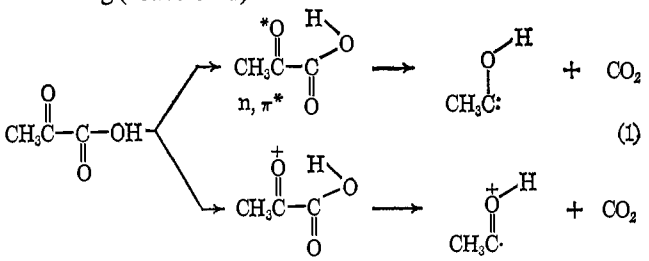
spectrometer to yield the ion fragments C_2H_4O and C_2H_3OD from pyruvic acid and pyruvic acid-OD, respectively. Since hydrogen rearrangement *via* a five-membered transition state is uncommon in the mass spectra of carbonyl compounds,[6] the analogy between the photolysis and mass spectral decomposition is striking (reaction 1).



(1)

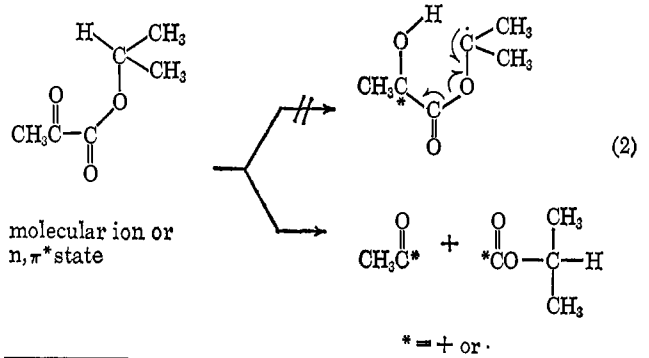
The photolysis of $CH_3COCO_2CH(CH_3)_2$ (**1**) in the vapor phase[7] or in benzene solution[8] yields acetone and carbon monoxide as major products and only a low yield of acetaldehyde. Leermakers[8] has explained these and related results by proposing a mechanism involving α cleavage as the primary photochemical act followed by loss of CO rather than the intuitively reasonable type II photorearrangement. The mass spectral behavior of the molecular ions of **1** and $CH_3COCO_2CD(CH_3)_2$ (**2**), shown in Table II, appears to

Table II. Partial Monoisotopic Mass Spectra (75 ev) of **1** and **2**[a]

$CH_3COCO_2CH(CH_3)_2$ (1)		$CH_3COCO_2CD(CH_3)_2$ (2)	
%	Ion	%	Ion
0.4	$C_6H_{10}O_3$	0.5	$C_6H_9DO_3$
4.1	$C_4H_7O_2$	4.6	$C_4H_6DO_2$
4.4	C_2H_5O	3.6	C_2H_4DO
100	C_2H_3O	100	C_2H_3O

[a] Analysis conditions given in Table I, except that inlet and source temperatures were 165°. [b] Greater than 98% d_1. The sample was kindly donated by Professor P. A. Leermakers.

be quite analogous to the photochemical behavior of their n,π^* excited states. A striking feature of the mass spectra is the conspicuous absence of $C_3H_4O_2$, $C_3H_3DO_2$, C_2H_4O, and C_2H_3DO ions. The $C_3H_4O_2$ and $C_3H_3DO_2$ ions in the spectra of **1** and **2**, respectively, would correspond to products of the very general McLafferty rearrangement,[6] and these ions might be expected to decompose further to $C_2H_4O\cdot^+$ and $C_2H_3DO\cdot^+$ by analogy to reaction 1.[9] Indeed, the ions



(2)

$C_4H_7O_2^+$, $C_4H_6DO_2^+$, and $C_2H_3O^+$ serve as evidence of the importance of cleavage of the CO–CO bond (reaction 2).

Further studies of these and other systems are being pursued in order to understand better the chemistry of molecules ionized by electron impact and to determine how the structures and reactivities of electronically excited states and molecular ions may be correlated.

(6) F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, Inc., New York, N. Y., 1966, p 123 ff.
(7) P. A. Leermakers, M. E. Ross, G. F. Vesley, and P. C. Warren, *J. Org. Chem.*, 30, 914 (1965).
(8) P. A. Leermakers, P. C. Warren, and G. F. Vesley, *J. Am. Chem. Soc.*, 86, 1768 (1964).
(9) Also there are no $C_3H_5O_2^+$ ions which might be expected by analogy to the double hydrogen rearrangement common in esters.[6]

(10) Alfred P. Sloan Fellow, 1966–1968.
(11) National Institutes of Health Predoctoral Fellow, 1966–1967.

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On the Mechanism of Lanosterol Biosynthesis from Squalene 2,3-Oxide

Sir:

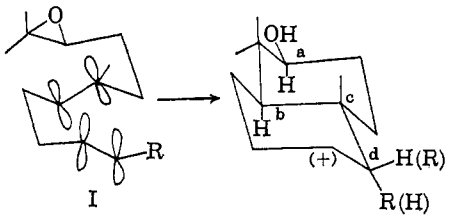
In connection with our continuing program concerned with the organic and biological chemistry of terpenoid terminal epoxides,[1] we wish now to present new findings and considerations which further delineate the role of squalene 2,3-oxide in the biosynthesis of lanosterol and therefore other members of the sterol class.

Although recent experiments in these laboratories[2] and elsewhere[3] indicated that ^{14}C-labeled squalene 2,3-oxide[1a] can be biosynthesized and also act as a natural triterpene source of lanosterol and cholesterol, the fate of *oxygen* in the original epoxide moiety was left unsettled. The following experiments elucidate this matter. Squalene 2,3-oxide-^3H,^{18}O (4150 dpm/μg, 30% ^{18}O by mass spectral comparison[4] of normal and ^{18}O-labeled oxides) was prepared from squalene-^3H (4350 dpm/μg) by the action of N-bromosuccinimide[1a] in 3:1 THF–water (30% ^{18}O-labeled) and was incubated anaerobically with washed microsomes of rat liver in 0.08 *M* potassium phosphate buffer, pH 7.4. The sterol fraction was isolated, and lanosterol (R_f, 0.43; 200,000 dpm) was separated by tlc on silica gel in 15% ethyl acetate–hexane. Purification by glpc of the trimethyl silyl ether on a 6 ft × 0.25 in. column of 5% Carbowax on Chromosorb W at 235° gave lanosterol trimethylsilyl ether (retention time relative to cholestane = 3.7) which on mass spectral analysis was found to contain 29% excess ^{18}O. The retention of the original epoxy oxygen as the 3β-hydroxyl group of lanosterol supports the mechanism proposed earlier[2,3] for the proton-initiated enzymic cyclization of squalene 2,3-oxide to lanosterol. Moreover, our inability to demonstrate any cofactor requirements for the microsomal enzyme system is also consistent with the proposed mechanism.

(1) Initial publications in this series: (a) E. E. van Tamelen and T. J. Curphey, *Tetrahedron Letters*, 121 (1962); (b) E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *J. Am. Chem. Soc.*, 85, 3295 (1963).
(2) E. E. van Tamelen, J. D. Willett, R. B. Clayton, and K. E. Lord, *ibid.*, 88, 4752 (1966).
(3) E. J. Corey and W. E. Russey, *ibid.*, 88, 4750 (1966), have also recorded the biochemical conversion of squalene 2,3-oxide[1a] to sterols.
(4) K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 204–205.

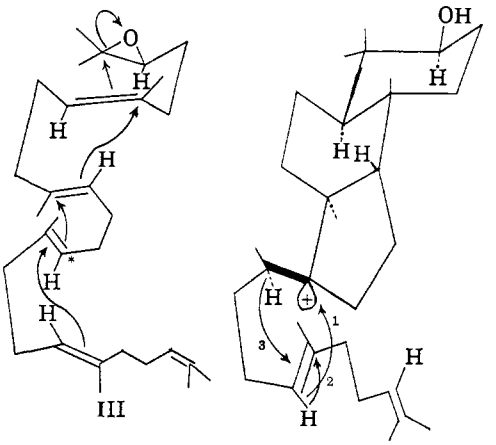
In an effort to locate additional intermediates in the over-all squalene → lanosterol conversion, other oxidation products of squalene were prepared and tested for incorporation. Through the use of techniques previously described,[2] labeled lanosterol was not detected after incubation of ^{3}H-labeled 2,3-dihydrosqualene-2,3-diol,[5] 2,3-dihydrosqualen-2-ol,[6] and squalene 2,3:22,23-dioxide[1a] with rat liver homogenate.

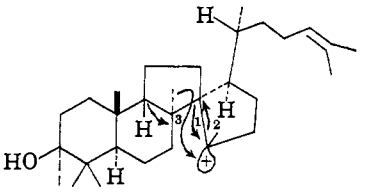
Previous chemical investigations of the synthesis and cyclization of terpenoid terminal epoxides have revealed striking similarities between nonenzymic behavior on the one hand and squalene–squalene oxide biochemistry on the other. First, the unique, highly selective terminal oxidation of squalene by NBS in aqueous–organic solution[1a] simulates the observed biological conversion of squalene to its 2,3-oxide.[2,3] Second, laboratory cyclization of sesqui-[1b,7] or diterpenoid[8] terminal epoxides (I) to 3-hydroxylated polycyclic systems (II) with either "natural" (a-b-c-d *cis, trans,trans*) or biosynthetically attractive[9] (a-b-c-d *cis,trans,cis*) stereochemistry closely resembles genera-

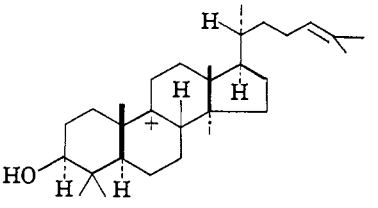


tion of the AB moiety of lanosterol and other polycyclic terpenes in living systems. Third, just as most intermediary mono-, bi-, or tricyclic olefins which would have to reprotonate before enzymic conversion to lanosterol are ruled out,[10,11] monocyclohexenic products resulting from nonenzymic partial cyclization of sesquiterpenoid terminal epoxides are not intermediates in the conversion of these acyclic epoxides to 3-hydroxylated bicyclic (II) materials.[7,12]

The above parallelism encourages us to attempt further extrapolation from the purely organic to the biochemical area. Thus, it is noted that in epoxide cyclizations of type I → II, the π-electron orbitals of the closest olefinic bond are ideally directed in space for interaction with a developing empty orbital at the more highly substituted position of the epoxide unit, implying that a combined oxide ring opening–carbocyclization process having SN2 character is easily possible and may well be anchimerically assisted. By superimposition of this epoxide cyclization picture on the now familiar portrayal of lanosterol (or presterol) formation from acyclic precursor,[9,13] mechanism III (→ → VI) emerges. Present biochemical evidence does not distinguish between a concerted cyclization and a stepwise annelation process involving conformationally rigid carbonium ions or the corresponding tertiary alcohols (or derivatives thereof, such as phosphates). An alternative possibility which is also completely consistent with the body of biochemical tracer







experiments[14] features cyclization of squalene oxide to a tricyclic intermediate with a five-membered C ring, followed by hydrogen migration to IV, this over-all process being identical (but not necessarily with regard to stereochemistry) with that observed during the nonenzymic cyclization of squalene oxide.[15] Completion of the biosynthetic scheme involves cyclization to a spiro system (IV → V) coupled with and succeeded by concerted hydrogen, methyl, and alkyl migration (V → VI).[16] Presentation of the above considerations should in no way be taken to indicate mechanistic preferences by us at the present time.

(5) Prepared by perchloric acid catalyzed ring opening of squalene oxide.

(6) Prepared by lithium aluminum hydride reduction of squalene oxide.

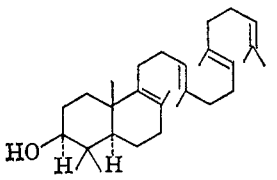
(7) E. E. van Tamelen, M. Schwartz, E. J. Hessler, and A. Storni, *Chem. Commun.*, 409 (1966); E. E. van Tamelen and R. M. Coates, *ibid.*, 413 (1966).

(8) E. E. van Tamelen and R. G. Nadeau, *J. Am. Chem. Soc.*, **89**, 176 (1967).

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

(10) T. T. Tchen and K. Bloch, *J. Am. Chem. Soc.*, **78**, 1516 (1956).

(11) Previous data[10] do not exclude (i) since the proton lost in its formation does not appear in any case in the final product, lanosterol.



i

(12) E. E. van Tamelen and E. J. Hessler, *Chem. Commun.*, 411 (1966).

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

(14) R. B. Clayton, *Quart. Rev.* (London), **19**, 168 (1965).

(15) E. E. van Tamelen, J. Willett, M. Schwartz, and R. Nadeau, *J. Am. Chem. Soc.*, **88**, 5937 (1966).

(16) Although somewhat lengthier, this alternative mechanism features conventional carbonium ion chemistry (including a well-precedented 1,3-hydrogen migration,[17] avoiding involvement of secondary carbonium ion (C*) in preference to tertiary.

Acknowledgment. The authors are grateful to the National Institutes of Health for financial support (GM 12493 and 10421). The mass spectral (^{18}O) determination was carried out by Dr. Heinrich Schnoes in the laboratories of A. Burlingame, University of California (Berkeley) and the enzymic incubations were skillfully carried out by Miss Kathryn E. Lord. One of us (R. B. C.) acknowledges a grant-in-aid from the American Heart Association.

(17) (a) S. Winstein and D. Trifan, *J. Am. Chem. Soc.*, **74**, 1154 (1952); (b) J. D. Roberts, C. C. Lee, and W. H. Saunders, *ibid.*, **76**, 4501 (1954); (c) G. J. Karabatsos and C. F. Orzech, *ibid.*, **84**, 2838 (1962); (d) P. S. Skell and M. Starer, *ibid.*, **84**, 3962 (1962); (e) A. A. Aboderin and R. L. Baird, *ibid.*, **86**, 2300 (1964).

(18) National Institutes of Health Postdoctoral Fellow.

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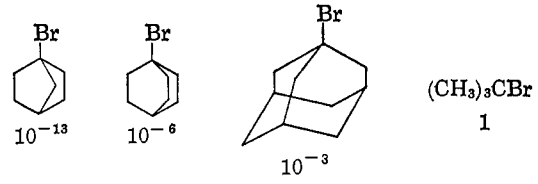
Received May 1, 1967

Solvolytic Reactivity of 1-Chlorobicyclo[1.1.1]pentane[1]

Sir:

It is generally observed that the reactivity of bridgehead halides decreases markedly as the size of the bridging rings decreases.[2] Thus, the reactivities of several bridgehead halides are



$(CH_3)_3CBr$
1

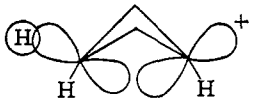
The changes in reactivity have been attributed to the difficulty in creating a planar carbonium ion at the bridgehead position, increasing deviation from planarity increasing the energy of the ion formed.[3]

A significant exception to the trend is found with 1-bromobicyclo[2.1.1]hexane, which reacts 10^7 more rapidly than 1-bromonorbornane.[4] We now wish to report that the next lower homolog, 1-chlorobicyclo[1.1.1]-pentane, is three times more reactive than *t*-butyl chloride and about 10^{14} more reactive than 1-chloronorbornane.

1-Chlorobicyclo[1.1.1]pentane was prepared by the photochlorination of bicyclo[1.1.1]pentane.[5] The products were the 1-chloro derivative (25%), the 2-chloro derivative (7%), the 1,3-dichloride (5%), the 2,2-dichloride (33%), the 1,2-dichloride (5%), and 3-methylenecyclobutyl chloride (25%). The predominant attack by chlorine atoms at the bridgehead position, as contrasted to norbornane,[6] appears to result from the marked deactivation of the methylene positions as compared with cyclohexane.[7]

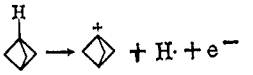
The 1-chloro derivative underwent solvolysis in 80% ethanol with rate constants of 3.03×10^{-5} sec^{-1} at 25° and 6.26×10^{-4} sec^{-1} at 50°, giving $\Delta H^{\ddagger} = 12.0$ kcal/mole and $\Delta S^{\ddagger} = +4$ eu. The products were 3-methylenecyclobutanol and its ethyl ether. Under the same conditions, the rate constant for *t*-butyl chloride was found to be 9.67×10^{-6} sec^{-1} at 25°.[8]

The high reactivity of the chloride may be attributed to the driving force for ring fragmentation, relieving considerable strain. However, the same is true with the bicyclo[2.1.1]hexane derivative which is 10^7 less reactive. An alternative explanation is derived from our examination of the energy of the cyclobutyl cation[11] using the CNDO method.[12] Here, we assume that the activated complex for the solvolysis still retains significant bonding to the leaving group, thus making appropriate a tetrahedral geometry for the reacting center. The previous calculations suggested that an equatorial leaving group would be strongly preferred over an axial leaving group because of the possibility of a cross-ring interaction with the former.



This is in good accord with the experimental observations.[9,10] An extension to the bicyclo[1.1.1]pentane case would seem favorable because of the collinear geometry of the bridgehead bonds and the extremely short cross-ring distance (1.8–1.9 A). The calculated energies for conversion of the corresponding hydrocarbon to the cation, a hydrogen atom, and an electron are indicated in Table I. It can be seen that the energy

Table I. Energy of Formation of Some Cations

Reaction	ΔE, au
$CH_4 \longrightarrow CH_3^+ + H\cdot + e^-$	0.9190
$C_2H_6 \longrightarrow C_2H_5^+ + H\cdot + e^-$	0.8230
$C_3H_8 \longrightarrow i\text{-}C_3H_7^+ + H\cdot + e^-$	0.7559
$i\text{-}C_4H_{10} \longrightarrow t\text{-}C_4H_9^+ + H\cdot + e^-$ (planar)	0.7004
$\longrightarrow t\text{-}C_4H_9^+ + H\cdot + e^-$ (pyramidal)	0.7766
	0.7299

for the bicyclo[1.1.1]pentane derivative is between that of the planar and pyramidal *t*-butyl cations. The results provide an explanation for the high reactivity of the bridgehead halides and for the formation of 3-methylenecyclobutanol as the product. Considerable charge is transferred to the 3 position as a result of

(1) This investigation was supported by the U. S. Army Research Office (Durham).

(2) *Cf.* R. C. Fort, Jr., and P. von R. Schleyer, *Advan. Alicyclic Chem.*, **1**, 284 (1966).

(3) P. D. Bartlett and L. H. Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939); W. von E. Doering, M. Levitz, A. Sayigh, M. Sprecher, and W. P. Whelan, *ibid.*, **75**, 1008 (1953); G. J. Gleicher and P. von R. Schleyer, *ibid.*, **89**, 582 (1967).

(4) K. B. Wiberg and B. R. Lowry, *ibid.*, **85**, 3188 (1963).

(5) We have previously reported the isolation and characterization of the 1- and 2-chlorides *via* the photochemical reaction of the hydrocarbon with *t*-butyl hypochlorite: K. B. Wiberg and D. S. Connor, *ibid.*, **88**, 4437 (1966).

(6) E. C. Kooyman and G. C. Vegter, *Tetrahedron*, **4**, 382 (1958).

(7) A comparison of the reactivity in chlorination of bicyclo[1.1.1]-pentane and other hydrocarbons will be presented subsequently.

(8) As might be expected based on our results with bicyclo[2.1.1]-hexyl 5-tosylate[9] and bicyclo[3.1.1]heptyl 6-tosylate,[10] 2-chlorobicyclo-[1.1.1]pentane is also quite reactive ($k = 1.16 \times 10^{-3}$ sec^{-1} at 100°). However, it is not as reactive as the 1-chloro derivative.

(9) K. B. Wiberg and R. Fenoglio, *Tetrahedron Letters*, 1273 (1963).

(10) K. B. Wiberg and B. A. Hess, Jr., *J. Am. Chem. Soc.*, **89**, 3015 (1967).

(11) K. B. Wiberg, *Tetrahedron*, in press.

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