other hand, our own and previous data of others[6] reveal that in the presence of a C-8 β(axial) substituent the C-10 methyl signal appears at distinctly lower field (Δ = 0.076–0.25 ppm) than in the presence of the corresponding C-8 α(equatorial) substituent. The identity of the C-10 methyl chemical shifts in **1** and **11** thus indicates like chirality at C-8 in the pair of compounds.

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(6) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964.

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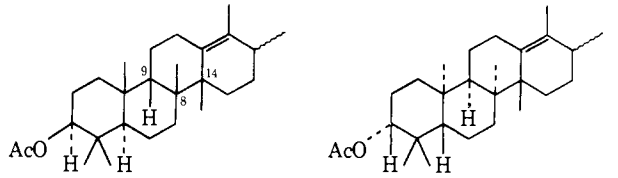
Cyclization of a Terpenoid Diene with Preformed A–B–D Rings and Its Significance for the Mechanism of Terpenoid Terminal Epoxide Cyclizations

Sir:

In order to illuminate the conformational and mechanistic course of terpenoid terminal epoxide cyclizations, of which enzymic formation of lanosterol is the most notable example, it became of interest to study the further cyclization of tricyclic **1**,[1] which possesses a preformed ring sequence, substitution pattern, and stereochemical arrangement appropriate for conversion *via* tetracycle **2** (R = CH_3) to the (pentanor) lanosterol system.[2] Although nonenzymic BF_3 or $SnCl_4$ catalyzed cyclization of epoxide **3** (R = $(CH_2)_3CH(CH_3)_2$) in CH_3NO_2 generates, presumably through chair–boat–chair folding, 24,25-dihydo-$\Delta^{13(17)}$-protosterol and 24,-25-dihydroparkeol (convertible to 24,25-dihydrolanosterol),[3] laboratory cyclization of **1** or its A–B antipode **1A** under similar conditions provides no detectable amount of cyclopentanohydrophenanthrene-type product. On treatment at room temperature with H_2SO_4–CH_3NO_2, H_2SO_4–HCO_2H, or $BF_3\cdot(C_2H_5)_2O$–CH_3NO_2, the crystalline member of the **1–1A** pair generated in up to 75% yield isomer Y, mp 141–143.5°; vpc R_f = 7.2 min on 3% OV-17 at 235°; tlc R_f = 0.46 on silica gel; ir (CCl_4), cm^{-1} 2950, 2870, 1735, 1465, 1373, 1242, and 1025; nmr ($CDCl_3$) δ 0.90 (m, 9–12, CH_3), 0.97 (s, 3, CH_3), 1.10 (s, 3, CH_3), 1.62 (m, 3–6, C=CCH$_3$), 2.05 (s, 3, CH_3CO_2–), 2.70 (broad m, 1, C=CCH), 4.48 (broad m, 1, –OCH); mass spectral (20 eV) *m/e* (rel intensity) M^+ 400 (3), 149 (100), 136 (45), 121 (8), 107 (4), 93 (2); (70 eV) M^+ 400 (3), 189 (2), 161 (1), 149 (100), 136 (34), 121 (18), 107 (11), 93 (9), 81 (6), 69 (6), 43 (11); calcd for $C_{27}H_{44}O_2$, 400.3340; found, 400.3352. Ruthenium tetroxide oxidation of Y afforded in high yield a diketone, $C_{27}H_{44}O_4$, the nmr and high resolution mass spectra of which revealed, *inter alia*, the presence of one methyl ketone function and the absence of an aldehyde unit; nmr ($CDCl_3$) δ 0.85 (s, 3, CH_3), 0.87 (s, 3, CH_3), 1.04 (broad, s, 7.5, CH_3), 1.10 (s, 4.5, CH_3), 2.05 (s, 3, CH_3CO_2–) 2.13 (s, 3, CH_3-CO–), 4.48 (broad m, 1, –OCH); mass spectral (20 eV) *m/e* (relative intensity) M^+ 432 (<1), 389 (16), 372 (6), 334 (2), 329 (85), 311 (39), 243 (37), 189 (74), 182 (30), 169 (100), 151 (95), 135 (77), 121 (88), 107 (89), 71 (98), 55 (14); high resolution mass spectral (70 eV) 414 (1, $C_{27}H_{42}O_3$), 389 (27, $C_{25}H_{41}O_3$), 372 (8, $C_{25}H_{40}O_2$), 357 (3, $C_{24}H_{37}O_2$), 334 (2, $C_{21}H_{34}O_3$), 329 (92, $C_{23}H_{37}O$), 311 (10, $C_{23}H_{35}$), 189 (35, $C_{14}H_{21}$), 182 (14, $C_{11}H_{18}O_2$), 169 (73, $C_{10}H_{17}O_2$), 71 (52, C_4H_7O), 55 (7, C_3H_3O), 43 (100, C_2H_3O).

Subjection of the noncrystalline **1–1A** diastereoisomer to the action of $BF_3\cdot(C_2H_5)_2O$–CH_3NO_2 resulted in formation of the closely related isomer Z, mp 198–200°. Mass, nmr, and ir spectral studies of Z and its RuO_4 oxidation product lead to the conclusion that Z is stereoisomeric with Y. By reason of detailed analysis of the above and other spectral information, including comparison with mass spectra of $\Delta^{13(18)}$-oleanene,[4] isoeuphenyl acetate, and its RuO_4 oxidation product,[5] we propose structures **4–5** for cyclization products Y and



4 **5**

Z, with stereochemical assignments based on the most reasonable conformational course of each cyclization, after which rearrangement (*e.g.*, 6 → 7 → 8 → 4–5) ensues.[6–8]

Quite apart from the nature of products actually formed from **1** and **1A**, nonformation of the protosterol, lanosterol, or parkeol system signifies that tricyclization (*vide supra*) of epoxide **3** does not involve the type of carbonium ion which arises by C-7 portonation of **1** or **1A** and proceeds to **4** or **5**. On the basis of the preferred conformation of starting **1**, this carbonium ion would possess the structure, the stereochemistry, and the initial, most stable conformation portrayed in **9** (R

(1) E. E. van Tamelen, A. Grieder, and R. G. Lees, *J. Amer. Chem. Soc.*, **96**, 2253 (1974).

(2) "Pentanorlanosterol" is formed by enzymic cyclization of either terminal epoxide **3** (R = CH_3) [E. E. van Tamelen and J. H. Freed, *J. Amer. Chem. Soc.*, **92**, 7206 (1970)]; or pentanorsqualene 1,2-oxide [R. J. Anderson, R. P. Hanzlik, K. B. Sharpless, E. E. van Tamelen, and R. B. Clayton, *Chem. Commun.*, 53 (1969)].

(3) E. E. van Tamelen and R. J. Anderson, *J. Amer. Chem. Soc.*, **94**, 8225 (1972).

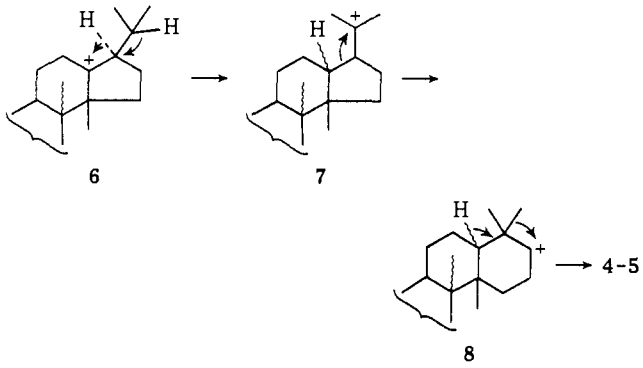
(4) H. Budzikiewicz, J. M. Wilson, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 3688 (1963).

(5) E. E. van Tamelen, G. M. Milne, M. I. Suffness, M. C. Rudler-Chauvin, R. J. Anderson, and R. S. Achini, *J. Amer. Chem. Soc.*, **92**, 7202 (1970).

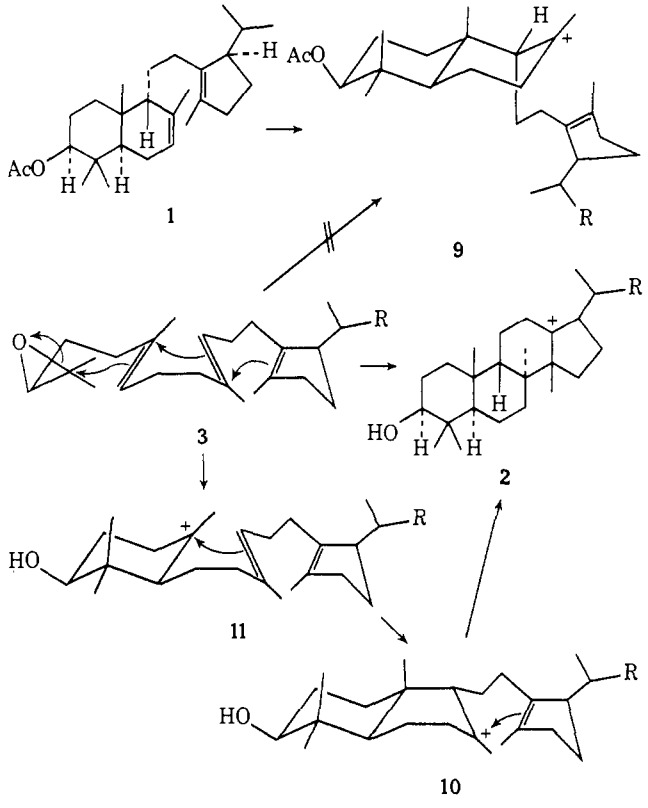
(6) Similar acid-promoted ring expansions have been reported: (a) P. de Mayo, "The Higher Terpenoids," Interscience, New York, N. Y., 1959, pp 182–185; (b) M. Uskokovic, M. Gut and R. I. Dorfman, *J. Amer. Chem. Soc.*, **82**, 3668 (1960).

(7) That no epimerization at C-9 occurs during formation of Y and Z is suggested by the behavior of **1–1A** in $BF_3\cdot(C_2H_5)_2O$ in *CHCl*$_3$. Under these conditions an equilibrium is established between (*inter alia*) **1** and its 1-isopropyl-3-methylcyclopentene isomer **13** as well as **1A** and the counterpart isomer **13A** (structural assignments based on preservation of nmr signal due to C-7 hydrogen and dissappearance of that due to a nonequivalent methyl in the isopropyl side chain of **1–1A**), after which cyclization begins. Separate cyclization of isolated **13** or **13A** with $BF_3\cdot(C_2H_5)_2O$–CH_3NO_2 gave rise to less than half the yields of Y or Z secured from **1** or **1A**, thus supporting the belief that Y and Z are direct products from **1** and **1A**, formed with preservation of AB stereochemistry.

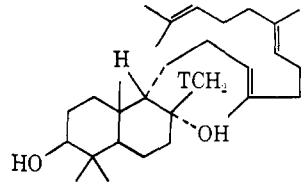
(8) In the 3-desoxy series it was shown that the C-8 tertiary alcohol corresponding to **1**, on treatment with various acids, merely dehydrates to Δ^7 diene, which then cyclizes to 3-desoxy, Y–Z counterparts.



= CH_3). In the nonenzymic formation of sterol from polyene epoxide **3**, therefore, the B–C portion of the cyclization must proceed in concert with the remainder of the overall process or must utilize a "frozen," less stable, ring B boat-like conformation, **10**, which does



not equilibrate with the conformationally isomeric **9** (R = $(CH_2)_3CH(CH_3)_2$). Taken together with previous conclusions regarding the synchronousness of the cyclization pathway by which the A–B rings are built up from acyclic terminal epoxide,[9] this new result allows the view that the *entire* A–B–C elaboration also is either wholly concerted or involves intermediate frozen mono- or bicyclic carbonium ion entities (**10–11**). Assuming that biological systems can, in a suitable environment, avail themselves of any purely organic behavior, one may surmise that, especially with the help of an enzyme system, this same mechanistic characterization applies to the formation of sterol from squalene 2,3-oxide.[10,11] In order to detect a stable ground-state bicyclic intermediate in lanosterol synthesis, radioactive **10**[1] was assayed as a substrate for the cyclase system, both in whole animal experiments and with isolated enzyme, using procedures already described.[12] Lack of conversion of **12** to radiolabeled lanosterol, under conditions where a variety of unnatural squalene oxide variants are transformed to lanosterol-like products, is consistent with the mechanistic views presented herein.



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(9) E. E. van Tamelen and J. P. McCormick, *J. Amer. Chem. Soc.*, **91**, 1847 (1969).

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

(11) G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, 77, 5068 (1955).

(12) J. D. Willett, K. B. Sharpless, K. E. Lord, E. E. van Tamelen, and R. B. Clayton, *J. Biol. Chem.*, **242**, 4182 (1967).

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Selective Reduction of the Benzene Ring in Quinolines and Isoquinoline

Sir:

It is generally known[1] that partial hydrogenation of quinolines and isoquinolines involves preferentially the nitrogen-containing ring giving rise to 1,2,3,4-tetrahydroquinolines and -isoquinolines. Only when the pyridine ring is substituted is there some concomitant, but by no means predominant, reduction of the benzene ring.[2]

We now wish to report a selective reduction of the benzene moiety in quinolines and isoquinoline leading to the 5,6,7,8-tetrahydro compounds in yields ranging from 53 to 98%. The method calls for use of a strongly acid medium (such as concentrated hydrochloric acid), a platinum oxide catalyst, and long hydrogenation times.[3] A typical experiment is as follows. The quinoline or isoquinoline (50 mmol) was dissolved in 40 ml of cold concentrated (37–38%) hydrochloric acid, 750 mg of PtO_2 (83%, Engelhard Inc.) was added, and the mixture was hydrogenated at room temperature and 50 psi H_2 in a Parr apparatus. When the theoretical amount of hydrogen had been consumed,[4] the catalyst

(1) (a) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, New York, N. Y., 1967, p 385; (b) M. Freifelder, "Practical Catalytic Hydrogenation," Wiley-Interscience, New York, N. Y., 1971, p 601; (c) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, p 106.

(2) J. von Braun, W. Gmelin, and A. Schultheiss, *Ber.*, **56**, 1338 (1923); see also ref 1b.

(3) The same recipe has previously been reported to lead to *cis*-decahydroquinoline when even longer reduction times were employed: H. Booth and A. H. Bostock, *J. Chem. Soc., Perkin Trans. 2*, 615 (1972).

(4) Reduction time varies between 30 (quinoline) and 130 hr (6- and 8-methylquinoline). Much longer reduction times and elevated temperatures (~70°) lead to high yields of *cis*-decahydroquinolines (see also ref 3).