Some New Chemical Properties of Unsaturated C_{18} Acids[†]

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In recent years many fields of chemistry have experienced surges of new life. New analytical methods have enabled things to be done that could not be done before, and new theoretical concepts have provided insight into previously inscrutable phenomena. The chemistry of fats or lipids has enjoyed its surge along with the rest.

Although my main concern in this Account is new chemical reactions of unsaturated C_{18} acids, especially several that involve neighboring group participation, I want to mention briefly some of the analytical methods that notably aid the lipid chemist. Gas chromatography is of course a great help, and is now being used even for complex molecules such as triglycerides with molecular weights of 1000 and above.[1] So also are column chromatography and thin layer chromatography; silver ion procedures which permit separation according to the degree of unsaturation are particularly useful.[2]

The development of powerful magnets and of high-frequency ^{1}H NMR (100, 220, and 300 MHz) has enabled the production of highly resolved spectra replete with structural information. With a 220-MHz spectrometer, almost all of the 31 isomeric octadecenoates can be distinguished. Also, knowledge of long-range deshielding effects now allows prediction of the ^{1}H NMR spectrum for almost any usaturated fatty acid.[3] ^{13}C NMR promises to provide not only structural information but also evidence of conformation and "mobility" of the acyl chains in lipid bilayers.

Enzymic reagents such as pancreatic lipase or phospholipase A, being more specific than ordinary hydrolysis catalysts, have made it possible to study the distribution of acyl groups in triacylglycerols and phosphoglycerides, and thereby to provide unique insight into the composition of such materials. Using such procedures in appropriate combinations, one can now determine the fatty acids attached at each of the three sites in glycerol. Most natural lipids show a marked selectivity in the distribution of acyl groups.

The most common natural fatty acids have an even number of carbon atoms per molecule and seldom contain functionalities other than cis (Z) olefinic saturation, which usually occurs in a methylene-interrupted pattern in polyenes (e.g., arachidonic acid,


arachidonic acid
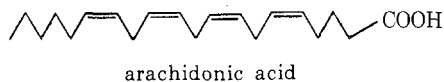
20:4). However, once an unusual feature such as an acetylenic group, an epoxide, or a cyclopropane ring appears, it is likely to be combined in many different ways with other structural features. Acids sharing a common structural feature can usually be correlated through basic biosynthetic reactions such as chain extension, chain degradation, and desaturation that are readily accommodated in the main framework of fatty acid biosynthesis.

Procedures for synthesizing unsaturated acids have also been developed and improved, and synthetic compounds are frequently used in the study of physical and biological properties of closely related isomeric acids.[4]

Formation of Cyclopropane Esters from 4,5-Epoxyalkenoates and from 4-Hydroxyalkenoates

The chemical reactions of natural long-chain acids are essentially those of the carboxyl group, the olefinic double bond, and occasionally a mid-chain oxygenated function. Neighboring group participation may be observed when reactions occurring at one functional group in a molecule are influenced by a second functional group in the same molecule and may result in an enhanced reaction rate or in a product of unexpected stereochemistry or structure. The reactions discussed here are mainly of the latter type. Since the second functional group frequently replaces an intermolecular reagent, the product is cyclic—sometimes carbocyclic, sometimes heterocyclic.

Reactions of Methyl Vernolate Occurring with Rearrangement. The conversion of methyl 9,10-epoxystearate to a mixture of methyl 9- and 10-oxo-stearates when treated with boron trifluoride etherate in boiling dioxane is a typical epoxide reaction.[5]

9,10-epoxystearate   10-oxostearate
(partial structure)   9-oxostearate
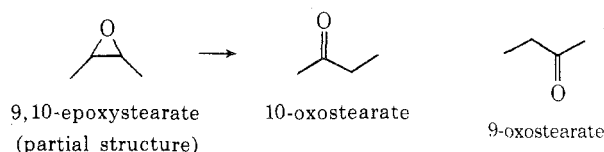
† In this Account a symbol such as 18:2(9c12c) refers to the acid or its ester having 18 carbon atoms and two unsaturated centers which are designated cis-9,cis-12. Other symbols such as *a*, *e*, and *t* refer to acetylenic, ethylenic, and trans olefinic unsaturation respectively.

The formulas used are frequently partial structures showing only those atoms involved in the reaction under discussion. The following trivial names are used: arachidonic [20:4(5c8c11c14c)], elaidic [18:1(9t)], linoleic [18:2(9c12c)], oleic [18:1(9c)], palmitic (16:0), ricinoleic [12-OH-18:1(9c)], stearic [18:0], and vernolic [12,13-epoxy-18:1(9c)].

(1) R. D. Harlow, C. Litchfield, and R. Reiser, *Lipids,* 1, 216 (1966).

(2) L. J. Morris, *J. Lipid Res.,* 7, 717 (1966).

(3) D. J. Frost and F. D. Gunstone, *Chem. Phys. Lipids,* in press; D. J. Frost, Ph.D. thesis, University of Amsterdam, 1974.

(4) F. D. Gunstone, Fifth Hilditch Lecture, December 1975; to be published in *Chem. Ind.*

(5) H. A. Walens, R. P. Koob, W. C. Ault, and G. Maerker, *J. Am. Oil Chem. Soc.,* 42, 162 (1965).

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Scheme I
Conversion of Methyl Vernolate to Cyclopropane Oxo Esters

12,13-epoxyoleate
(partial structure)

BF$_3$

2, 12-oxo-9c   1, 13-oxo-9c

3, 12-oxo-10t

6

5   4
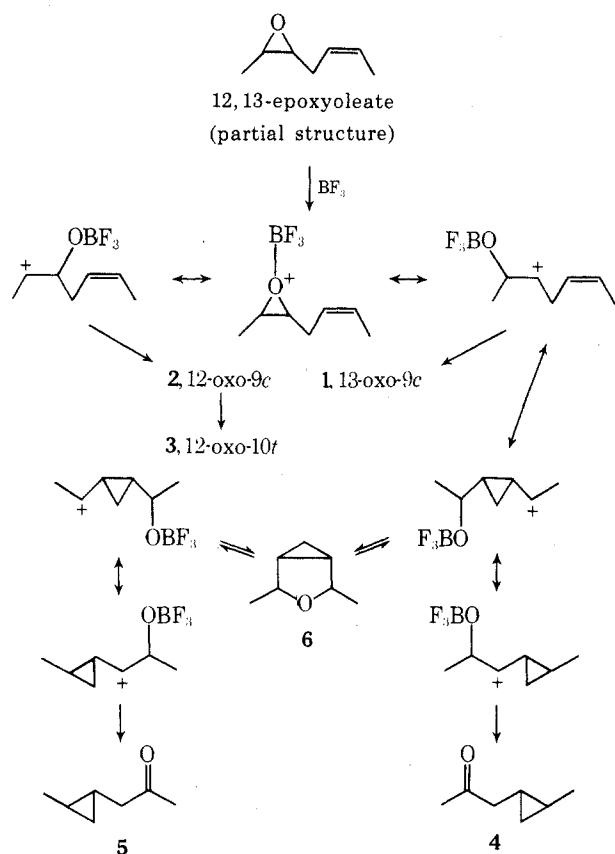
With the unsaturated epoxy ester, methyl vernolate, however, the reaction follows a different course.[6] In boiling dioxane the major product (70%) is a mixture of oxo esters including, in addition to the expected 13-oxo-9c (**1**, 18%) and 12-oxo-9c (**2**, 28%) compounds, the 12-oxo-10t (**3**, 14%) ester and saturated oxo esters (**4** and **5**, 10%). In the same solvent at 0° no 12-oxo-10t ester is formed, and the other three esters are present in 20 (**1**), 51 (**2**), and 8% (**4** and **5**) yields, respectively. In benzene solution at 20° no 12-oxo ester is present and the oxo products are confined to 13-oxo-9c (**1**, 31%) and saturated oxo esters (**4** and **5**, 34%). This last result was confirmed by Ward and van Dorp[7] who recommend the reaction as a source of 13-oxooleate and of its reduction product, 13-hydroxyoleate. The saturated oxo ester was shown to be a mixture of methyl 9,10-methylene-12-oxoheptadecanoate (**4**, major product) and methyl 11,12-methylene-9-oxoheptadecanoate (**5**, minor product). The mechanism set out in Scheme I was proposed. Much of this work was confirmed by an Italian group who also isolated and identified the cyclic ether **6**.[8]

Reactions of Methyl Ricinoleate Occurring with Rearrangement. If the mechanism in Scheme I is correct, other reactions proceeding via a homoallylic carbonium ion should also furnish cyclopropane derivatives. A potential source of such an ion is the


7   8   and/or   9
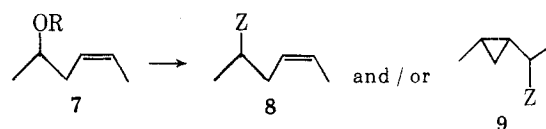
4-hydroxyalkene unit in ricinoleic acid (**7**, R = H). However, the intermediate carbonium ion is more likely to be formed if the OH group is modified to give a better leaving group, increasing the likelihood that reaction tends toward a unimolecular process. Using the methanesulfonate of ricinoleic ester (**7**, R = SO$_2$Me), we obtained cyclopropane esters (**9**) with NaOMe–MeOH (56%, Z = OMe), AcONa–AcOH (30%, Z = OAc), and H$_2$O–CH$_3$CN–CaCO$_3$ (63%, Z = OH).[9] These products were accompanied by the 12-substituted oleate (**8**, 20–50%) and by diene esters (**10**–15%) produced by an elimination reaction. With MeOH alone, MeOH–H$_2$SO$_4$, or NaOOCH–HCOOH the product contained little or no cyclopropane derivatives but substituted alkenoate which was largely the 9t isomer. We believe that acid-labile cyclopropane compounds (**9**) are formed, but revert to the olefinic isomers in cis and trans forms. Cyclopropane derivatives were also formed from the mesylate[9] and tosylate[10] derivatives of the *trans*-alkenoate.

Cyclic products were not observed in reactions of 12-MsO-9c with LiCl, MgBr$_2$, KI, NaHS, or KSAc, from 12-MsO-9a (which gave almost entirely elimination products), or from the 5-hydroxyalkenoate (9-MsO-12c) in reactions with NaOMe–MeOH.[9,11,12]

Formation of 1,4-Epoxy Esters (Tetrahydrofurans) and 1,5-Epoxy Esters (Tetrahydropyrans)

In the reactions now to be described, suitably substituted and/or unsaturated C_{18} esters are converted to 1,4- or 1,5-epoxides such as compounds **10** and **11**.

CH$_3$(CH$_2$)$_5$——O——(CH$_2$)$_7$CO$_2$Me

10

CH$_3$(CH$_2$)$_4$——O——(CH$_2$)$_7$CO$_2$Me

11
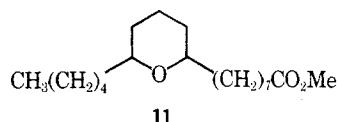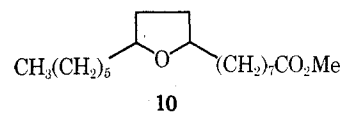
It is convenient to describe these as methyl 9,12- and 9,13-epoxystearates since this shows immediately their chain length and their relation to the C_{18} esters from which they are prepared. Natural furan-containing acids have been identified from a number of plant and animal sources.[13]

This new type of fatty acid is readily recognized by its characteristic chromatographic (TLC and GLC) and spectroscopic behavior (NMR and MS). The 1,4-

(6) H. B. S. Conacher and F. D. Gunstone, *Chem. Phys. Lipids*, **3**, 203 (1969).

(7) J. P. Ward and D. A. van Dorp, *Recl. Trav. Chim. Pays-Bas*, **88**, 1345 (1969).

(8) L. Canonica, M. Ferrari, J. M. Pagnoni, J. Pelizzoni, S. Maroni, and T. Salvatori, *Tetrahedron*, **25**, 1 (1969).

(9) F. D. Gunstone and A. I. Said, *Chem. Phys. Lipids*, **7**, 121 (1971).

(10) E. Ucciani, A. Vantillard, and M. Naudet, *Chem. Phys. Lipids*, **4**, 225 (1970).

(11) F. D. Gunstone, M. G. Hussain, and D. M. Smith, *Chem. Phys. Lipids*, **13**, 71 (1974).

(12) F. D. Gunstone, M. G. Hussain, and D. M. Smith, *Chem. Phys. Lipids*, **13**, 92 (1974).

(13) L. J. Morris, M. O. Marshall, and W. Kelly, *Tetrahedron Lett.*, 4249 (1966); Sho Ito, K. Endo, and S. Inoue, *ibid.*, 4011 (1971); C. Pace-Asciak and L. S. Wolfe, *Chem. Commun.*, 1234 (1970); *Biochemistry*, **10**, 3657 (1971); C. Pace-Asciak, *ibid.*, **10**, 3664 (1971); E. Crundwell and A. L. Cripps, *Chem. Phys. Lipids*, **11**, 39 (1973); R. L. Glass, T. P. Krick, and A. E. Eckard, *Lipids*, **9**, 1004 (1974).

and 1,5-epoxides can usually be separated by careful TLC. Gas chromatography of a TLC homogeneous fraction often gives a twin peak of tetrahydrofurans which we believe to be due to cis and trans isomers.

Acid-Catalyzed Cyclization of Diene Esters in an Oxygen-Containing Solvent. When methyl linoleate is treated with p-toluenesulfonic acid at 100° in enough methanol or dioxane to make the reaction mixture homogeneous, the product contains 1,5-epoxy esters (~4%, mainly methyl 9,13-epoxystearate but also some 8,12 and 10,14 isomers) and 1,4-epoxy esters (~44%, mainly methyl 9,12- and 10,13-epoxystearates with small amounts of the 8,11 and 11,14 isomers).[14] Similar products are obtained with the 9t12t and 9t12c/9c12t stereoisomers of methyl linoleate and from several related oxygenated monoene esters including methyl 12-hydroxyoleate, 12-hydroxyelaidate, 12-methoxyoleate, and 9-hydroxyoctadec-cis-12-enoate. Cyclic esters were not obtained from the mixed 9,11 and 10,12 conjugated dienoates. The reaction probably occurs by the following sequence with the intermediates being representative of several possible isomers.
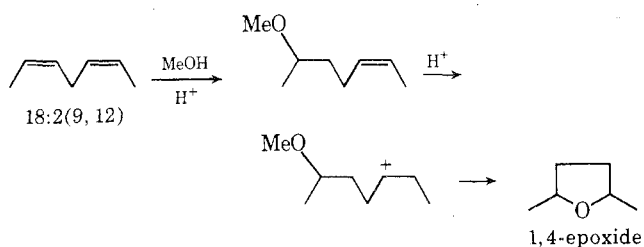

Acid-Catalyzed Cyclization of Polyhydroxy Acids. Methyl 9,12-epoxystearate (10) was first prepared as a mixture of cis and trans isomers by acid-catalyzed cyclization of 9,12-dihydroxystearic acid.[14] An attempt to esterify the 9,12-dioxo acid (12) gave the furanoid ester (13) as major product.
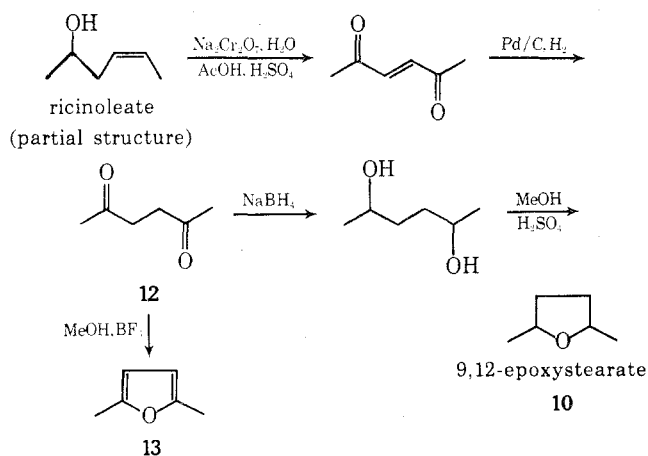

This simple cyclization was extended to the two series of readily available 1,4-diols resulting from hydroxylation of ricinoleic acid and its isomer 9-hydroxyoctadec-cis-12-enoic acid.[15]

Ricinoleic acid contains one chiral center of known absolute configuration (D or R). Hydroxylation by KMnO4 or with performic acid furnishes, in all, four

(14) G. G. Abbot, F. D. Gunstone, and S. D. Hoyes, *Chem. Phys. Lipids,* 4, 351 (1970).

(15) G. G. Abbot and F. D. Gunstone, *Chem. Phys. Lipids,* 7, 279 (1971).

diastereoisomeric 9,10,12-trihydroxystearic acids which can be separated by crystallization followed by preparative TLC on silica impregnated with sodium arsenite. Each isomer, of known absolute configuration, was cyclized (1.5 M methanolic H_2SO_4) and the resulting hydroxy epoxide was oxidized to an oxo epoxide with one less chiral center. Since each isomeric
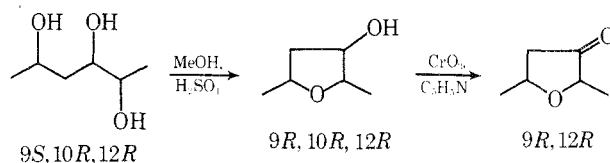
triol gave one (or mainly one) product, the four triols furnished four hydroxy epoxides which were oxidized to two oxo epoxides. One example of the stereochemical relationships is given along with the reaction sequence. From several lines of evidence it was concluded that reaction involved attack by the C-12 hydroxyl on C-9 bearing a protonated hydroxyl. It follows that there is inversion at C-9 and retention of configuration at C-12. The most significant evidence for this was the observation that the pair of triols with an erythro 9,10-diol system gave the same pair of diastereoisomeric cyclic ethers as those derived directly from the 9,10-epoxy-12-hydroxy ester where the mechanism is less in doubt (vide infra).
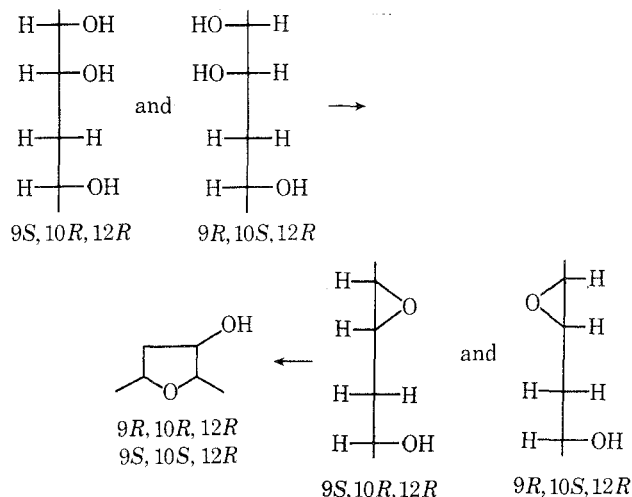
9-Hydroxyoctadec-cis-12-enoic acid also contains one chiral center of known absolute configuration (D or S), but the four 9,12,13-trihydroxystearic acids derived from it have never been fully characterized with respect to their absolute configuration. Again each triol produced a single (or major) hydroxy epoxide which was oxidized to one of two possible oxo epoxides. Although the 9,12,13-triols could also give
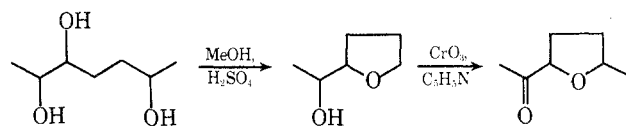

tetrahydropyrans, there was no evidence that such compounds were formed.

Rearrangement of Hydroxy 1,2-Epoxides. Methyl ricinoleate is readily epoxidized by m-chloroperbenzoic acid to a diastereoisomeric mixture of the 9,10-epoxides which is readily rearranged by boron

trifluoride to the same diastereoisomeric mixture of hydroxy 9,12-epoxides as result from the 9,10,12-tri-hydroxy acids with erythro configuration for the 9,10-diol system.[16] As already indicated, this observation was important in unraveling the stereochemistry of the cyclization of the 9,10,12-triols since it is reasonable to assume that in this rearrangement the OH group attached to C-12 attacks the C-9 position with cleavage of the epoxide bond (14).

14
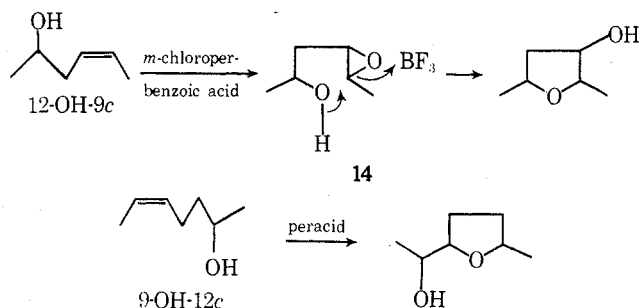
The reaction with methyl 9-hydroxyoctadec-*cis*-12-enoate (a 5-hydroxyalkene) was different from that with methyl ricinoleate (a 4-hydroxyalkene) in two respects: (i) the 12,13-epoxide could not be isolated and the product of the reaction with performic acid (69% yield) or *m*-chloroperbenzoic acid (90% yield) was a diastereoisomeric mixture of 9,12-epoxy-13-hydroxystearates, and (ii) this mixture was the same as that resulting from the acid-catalyzed cyclization of the 9,12,13-trihydroxy acids in which the 12,13-diol was threo. This unexpected result indicates that either the 9,12,13-triol cyclization or the 5-hydroxyalkene epoxidation follows an unexpected pathway. The latter alternative was preferred, and the result was rationalized in terms of either a four-center reaction of the preformed 12,13-epoxide with retention of configuration at C-12 (15) or a direct formation of the 9,12-epoxide via the complex (16) in which the peracid is hydrogen bonded to the hydroxy group and π-bonded to the *cis*-alkene. Intermediates of type 16 are unlikely to be formed with 4-hydroxy-*cis*-alkenes for steric reasons. The 5-hydroxyalkene ester was epoxidized in the normal way when the hydroxyl group was first acetylated (this was an important step in the trans hydroxylation required to prepare the isomeric 9,12,13-triols) but deacetylation with NaOMe again gave the hydroxy 9,12-epoxide.
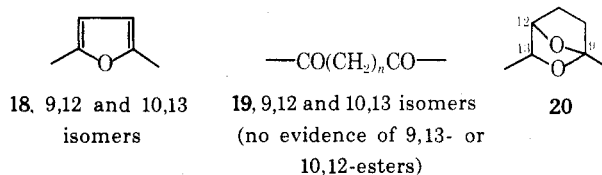
15   **16**
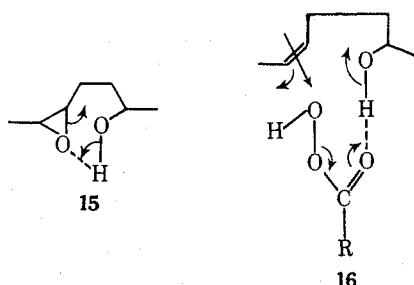
When methyl *threo*-12,13-dihydroxyoleate is treated with peracid the 5-hydroxyalkene reaction is dominant and the product is a diastereoisomeric mixture of dihydroxy 10,13-epoxides (17).

When the 9,10:12,13-diepoxides, produced from methyl linoleate, are treated with boron trifluoride

17, 9,12-dihydroxy-10,13-epoxide
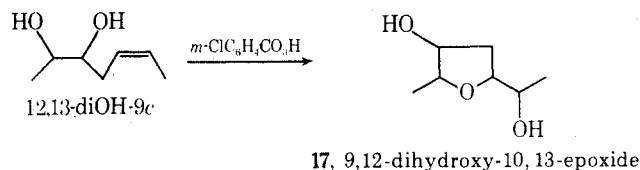
etherate at room temperature the reaction product contains furanoid esters (18, 21%), dioxostearates (19, 20%), and an ester of molecular formula $C_{19}H_{34}O_4$ (17%) which is possibly a mixture of ketals such as 20.

18, 9,12 and 10,13   19, 9,12 and 10,13 isomers   20
isomers   (no evidence of 9,13- or
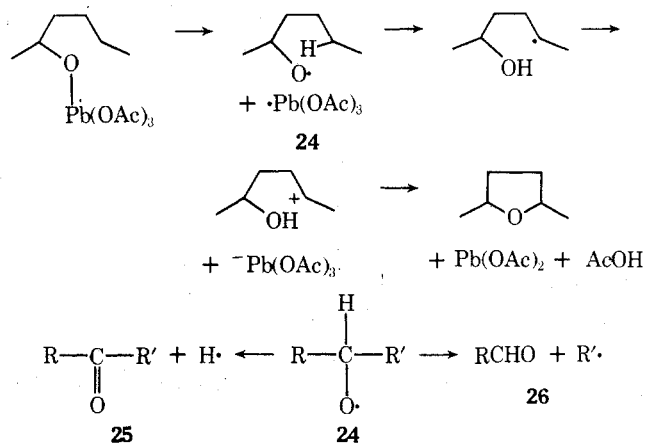   10,12-esters)

The *cis*-6,7:*cis*-9,10-diepoxystearate behaved in a similar manner and the 6,9- and 7,10-furanoid esters (33%) and 7,9-dioxostearate (15%) were identified. The *cis*-8,9:*cis*-12,13-epoxide, in contrast, gave neither furanoid nor dioxo ester but compounds having the structure 21 25%) and a mixture of 22 and 23 (21%).[17]

21   22   23

$n = 2$ (8,9,12 or 9,12,13) or 3 (8,9,13 or 8,12,13)
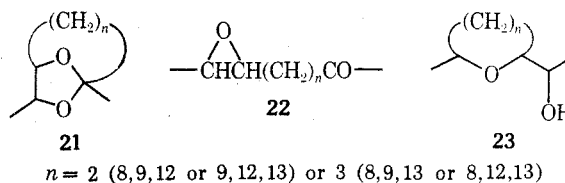
Oxidative Cyclization of Hydroxy Esters. The conversion of alcohols to cyclic ethers by Pb(OAc)₄, Ag₂O–Br₂, or HgO–I₂ has been widely applied to steroids and to some shorter chain aliphatic compounds.[18]

With each of these reagents, methyl 12-hydroxy-stearate gave a mixture of the cis and trans isomers of methyl 9,12- and 12,15-epoxystearates and methyl 9-hydroxystearate gave the mixed cis and trans isomers of methyl 6,9- and 9,12-epoxystearates. These epoxy esters (~60% yield) were accompanied by smaller amounts of methyl 12- and 9-oxostearate, respectively.[19]

Reaction with Pb(OAc)₄ is believed to follow the reaction sequence shown. The oxygen radical species

24

$R—\underset{\underset{O}{\|}}{C}—R' + H\cdot \longleftarrow R—\underset{\underset{O\cdot}{|}}{\overset{H}{\underset{|}{C}}}—R' \longrightarrow RCHO + R'\cdot$

25   **24**   **26**

(16) G. G. Abbot and F. D. Gunstone, *Chem. Phys. Lipids*, **7**, 290 (1971).

(17) F. D. Gunstone and H. R. Schuler, *Chem. Phys. Lipids*, in press.
(18) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 551.
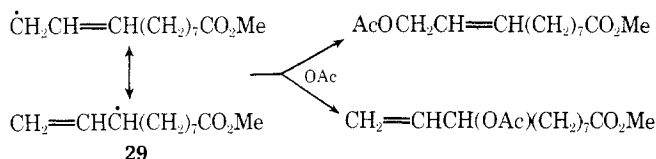(19) G. G. Abbot and F. D. Gunstone, *Chem. Phys. Lipids*, **7**, 303 (1971).

(24) can suffer other fates than the one indicated. Loss of hydrogen radical would furnish the oxo ester **25**, and homolytic cleavage of a carbon–carbon bond might occur when the radical R′ (**26**) is resonance stabilized.

Interesting results were obtained when the Pb(OAc)$_4$ oxidation was applied to unsaturated hydroxy esters such as methyl ricinoleate (a 4-hydroxyalkene) and methyl 9-hydroxyoctadec-*cis*-12-enoate (a 5-hydroxyalkene). With the latter the oxygen radical, instead of abstracting hydrogen from C-6, interacts with the π electrons of the double bond and the product was a mixture of the 9,12- (**27**, 28%) and 9,13- (**28**, 32%) epoxides. This was the first reaction we studied to give an appreciable yield of a tetrahydropyran derivative.

from 9-OH-12*c*

27, 13-acetoxy-9, 12-epoxide   28, 12-acetoxy-9,13-epoxide
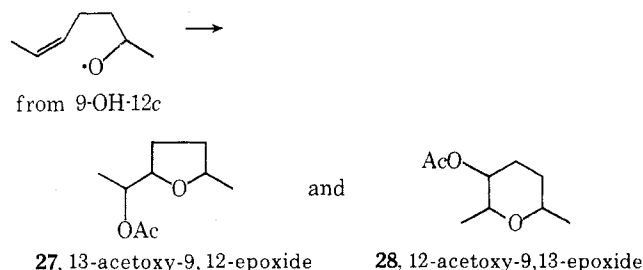
With methyl ricinoleate chain cleavage became prominent, presumably because the allylic radical **29** is resonance stabilized, and the major product was a C$_{11}$ acetoxy ester (70%) which proved to be a mixture of the 9*t* (82%) and 10*e* (18%) isomers. The conversion of the 9*c* substrate to the 9*t* product is unsurprising, but regrettable, for the C$_{11}$ acetoxy ester

$\dot{C}H_2CH{=}CH(CH_2)_7CO_2Me$ $AcOCH_2CH{=}CH(CH_2)_7CO_2Me$

$CH_2{=}CH\dot{C}H(CH_2)_7CO_2Me$ $CH_2{=}CHCH(OAc)(CH_2)_7CO_2Me$
**29**

would have been a valuable relay in the synthesis of long-chain compounds having unsaturation at C-9 and C-12. This difficulty was overcome by using the acetylenic analog of methyl ricinoleate, though other problems were encountered in the later stages of the synthetic sequence.[17]

12-OH-9*a*

$AcOCH_2C{\equiv}C(CH_2)_7CO_2Me \xrightarrow{H_2, Pd} AcOCH_2CH{\overset{c}{=}}CH(CH_2)_7CO_2Me$
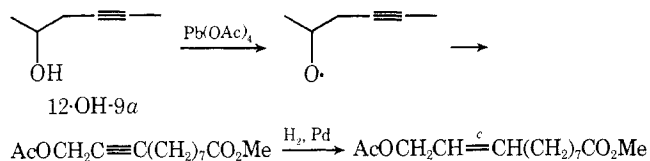
Halogenation. It has long been known that halogenation of alkenes is frequently a two-step process involving formation of a halonium ion followed by interaction of this ion with halide ion. The second step can be diverted by an alternative nucleophile which may be added to the reaction mixture or may be present within the reacting alkene. On this basis halogenation of appropriate hydroxyalkenes and hydroxyalkenoic acids should furnish cyclic ethers and lactones, respectively. With methyl ricinoleate there was no evidence of any cyclic ether during chlorination, bromination, or chloroiodination except for a small amount of 10-chloro-9,12-epoxide (12%) in the

last of these reactions.[20] Neither did methyl ricinelaidate furnish any cyclic ether during bromination. Halogenation of methyl 9-hydroxyoctadec-*cis*-12-enoate, on the other hand, gave cyclic ethers during chlorination (32%), bromination (40%), and chloroiodination (84%). Bromination of the trans isomer gave

9-OH-12*c*
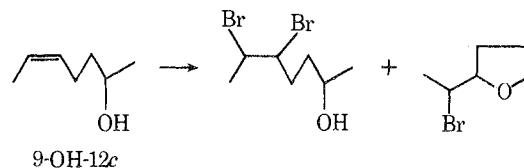
a similar result. This pattern was confirmed with the octadecenols. Siouffi and Naudet[21] also obtained 9,12-epoxides from methyl ricinoleate and its acetate during reaction with *tert*-butyl hypobromite in methanol.

9-Hydroxyoctadec-12-enoic acid and its esters give unexpectedly high iodine values in an analytical determination based on reaction with ICl.[22] Its acetate behaves normally, and so does ricinoleic acid. It is now apparent that reaction with ICl occurs mainly via the cyclic ether, but this does not immediately indicate why less iodine than expected is liberated when KI is added to decompose the excess ICl.

The observation made with short-chain molecules that halogenation of unsaturated acids can produce lactones has been confirmed for octadecenoic acids. The 4*c* acid gave the γ-lactone (61%) with ICl and the 3*c* acid gave a mixture of bromo β- and γ-lactones as the only products of bromination.

$RCH{=}CHCH_2COO^- \xrightarrow{Br_2} R\dot{C}HCHCH_2COO^-$
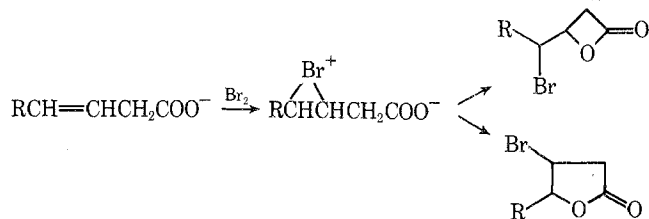
Oxymercuration–Demercuration. Oxymercuration–demercuration gives a high yield of products when carried out in solvents such as MeOH (to give methyl ethers), EtOH (ethyl ethers), AcOH (acetates), and H$_2$O (alcohols).[23] Intramolecular reaction

$-CH{=}CH- \xrightarrow{Hg(OAc)_2, ROH}$

$-CH(HgOAc)CH(OR)- \xrightarrow{NaOH, NaBH_4} -CH_2CH(OR)-$
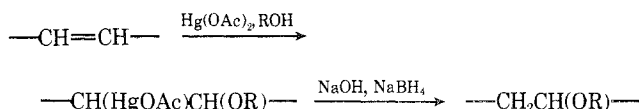
becomes dominant when appropriately placed hydroxyl groups are present in the alkene. Even in methanol solution, oxymercuration–demercuration of methyl 9-hydroxyoctadec-*cis*-12-enoate gave a virtually quantitative yield of cyclic ether **10** with no evidence of a methyl ether.[24] With the *trans*-alkenoate ~8% of 9,13-epoxystearate accompanied the larger proportion of 9,12-epoxystearate. Although methyl ricinoleate gave very little cyclic ether (17% in water 10% in methanol), its trans isomer gave an almost quantitative yield of methyl 9,12-epoxystearate even
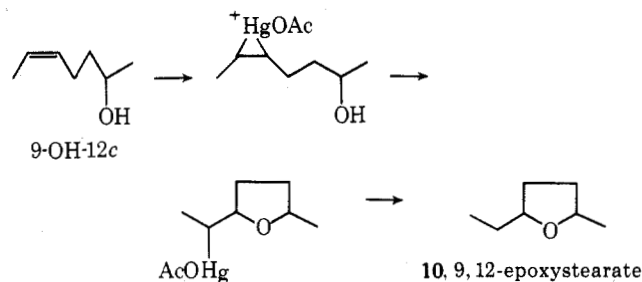
(20) F. D. Gunstone, and B. S. Perera, *Chem. Phys. Lipids*, 11, 43 (1973).
(21) A. M. Siouffi and M. Naudet, *Chem. Phys. Lipids*, 11, 103 (1973).
(22) F. D. Gunstone, *J. Chem. Soc.*, 1274 (1952); R. G. Powell, R. Kleiman, and C. R. Smith Jr., *Lipids*, 4, 450 (1969).
(23) F. D. Gunstone and R. P. Inglis, *Chem. Phys. Lipids*, 10, 73 (1973).
(24) F. D. Gunstone and R. P. Inglis, *Chem. Phys. Lipids*, 10, 89 (1973).

9-OH-12c

AcOHg → 10, 9,12-epoxystearate

when methanol was the reaction solvent. Steric factors probably inhibit intramolecular reactions with the 4-hydroxy-*cis*-alkene.

The difference in reactivity between 4- and 5-hydroxyalkenes is reflected in the products of oxymercuration–demercuration of two unsaturated C$_{18}$ hydroxy acids containing both systems (30 and 31). The only observed product in each case is the cyclic ether resulting from the 5-hydroxyalkene unit.


30, 12,13-diOH-9c → 10,13-epoxy-12-hydroxystearate

31, 12-OH-9c15c → 12,15-epoxyoleate
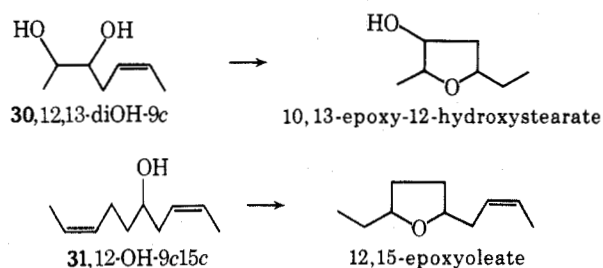
Oxymercuration–demercuration of a diene in aqueous DMF is likely to proceed consecutively at the two double bonds. The intermediate product will be a hydroxy monoene which might have a structure suitable for intramolecular reaction at the second stage. Methyl linoleate (9c12c), for example, yielded a mixture of 9,12- and 10,13-epoxystearates (46%) along with several dihydroxystearates (52%). Some of the latter were cyclized by acid, raising the yield of cyclic ether to about 70%. The isomeric 8c12c diene gave 9,12-epoxystearate (23%), 8,12- and 9,13-epoxystearates (36%), and some dihydroxystearates (14%).

The differing reactivity of the various types of hydroxyalkenes was further illustrated by a study of the oxymercuration–demercuration of a series of octadecenols prepared by reduction of appropriate synthetic esters. When MeOH (or DMF) was used as solvent, the 2c, 2t, 3c, and 6c isomers did not undergo intramolecular reaction (except that the 3c alcohol gave ~7% of cyclic ether) but furnished the expected methoxyoctadecenols. The 3t, 4c, 4t, 5c, and 5t isomers, on the other hand, gave virtually quantitative yields of cyclic ethers even when the reaction was conducted in methanol solution. The 3t and 4c alcohols gave substituted tetrahydrofurans (32), the 5c and 5t alcohols gave substituted tetrahydropyrans (33), and the 4t isomer gave some of both (88% and 12%, respectively).

RCH=CH(CH$_2$)$_n$OH →

32, n = 3 or 4   33, n = 5
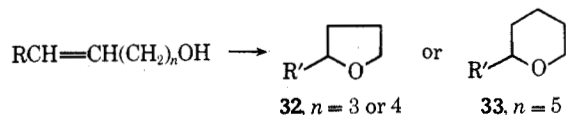
These are significant observations since acids with 3t, 4c, or 5c unsaturation include some members of
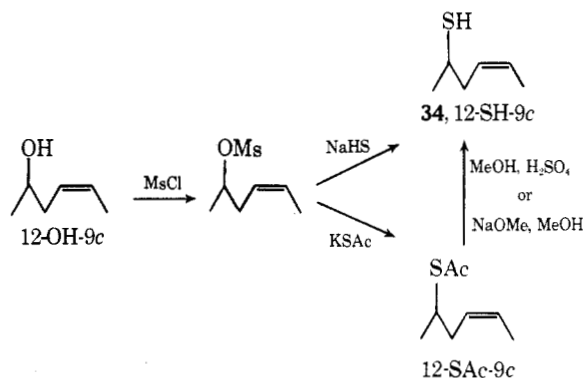
considerable importance. The 16:1(3t) acid is present in photosynthetic tissue and some unsaturated C$_{18}$ acids with 3-unsaturation have also been reported. Polyunsaturated acids with methylene-interrupted polyene systems starting at Δ^4 or Δ^5 occur in animal tissues and are characteristic of structural lipids rather than reserve lipids. Among C$_{20}$ acids, unsaturation usually starts at Δ^5 and arachidonic acid [20: 4(5c8c11c14c)] is the best known of this class. C$_{22}$ acids with unsaturation starting at Δ^4—especially 22:5(4c7c10c13c16c) and 22:6(4c7c10c13c16c19c)— are also important acids. Oxymercuration–demercuration provides a useful method of recognizing, analyzing, and separating such compounds (as their alcohols).[25] In dimethylformamide as solvent, reaction is confined to the intramolecular process and the products are then simpler to identify, particularly after hydrogenation.

arachidonyl alcohol →

C$_{15}$H$_{25}$ $\xrightarrow{H_2, Pd}$ C$_{15}$H$_{31}$
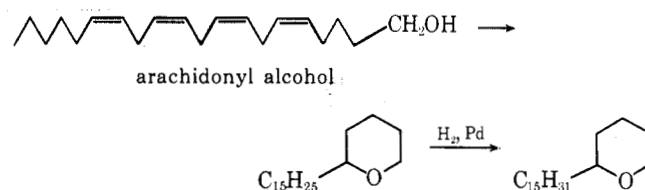
The cyclic ethers are easily separated by chromatography from alcohols unable to react. With care, tetrahydrofurans can be separated from tetrahydropyrans. These two classes of cyclic ethers are also separated by gas chromatography. Unsaturated cyclic ethers can be further separated by silver ion chromatography. The analytical procedure has been applied to tall oil, to liver lipids, and to fish oils before and after partial hydrogenation.[25]

Sulfur Compounds. The previous sections have been devoted to an account of the formation of cyclic ethers. The corresponding sulfur compounds have also been examined.

Long-chain hydroxy compounds are converted to thiols by reaction of their mesylates with NaHS or with KSAc followed by deacylation (preferably in a reducing atmosphere)[11] as in the conversion of methyl ricinoleate to methyl 12-mercaptooleate (34).

34, 12-SH-9c

12-OH-9c $\xrightarrow{MsCl}$ OMs $\xrightarrow{NaHS}$ / $\xrightarrow{KSAc}$

MeOH, H$_2$SO$_4$ or NaOMe, MeOH

12-SAc-9c

When this sequence is applied to the 5-hydroxyalkene system of methyl 9-mesyloxyoctadec-*cis*-enoate, the major product is methyl 9,12-epithiostearate (35, 70–75%). Since the thiol can be observed under appropriate conditions, the cyclic sulfide may be formed via the thiol radical:

(25) F. D. Gunstone and R. P. Inglis, *Chem. Phys. Lipids*, 10, 105 (1973).

35, 9,12-epithiostearate

35, 9,12-epithiostearate
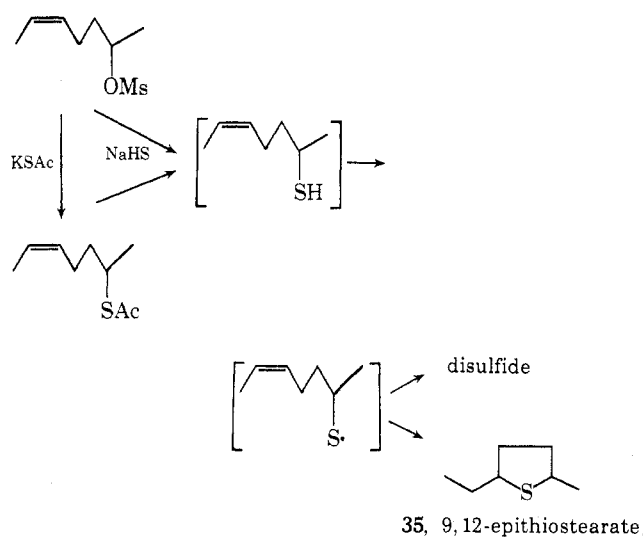
Octadec-4-enol submitted to the same reaction sequence gave both thiol and cyclic sulfide, but the Δ⁵ isomer gave only the thiol which was oxidized by iodine to a tetrahydrothiopyran (36).


18:1-5c

36
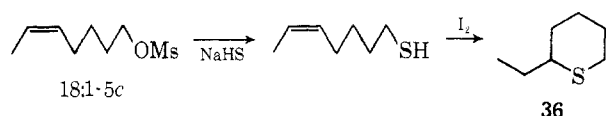
These reactions differ slightly from those of the corresponding oxygen radicals produced by Pb(OAc)₄ oxidation. There is no evidence of cleavage of the radicals from 4-mercaptoalkenes, while 5-mercaptoalkenes give tetrahydrothiofurans only.

Some epithio- and epidithiostearates were produced in attempts to prepare dithiols.[12] Not surprisingly, methyl 12,13-dimesyloxyoleate, when treated with NaHS, behaved like a 4,5-disubstituted alkene and formed a cyclic sulfide (37).

12,13-diMsO-9c

37, 12-mercapto-10,13-epithiostearate
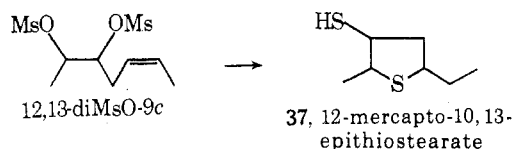
Methyl 9,12-dimesyloxystearate reacted with NaHS to give methyl 9,12-epithiostearate (35), possi-

bly by the sequence shown below. With KSAc the diacetylmercapto compound 38 was formed. This was converted to the dithiol 39 which was readily oxidized to the 9,12-epidithiostearate 40.

9,12-diMsO

35, 9,12-epithiostearate

38

39

40, 9,12-epidithiostearate
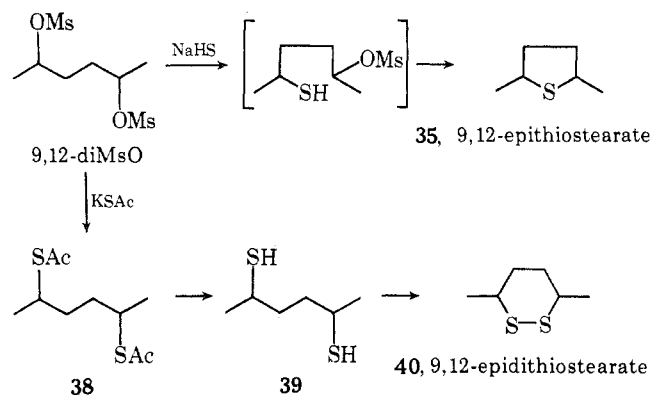
The 10,12-dimesyloxystearate gave methyl 10,12-epidithiostearate (41) with NaHS and the diacetyl-mercapto derivative 42 with KSAc. This was deacylated to the dithiol 43 under reducing conditions or to the epidithiostearate (41) without these precautions. The oxygen analogs of these dithio compounds are not known, except possibly as labile intermediates.

10,12-diMsO

41

42

43
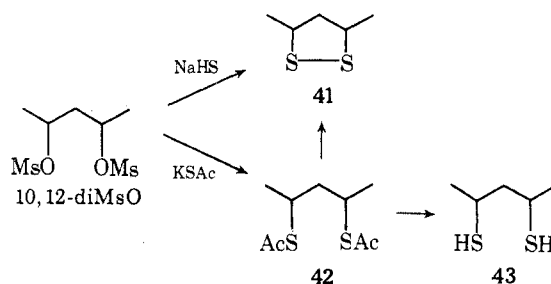
Similar epithio- and epidithiostearates have been identified among the products of photochemical interaction of methyl linoleate and H_2S.[26]

(26) A. W. Schwab, W. K. Rohwedder, L. W. Tjarks, and L. E. Gast, *J. Am. Oil Chem. Soc.*, **50**, 364 (1974).