic methyls appear at δ 1.05, 1.11, 1.17, and 1.19.[9,17]

Acknowledgment. The authors are indebted to Dr. J. R. Trudell, Stanford Medical Center, for mass spectral data and interpretations, Dr. M. Bramwell, Dr. Lois Durham, and Mrs. K. S. Rozema-Meyer for nmr determinations, and Mr. K. Hovius for technical assistance. Financial support was provided by the Netherlands government (J. A. S.), National Institutes of Health (GM 10421 to E. E. v. T.), American Heart Association (grant-in-aid), and a USPHS Research Scientist Award (MH 47413) (to R. B. C.).

(15) Assignment of C-10 stereochemistry in the abeo compound IX is not possible on the basis of available information.

(16) J. I. Musher, *J. Amer. Chem. Soc.*, **83**, 1146 (1961).

(17) This work, started at the University of Groningen and completed at Stanford University, is detailed and discussed in the doctoral thesis submitted to the University of Groningen (April 1971) by J. A. S.

* Address correspondence to this author at the Department of Chemistry, Stanford University.

E. E. van Tamelen,* J. A. Smaal
Department of Chemistry, University of Groningen
Groningen, Netherlands
Department of Chemistry, Stanford University
Stanford, California 94305

R. B. Clayton
Department of Psychiatry, Stanford University
Stanford, California 94305

Received April 30, 9171

Importance of σ-Bonding Effects in the Photolysis of *trans*-Difluorobis(ethylenediamine)chromium(III)

Sir:

The controversy concerning the explanation, or even correlation, of the facts thus far determined in studies on the photoaquation of Cr(III) complexes continues to be vibrant.[1–5] At the center of current discussion are the "rules" that Adamson proposed in 1967.[6] The first of these predicts the stoichiometry of the product of photoaquation of Cr(III) complexes by stating that the "axis having the weakest average crystal field will be the one labilized." Implicit in any attempt to rationalize this rule is, in our opinion, the assumption that photoaquation takes place from the lowest lying quartet excited state. In at least one case

(1) E. Zinato, R. D. Lindholm, and A. W. Adamson, *J. Amer. Chem. Soc.*, **91**, 1076 (1969).

(2) P. Riccieri and H. L. Schläfer, *Inorg. Chem.*, **9**, 727 (1970).

(3) V. Balzani and V. Carassiti, "Photochemistry of Coordination Compounds," Academic Press, New York, N. Y., 1970.

(4) M. F. Manfrin, L. Moggi, and V. Balzani, *Inorg. Chem.*, 10, 207 (1971).

(5) A. D. Kirk, *J. Amer. Chem. Soc.*, **93**, 283 (1971).

(6) A. W. Adamson, *J. Phys. Chem.*, 71, 798 (1967).