2.80 (sh), 2.88, 9.32, 9.43 μ. The infrared spectrum showed no carbonyl band.

*Anal.* Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.23; H, 10.48.

From the combined mother liquors 0.013 g. (2.6%) of 13α-androst-5-ene-3β,17β-diol, m.p. 154.5–156.5°, was obtained as colorless platelets. The residue from the remaining mother liquors was chromatographed on 10 g. of silica gel, and the column was eluted with varying proportions of benzene–ethyl acetate. Elution with 25% ethyl acetate in benzene gave an additional quantity of the 3β,17β-diol, which was crystallized from ether–pentane to yield 0.025 g. (5%) of colorless laths, m.p. 160.5–161°. The analytical sample of 13α-androst-5-en-3β,17β-diol was obtained as colorless rods from ether–pentane: m.p. 162.5–163.5°; $[\alpha]_D$ −99° (0.5%, $CHCl_3$); $\lambda^{KBr}$ 3.02, 9.50 μ. The infrared spectrum showed no carbonyl band.

*Anal.* Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.95; H, 10.31.

**Sodium Borohydride Reduction of 17-Keto-13α-androst-5-en-3β-ol (I).**—A solution of 0.432 g. (0.0015 mole) of 17-keto-13α-androst-5-en-3β-ol, m.p. 185.5–187°, and 0.5 g. (0.132 mole) of sodium borohydride in 50 ml. of methanol was stirred and heated under reflux for 3 hr. After 0.5 g. (0.132 mole) more of sodium borohydride was added, stirring and heating were continued for an additional 1 hr. The reaction mixture was treated with 10 drops of glacial acetic acid and diluted with water. Then it was concentrated under reduced pressure to remove the alcohol. The residue was cooled to 0–5°. The solid was collected, washed with water, and dried, yield 0.42 g., m.p. 167–172°. A sample of the crude product was submitted for paper chromatography as before, and the results revealed the presence of **13α-androst-5-ene-3β,17β-diol** in 20–25% yield in the mixture. The crude product was fractionally crystallized from ether to yield 0.314 g. (72%) of **13α-androst-5-ene-3β,17α-diol**, m.p. 183–189°, as colorless heavy plates. Recrystallization from ether raised the melting point to 190–193°; yield was 0.21 g. (48%). The residue from the combined mother liquors was chromatographed on 10 g. of silica gel. Elution of the column with 25% ethyl acetate in benzene gave 13α-androst-5-ene-3β,17β-diol, which was crystallized from ether–pentane to afford 0.030 g. (7%) of colorless laths, m.p. 157.5–161.5°. The melting point was raised to 162.5–164.5° upon further crystallization from ether–pentane.

**Oppenauer Oxidation of 13α-Androst-5-ene-3β,17α-diol.**—A solution of 0.122 g. of 13α-androst-5-ene-3β,17α-diol, 4 ml. of cyclohexanone, and 0.8 g. of aluminum isoproxide in 24 ml. of anhydrous toluene was heated under reflux for 1 hr.[18] After 20 ml. of a saturated solution of Rochelle salt was added, the reaction mixture was steam distilled for 30 min. The cooled residue was extracted with ether. The ether extract was washed successively with water and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the ether extract was evaporated to dryness to afford a viscous orange oil.

The oil was chromatographed on 2 g. of silica gel. Elution of the column with 5% ethyl acetate in benzene gave, in succession, 13α-androstene-3,17-dione and 13α,17α-testosterone.

The combined fractions of 13α-androstene-3,17-dione were crystallized from ether–pentane to yield 7 mg. (6%) of the dione, m.p. 145.5–148.5° (lit.[2] m.p. 148–149°). Its infrared spectrum was identical with that of an authentic sample.

The combined fractions of 13α,17α-testosterone were crystallized from ether–pentane to afford 46 mg. (38%) of a crystalline product, m.p. 129–130° (lit.[1] m.p. 129.5–131°). Its infrared spectrum was identical with that of an authentic sample.

**N.m.r. Signals of 13α-Testosterone and 13α,17α-Testosterone.**—13α-Testosterone, m.p. 154–157°, showed signals at 346 (4-H); 276.5 (water); 235, 233.5, 231.5, 230.5, 229.5, 228 (17-H); 68 (19-$CH_3$); and 50.5 (18-$CH_3$) c.p.s. 13α,17α-Testosterone, m.p. 126–127°, showed signals at 346.5 (4-H); 261.5, 254, 246.5 (17-H); 67.5 (19-$CH_3$); and 53 (18-$CH_3$) c.p.s.

(18) *Cf.* A. F. St. Andre's unpublished work cited by C. Djerassi in *Org. Reactions*, **6**, 207 (1951).

# Studies Directed toward the Synthesis of Plasmalogens. II. (±)-*cis*- and -*trans*-3-(*n*-Hexadec-1′-enyloxy)-1,2-propanediol[1]

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Condensation of 2-bromo-1,1-dimethoxy-*n*-hexadecane with 2-benzyloxypropan-1,3-diol gave the epimeric *trans*- and *cis*-2-(1′-bromopentadecyl)-5-benzyloxy-1,3-dioxane (IIa and IIIa), separated by chromatography. Catalytic debenzylation led to the epimeric alcohols IIb and IIIb. Debromination of either IIb or IIIb with lithium in 1,2-dimethoxyethane afforded the same mixture of (±)-*cis*- and -*trans*-3-(*n*-hexadec-1′-enyloxy)-1,2-propanediols (VIIa and b), separated by preparative gas–liquid partition chromatography of their diacetates (VIIc and d). Alkaline hydrolysis of VIIc and d gave the individual *cis*- and *trans*-1-alk-1′-enylglycerols VIIa and b, which after hydrogenation were identical with (±)-chimyl alcohol. The *cis* isomer VIIa and the *cis* diacetate VIIc were structurally identical with the alkenylglycerol obtained from natural plasmalogen and its diacetate. Although the allyl ether Xa rearranged to the desired *cis*-1-propenyl ether XIa, the crotyl ether Xb did not undergo this reaction, and a possible reason is discussed.

The plasmalogens[2] are a group of aldehydogenic lipids widely distribution in both the animal and plant kingdoms and are phosphorylated derivatives of *cis*-1-alk-1′-enylglycerol (VIIa) where R = mainly *n*-$C_{14}H_{29}$ and *n*-$C_{16}H_{33}$. The plasmalogens are of considerable chemical and biological interest in view of their probable biogenetic relationship to the 1,2-diacylglycerols either by hydration of the double bond to the hemiacetal and thence by oxidation,[3a] or by reduction of the 1-acyl moiety to the hemiacetal followed by a *cis* dehydration.[3b]

The availability of synthetic plasmalogens for chemical and biological studies requires the initial preparation of the appropriate *cis*-1-alk-1′-enylglycerols.

It has been demonstrated[4] that published methods[5]

(1) Supported by Research Grant HE-5881 from the National Heart Institute.

(2) (a) For review, see E. Klenk and H. Debuch, *Progr. Chem. Fats Lipids*, **6**, 3 (1963).

(3) (a) J. C. Craig and E. C. Horning, *J. Org. Chem.*, **26**, 2098 (1960); (b) H. Goldfine and N. Baumann, Proceedings of the 6th International Congress of Biochemistry, New York, N. Y., 1964, p. 574; N. A. Baumann, P. O. Hagen, and H. Goldfine, *J. Biol. Chem.*, **240**, 1559 (1965).

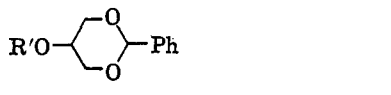
(4) J. C. Craig, D. P. G. Hamon, H. W. Brewer, and H. Härle, *J. Org. Chem.*, **30**, 907 (1965).

(5) (a) C. Piantadosi and A. F. Hirsch, *J. Pharm. Sci.*, **50**, 978 (1961); (b) C. Piantadosi, A. F. Hirsch, C. L. Yarbro, and C. E. Anderson, *J. Org. Chem.*, **28**, 2425 (1963).

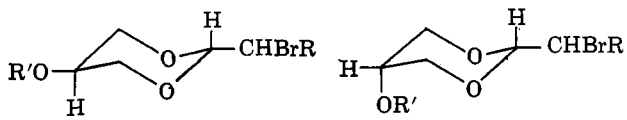
for the synthesis of 1-alk-1′-enylglycerols result in the simultaneous formation of the 2-alk-1′-enyl isomers. A synthetic route is now reported which yields solely the 1-alk-1′-enylglycerol without the possibility of contamination by the 2-alk-1′-enyl isomer.

The isolation of palmitaldehyde is well known to be attended with difficulty owing to the rapid formation of the cyclic trimer. A method has now been devised by which the pure aldehyde can be readily obtained in high yield by boiling a heterogeneous mixture of the bisulfite compound, sodium carbonate solution, and heptane. Reaction of the aldehyde with isopropenyl acetate under acidic conditions[6] afforded improved yields of palmitaldehyde enol acetate, free from the diacetate. The enol acetate was converted to 2-bromo-1,1-dimethoxyhexadecane as described.[4]

Reaction of the sodium salt of 1,3-benzylideneglycerol[7a] (Ia) with benzyl bromide gave 5-benzyloxy-2-phenyl-1,3-dioxane (Ib) by a route which was more convenient than the published preparation.[7b] Hydrolysis[7c] led to the required glycerol 2-benzyl ether,[7] which on transacetalation with 2-bromo-1,1-dimethoxyhexadecane gave a mixture of two compounds, IIa (m.p. 46–47°) and IIIa (m.p. 66–68°), which were separated by chromatography on alumina. Both gave expected infrared absorption and elemental analysis. Assuming that the bulky α-bromoalkyl side chain at C-2 remains in an equatorial conformation, it is concluded that these two isomers are epimeric about the benzyl ether linkage at C-5 of the 1,3-dioxane ring.



Ia, R′ = H
b, R′ = $PhCH_2$



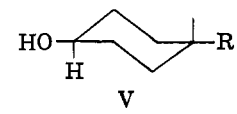
IIa, R′ = $PhCH_2$
b, R′ = H
c, R′ = $COCH_3$

IIIa, R′ = $PhCH_2$
b, R′ = H
c, R′ = $COCH_3$

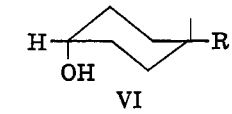
R = $n$-$C_{14}H_{29}$ throughout

The possibility that the two isomers were the five- and six-membered ring acetals IIa and IVa, respectively, could not be entirely excluded at this stage because of the possible formation of benzyl cation owing to intramolecular solvation of the benzylic carbon atom in II, followed by migration of the benzyl group to the α-carbon at the temperatures (140–170°) used. However, subsequent observations ruled out this possibility.

Hydrogenolysis[7c] of the benzyl ethers IIa and IIIa yielded the alcohols IIb (m.p. 74–75°) and IIIb (m.p. 81–82°), respectively. The configuration of these epimeric alcohols was proved as follows. The two isomers IIb and IIIb were acetylated independently and their n.m.r. spectra were determined before and after acetylation, with the objective of locating the hydrogen attached to C-5. Acetylation of IIb gave IIc, m.p. 47–49°, which showed in its n.m.r. spectrum (Figure 1) a distinct seven-line pattern centered at $\delta$ = 4.89 p.p.m., with 5-c.p.s. separation between lines for the hydrogen at C-5. The band width at half-height was 22 c.p.s. Owing to the fact that the chemical shift between the axial and equatorial protons on C-4 and C-6 (which constitute an $A_2B_2X$ system) was considerably larger than the coupling constant ($J_{AB}$) for these protons, a first-order interpretation was possible[8a] and gave numerical values for the coupling constants between the protons at C-5 and those at C-6 and C-4, as follows. For Figure 1, the chemical shift between the axial (a) and equatorial (e) protons at C-4 and C-6 is 48 c.p.s. in each case; $\delta_{H_e}^{4,6}$ = 4.29 p.p.m., being found downfield as a pair of doublets ($J$ = 12 and 5 c.p.s.), while $\delta_{H_a}^{4,6}$ = 3.48 p.p.m. and is located upfield, being a triplet formed from a pair of doublets in which $J$ = 12 and 10 c.p.s. The value of $J_{H_a,H_e}^{4} = J_{H_a,H_e}^{6}$ and is 12 c.p.s., while the coupling constant $J_{H_5,H_e}^{4}$ and $J_{H_5,H_e}^{6}$ = 5 c.p.s. and that for $J_{H_5,H_a}^{4}$ and $J_{H_5,H_a}^{6}$ = 10 c.p.s. These coupling constants are reflected in the seven-line pattern due to H-5, which may now be considered as a superposition of a triplet of triplets of $J$ = 10 and 5 c.p.s. From this it follows that the hydrogen at C-5 must be in the axial configuration, in agreement with the analytical values established for $J_{a,a}$ and $J_{a,e}$ by Lemieux, *et al.*,[9a] who showed that the spin–spin coupling constant between the axial hydrogen at C-1 in *trans* compounds of type V and the neighboring axial hydrogens is 2 to 3 times larger than that for the equatorial hydrogen at C-1 and its equatorial neighbors in the *cis* isomers VI. An entirely analogous case was recently[9b] reported in the n.m.r. spectrum of 5β-pregnane-3α,-12α-diol-20-one diacetate, in which the axial 3β-hydrogen appeared as a seven-line pattern centered at $\delta$ = 4.77 p.p.m., ascribed to the two diaxial splittings of the 2α- and 4α-hydrogens (10 c.p.s.) being twice the two axial–equatorial splittings of the 2β- and 4β-hydrogens (5 c.p.s.).



V



VI

Acetylation of IIIb similarly yielded IIIc (m.p. 95–96°). Although in the n.m.r. spectrum of this compound the hydrogen at C-5 appeared in the same region as the hydrogen at C-2, a comparison with the n.m.r. spectrum of the starting alcohol IIIb showed that a multiplet centered at $\delta$ = 3.51 p.p.m. which existed in the free alcohol had shifted downfield in the acetate. This multiplet was therefore assigned to the hydrogen at C-5, and, since the width at half-height of this multiplet was less than 7 c.p.s., this hydrogen exists in an equatorial configuration.[9a] From these observations it follows that the benzyl ether IIa has the benzyl group in an equatorial configuration, while IIIa is the axial

(6) H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

(7) (a) P. E. Verkade and J. D. van Roon, *Rec. trav. chim.*, **61**, 831 (1942); (b) W. A. West and B. J. Ludwig, *J. Am. Chem. Soc.*, **74**, 4466 (1952); (c) A. J. E. Porck and B. M. Craig, *Can. J. Chem.*, **33**, 1286 (1955).

(8) J. D. Roberts, "Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959: (a) p. 76; (b) p. 54.

(9) (a) R. U. Lemieux, K. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958); (b) D. H. Williams and N. S. Bhacca, *ibid.*, **86**, 2742 (1964).

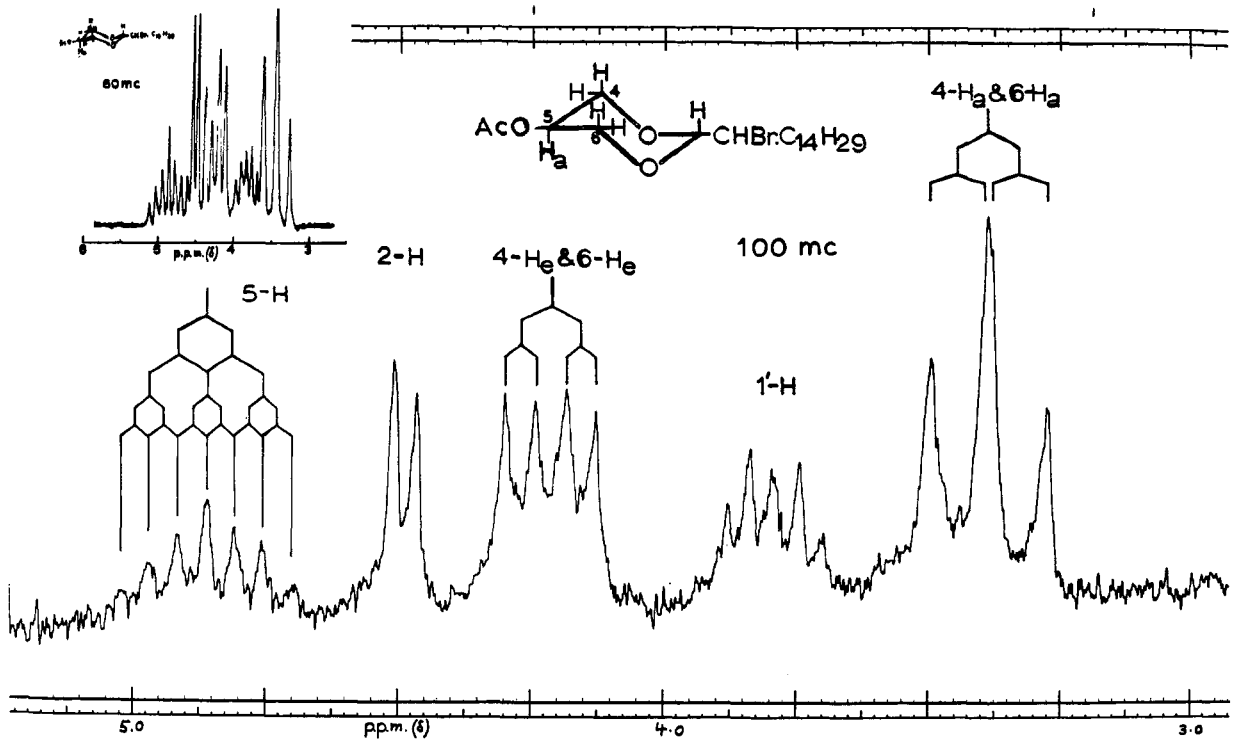
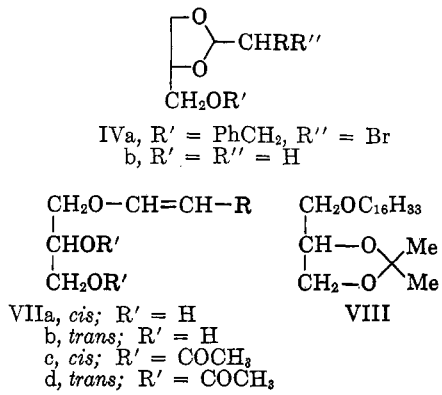



Figure 1.—N.m.r. spectrum of *trans*-5-acetoxy-2-(1'bromopentadecyl)-1,3-dioxane. Ring proton region.

epimer. A fuller interpretation of this spectrum was made impossible by the superposition of signals corresponding to the ring protons, owing to the very small chemical shifts between the axial and equatorial hydrogens at C-4 and C-6 in the alcohol and the acetate.

When either of the epimers IIb or IIIb was treated with lithium in 1,2-dimethoxyethane[4] at 65°, a mixture of *cis*- and *trans*-1-alk-1'-enylglycerol (VIIa and b) was obtained as a waxy solid. This was immediately acetylated because of the apparent ease of addition of one of the hydroxyl groups to the double bond of the vinyl ether to form a cyclic acetal IVb. The mixture of diacetates VIIc and d was characterized by infrared bands at 1739 (-OCOMe), 1678 and 1667 (-O—C=C), and 930 cm.$^{-1}$ (*trans* C=C). No *cis* double bond was obvious from the infrared spectrum. Vapor phase chromatography of the reaction mixture indicated the presence of only two components. The n.m.r. spectrum of the mixture of VIIc and d showed a signal in the olefinic proton region which was split into two doublets, one centered at $\delta$ = 6.16 p.p.m. ($J$ = 12.5 c.p.s.) and the other at $\delta$ = 5.84 p.p.m. ($J$ = 6.5 c.p.s.). This signal is attributable to the hydrogen attached to C-1 of the alkenyl chain. The existence of only four lines in this part of the spectrum proves that the mixture contains only *two alkenylglycerols* (VIIc and d), and (because of the significantly different coupling constants) that these are *cis* and *trans* isomers. This in turn confirms that the starting acetals (IIb and IIIb) were indeed the 1,3-dioxane compounds, since the corresponding 1,3-dioxolanes IVa have been shown[4] to give a mixture of four substances under these conditions. As both isomers IIb and IIIb afforded the same pattern in the n.m.r. spectrum after identical treatment, this also constitutes additional proof of their epimeric nature.

An assignment of the configuration of the double bond in the mixture of VIIc and d can be made from the observed coupling constants of this pair of doublets.[10] That centered at $\delta$ = 6.16 p.p.m. ($J$ 12.5 c.p.s.) is assigned to the *trans* configuration (VIId), whereas that centered at $\delta$ = 5.84 p.p.m. ($J$ = 6.5 c.p.s.) belongs to the *cis* isomer VIIc. The difference in the chemical shifts between the *trans* and *cis* protons agrees well with that found[10b] (0.32 p.p.m.) in similar enol ethers, in which $J_{cis}$ = 6.3 and $J_{trans}$ = 12.7 c.p.s.




The ratio of the amounts of *cis*- to *trans*-1-alk-1'-enylglycerol isomers obtained from IIb and IIIb, respectively, differed, as shown by the n.m.r. spectra of VIIc and VIId. The *cis*:*trans* ratio obtained from IIIb was about 1:4, while that from IIb was about 1:2. It was possible to separate the two isomers VIIc and d by preparative g.l.p.c., although some losses were caused by aerosol formation at the temperatures used. The ratio of the retention times was 1.30, in excellent agreement with the value reported (1.29) for the *trans* and *cis* isomers of methyl 1-dodecenyl ether.[10] The *cis* isomer VIIc was eluted first and had infrared absorption

(10) (a) H. R. Warner and W. E. M. Lands, *J. Am. Chem. Soc.*, **85**, 60 (1963); (b) F. Bohlmann, *Tetrahedron Letters*, **No. 24**, 1605 (1963).

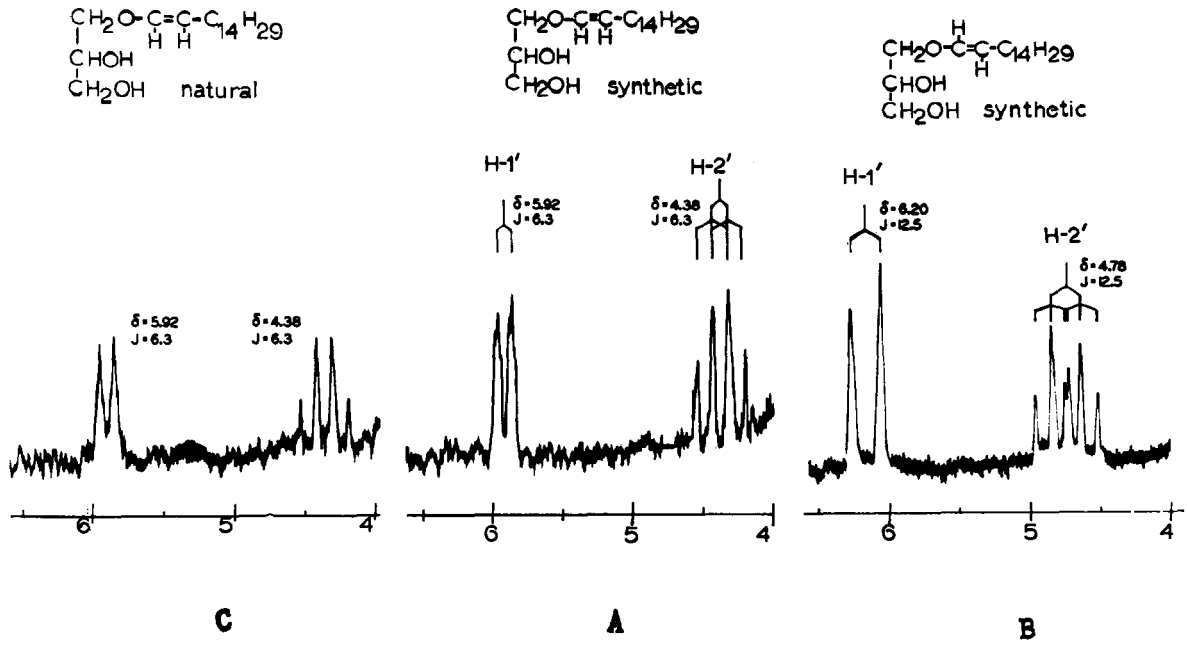



Figure 2.—N.m.r. spectra of 3-(hexadec-1′-enyloxy)-1,2-propanediol: (A) *cis* isomer, synthetic; (B) *trans* isomer, synthetic; and (C) natural product from plasmalogen. Olefinic proton region.

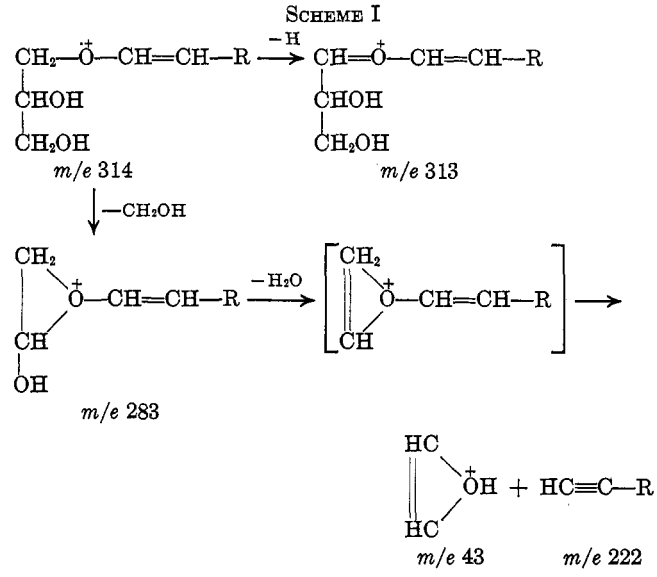
at 1739 (-OCOMe), 1677 (singlet, *cis* O—C=C), and 735 cm.$^{-1}$ (*cis* CH=CH), the last as a shoulder on the adjacent long-chain methylene absorption band. Its n.m.r. spectrum showed a doublet centered at $\delta$ = 5.87 p.p.m. ($J$ = 6.5 c.p.s.) assigned to the hydrogen on the olefinic C-1′. Higher resolution revealed that each half of this doublet was further split by long-range coupling into a triplet with a further coupling constant of *ca.* 1.5 c.p.s. This type of long-range coupling ($J$ = 1 to 2 c.p.s.) is known[8b] to be due to interaction of the olefinic hydrogen on C-1′ with the methylene hydrogens on C-3′ of the alkyl chain, four bonds away.

The spectrum also showed a broadened four-line pattern which could be interpreted as a pair of triplets centered at $\delta$ = 5.13 p.p.m. with a coupling constant of $J$ = 6.5 c.p.s. between the centers of the two. The coupling constant within each triplet was *ca.* 5.5 c.p.s. This signal is accordingly assigned to the proton on the olefinic C-2′ of the alkenyl group, which would be expected to show such a pattern.

The *trans* isomer VIId had m.p. 39–41° and was characterized by infrared absorption at 1739 (-OCOMe), 1677, 1655 (doublet, *trans* O—C=C), and 930 cm.$^{-1}$ (*trans* CH=CH). The n.m.r. spectrum disclosed a doublet centered at $\delta$ = 6.20 p.p.m. ($J$ = 12.5 c.p.s.) assigned to the hydrogen on C-1′ of the alkenyl chain. A pattern of six lines could be interpreted as a pair of triplets centered at $\delta$ = 4.78 p.p.m. ($J$ = 12.5 c.p.s.),[10] and a coupling constant within the triplets of 7 c.p.s., and is assigned to the hydrogen on C-2′ of the alkenyl group.

Alkaline hydrolysis[11] of the *cis* compound VIIc gave *cis*-1-hexadec-1′-enylglycerol (VIIa), purified by chromatography on silicic acid,[10a] as crystals, m.p. 45–47°. In the infrared spectrum, bands at 3356 (-OH), 3030 (w) (C—CH=), 1680 (singlet, *cis* O—C=C), and 740 cm.$^{-1}$ (*cis* CH=CH) could be seen. Its n.m.r. spectrum in the region of the olefinic protons (4–7 p.p.m.) is shown in Figure 2. The mass spectrum of the compound VIIa (Figure 3A) shows a weak molecular ion peak at mass $m/e$ 314, and a strong M − 1 peak at $m/e$ 313, typical of vinyl ethers and ketals. Its fragmentation pattern[12] may be accounted for by Scheme I (R = $n$-$C_{14}H_{29}$). Thermal cyclization to the acetal, followed by cleavage, gives the resonance-stabilized cationic fragment corresponding to the base peak of $m/e$ 103 (Scheme II, R = $n$-$C_{15}H_{31}$). The rest of the spectrum was consistent with the assigned structure and molecular weight for VIIa.

SCHEME I




Alkaline hydrolysis[11] of the acetate groups in the *trans* isomer VIId gave the *trans*-1-hexadec-1′-enylglycerol VIIb, m.p. 59–61°. Its infrared absorption at 3367 (-OH), 1680, 1656 (doublet of *trans* O—C=C), and 930 cm.$^{-1}$ (*trans* CH=CH) was in full agreement

(11) W. T. Norton, E. L. Gottfried, and M. M. Rapport, *J. Lipid Res.*, 3, 456 (1962).

(12) (a) K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962; (b) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964.

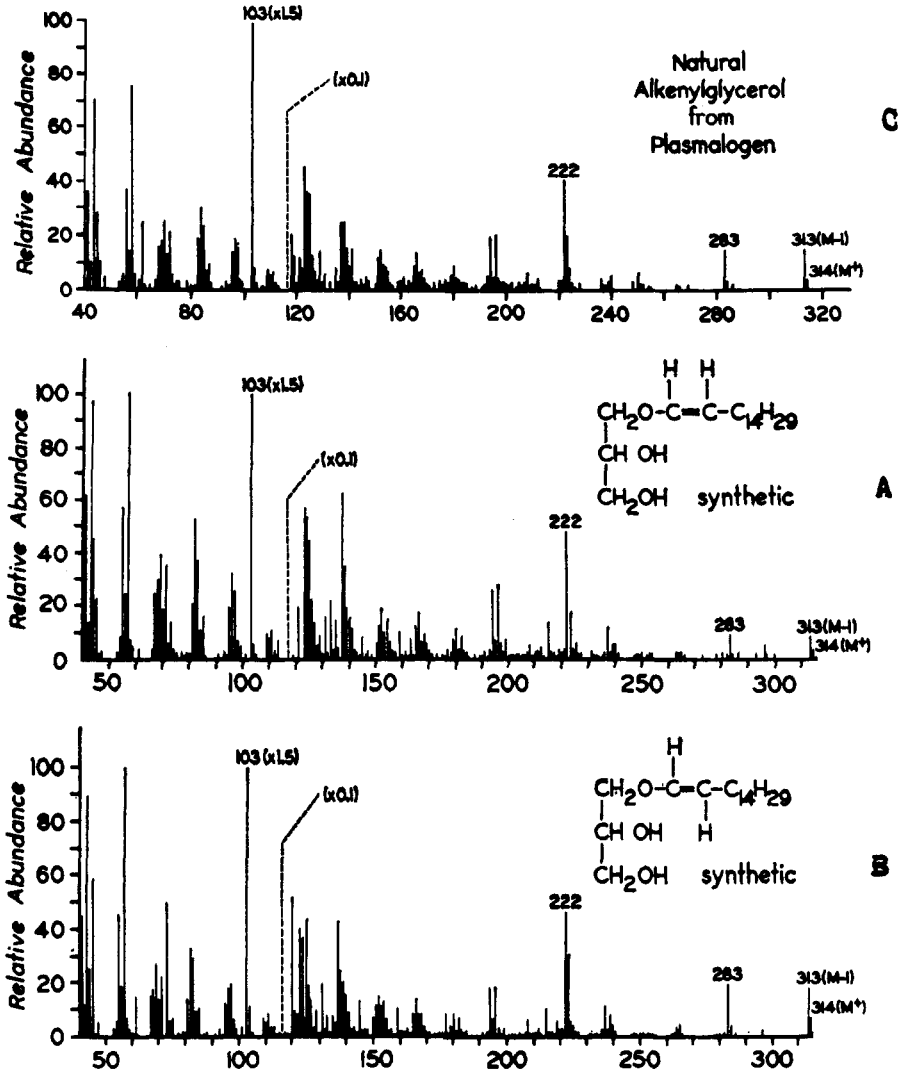
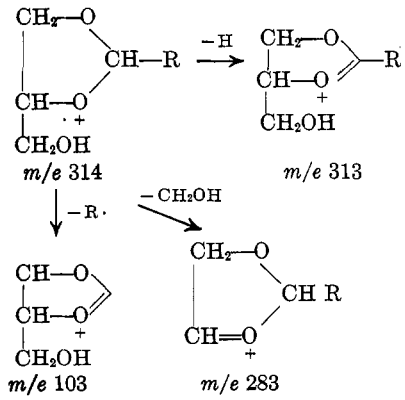



Figure 3.—Mass spectra of 3-(hexadec-1′-enyloxy)-1,2-propanediol: (A) *cis* isomer, synthetic; (B) *trans* isomer, synthetic; and (C) natural product from plasmalogen.

SCHEME II




with the structure assigned, as was the n.m.r. spectrum, shown in Figure 2B for the olefinic proton region (4–7 p.p.m.).

It is interesting that the positions of the olefinic protons in the *cis*-diol VIIa (Figure 2A) show that marked deshielding of the hydrogen at C-2′ of the alkenyl group had occurred in the *cis*-diacetate VIIc, whereas in both the *trans*-diacetate VIId and in the *trans*-diol VIIb, this hydrogen has the same chemical shift. A possible explanation may be found in the stereochemistry of VII about the double bond, which does not permit interaction between the acetate carbonyl and the *trans* hydrogen at C-2′, but allows it in the case of the *cis* isomer.

The mass spectrum (Figure 3B) of this *trans* isomer also gave a molecular ion at *m/e* 314 mass units and the same base peak of *m/e* 103. The intensity of this parent peak was greater in the *trans* than in the *cis* compound, suggesting that the thermal formation of the acetal occurs more easily in the *trans* isomer. The rest of the spectrum agreed with that of Figure 3A.

A sample of the natural optically active alkenylacylglycerol[10a] was hydrolyzed[11] and purified by silicic acid chromatography.[10a] The n.m.r. spectrum (Figure 2C) and mass spectrum (Figure 3C) of the natural alkenylglycerol agreed in all respects with those of the synthetic racemic *cis* isomer VIIa. The infrared spectra of the two compounds, taken in the solid state, showed only minor differences in the fingerprint (800–1300 cm.$^{-1}$) region which may be ascribed to the different crystal forms existing in the solid phase in the racemic and the optically active forms.[13] When the natural alkenylglycerol was converted into its liquid diacetate, both the n.m.r. and the infrared spectra of this and of the

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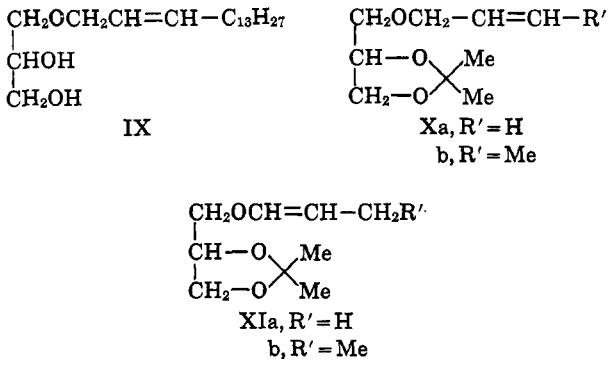
synthetic *cis*-diacetate VIIc were completely identical.

Racemic chimyl alcohol was synthesized by reaction of the *p*-toluenesulfonyl ester of 1,2-isopropylideneglycerol[14] with the sodium salt of *n*-hexadecanol, followed by hydrolysis of the resulting 4-(*n*-hexadecyloxymethyl)-2,2-dimethyldioxolane[15] (VIII). The synthetic (±)-chimyl alcohol was identical in melting point, mixture melting point, and infrared spectrum with the products of hydrogenation obtained from both the synthetic *cis*- and *trans*-1-hexadec-1′-enylglycerol VIIa and b.

The prototropic rearrangement of allylic ethers $R'OCH_2CH{=}CH_2$ to 1-alkenyl ethers $R'OCH{=}CH{-}CH_3$ is well known[16] for both aliphatic and cyclic cases (*e.g.*, 3-butoxy-2-methylpropene gave 1-butoxy-2-methylpropene, and 2,5-dihydrofuran rearranged to 2,3-dihydrofuran) and has been shown to take place by a highly stereospecific cyclic mechanism yielding exclusively the *cis* isomer of the 1-alkenyl compound. It was therefore of considerable interest to examine the applicability of this rearrangement to the allyl ether X which would be expected to lead to the desired *cis*-1-alkenylglycerol (VIIa) in one step.



IX



Xa, R′ = H
b, R′ = Me



XIa, R′ = H
b, R′ = Me

In order to avoid the risk of addition of one of the hydroxyl groups to the double bond to give a cyclic acetal[4] during the reaction, the alkali-stable isopropylidene ketals Xa and b were chosen as model compounds, and were prepared by alkylation of isopropylideneglycerol with the appropriate alkenyl bromide. The former compound has been previously obtained[17] from allyl bromide and isopropylideneglycerol benzoate. The rearrangement is normally carried out[16a] at 150–175° but has been found[16b] to proceed *ca.* $10^3$ times faster in dimethyl sulfoxide. When the allyl ether Xa was left at room temperature for 3 days with potassium *t*-butoxide in dry dimethyl sulfoxide, complete rearrangement to the desired 1-propenyl ether XIa took place as shown by the appearance of infrared bands at 1666 cm.$^{-1}$ (strong), corresponding to *cis* O—CH=CH, and 723 cm.$^{-1}$ (*cis* CH=CH), and the disappearance of the absorption at 1640 (–CH=$CH_2$) and 926 cm.$^{-1}$ (=$CH_2$) present in Xa. However, under the same conditions, the 2-butenyl compound Xb remained completely unchanged. It must therefore be concluded that the rearrangement may be applicable only to allyl ethers $R'OCH_2CH{=}CHR$ in which the substituent R is either hydrogen or has electron-attracting properties, whereas the electron movement leading to rearrangement is opposed by the inductive effect due to an electron-repelling alkyl group R, except in the favorable environment existing in 2,5-dihydrofuran where this inductive effect of the methylene group is neutralized by the adjacent ether oxygen of the ring. This explanation is supported by the ready isomerization of 2,5- into 2,3-dihydrofuran with *t*-butyl alcoholic potash,[18a] and by the resistance of 5,6-dihydro-α-pyran to potassium hydroxide in ethylene glycol.[18b] It is also in agreement with the numerous reported rearrangements of allyl to propenyl ethers,[16] and with the ready isomerization of 2-oxo-2,5-dihydrofuran (γ-crotonolactone) into 2-oxo-2,3-dihydrofuran under the influence of phenylhydrazine (as shown by the isolation of succinic hemialdehyde as the hydrazone–hydrazide[19]), whereas crotyl ethyl ether (1-ethoxy-2-butene) resisted prolonged refluxing with alcoholic alkali,[20] even though the anticipated rearrangement product (1-ethoxy-1-butene) has been prepared in another way.[21] Thus, the reported[16a] failure of 3-*n*-propoxycylohexene to isomerize to 1-*n*-propoxycyclohexene may be due to the same electronic effect which opposes the rearrangement of 5,6-dihydro-α-pyran and crotyl ethyl ether, and not to the *trans* structure of the product, as was proposed.[16a] The alkaline rearrangement of 2-ethoxy-2,5- to 2-ethoxy-4,5-dihydrofuran (and thence to γ-butyrolactone with acid) would be a test case, but the action of alkali on the first-named compound[22] was not reported.

In view of the failure of Xb to rearrange, this route was not further investigated.

## Experimental Section[23]

***n*-Hexadecanal from Bisulfite Compound.**—A solution of 40 g. of sodium carbonate in 400 ml. of water was heated to 90° and 400 ml. of heptane were added to form the top layer. The mixture was rapidly stirred (magnetic stirrer), and 20 g. of hexadecanal bisulfite compound was added gradually in small portions to the refluxing system. When the evolution of gas had ceased, the mixture was poured into water, and the organic phase was washed with water and filtered to remove traces of unchanged bisulfite compound. Evaporation of the dried (anhydrous magnesium sulfate) heptane layer *in vacuo* yielded 20 g. (96% yield) of *n*-hexadecanal as an oil which solidified on cooling, m.p. 32–34°, and showed $\nu_{max}$ 1724 cm.$^{-1}$ (–CHO). It was used immediately for the next step.

***n*-Hexadecen-1-ol-1 Acetate.**—A solution of 10.6 g. *n*-hexadecanal in 50 ml. of isopropenyl acetate was heated to boiling point in nitrogen, and 1 g. of *p*-toluenesulfonic acid was then added. The mixture was allowed to distil slowly for 6 hr., more isopropenyl acetate being added when necessary. It was then cooled and poured into sodium bicarbonate solution, and the organic layer was washed with sodium bicarbonate solution and then with water and dried over anhydrous sodium sulfate. Dis-

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(23) Melting points were determined using a Kofler hot stage and are corrected. Infrared spectra were measured on a Perkin-Elmer 337 instrument. N.m.r. spectra were obtained on a Varian A-60 spectrometer in deuteriochloroform solution and chemical shifts are reported in parts per million (δ) measured downfield from an internal tetramethylsilane reference. Analyses were carried out by the Microanalytical Laboratory, University of California, Berkeley, Calif.

tillation gave 9.0 g. (72% yield) of the enol acetate, b.p. 125–130° (0.1 mm.), $n^{25}D$ 1.4494, $\nu_{max}$ 1760 (-OCOCH$_3$) and 1675 cm.$^{-1}$ (-O—C=C).

**5-Benzyloxy-2-phenyl-1,3-dioxane (Ib).**—Sodium hydride (6.5 g. of a 50% suspension in mineral oil) was mixed with 20 ml. of 1,2-dimethoxyethane, and to this was added slowly, with stirring and cooling, 20 g. of 1,3-benzylideneglycerol[7a] in 120 ml. of 1,2-dimethoxyethane. After the evolution of hydrogen had ceased, 21.5 g. of benzyl bromide was added and the mixture was allowed to stir overnight. It was then poured into water, extracted with ether, washed (water), dried (magnesium sulfate), and evaporated to yield a crystalline product which was washed with hexane to remove mineral oil, yielding 29.0 g. (96% yield) of the benzyl ether, m.p. 77–78° after crystallization from benzene–hexane (lit.[7c] m.p. 77–78°).

**Transacetalation of Glycerol 2-Benzyl Ether with 2-Bromo-1,1-dimethoxyhexadecane.**—A mixture of 7.56 g. of 2-bromo-1,1-dimethoxyhexadecane[4] and 3.89 g. of glycerol 2-benzyl ether (m.p. 36–38°, lit.[7c] m.p. 37–39°) was heated to 140° with stirring, when methanol began to distil off. After 20 min. the temperature was gradually raised to 165° during which time the mixture became homogeneous and distillation of methanol ceased. The light brown liquid was poured into very dilute sodium hydroxide solution, extracted with ether, washed with water, and dried over magnesium sulfate. Evaporation yielded 9.7 g. of a pale brown liquid which crystallized overnight at room temperature and had m.p. 31–43°.

The mixture was put on an alumina column (250 g. of P. Spence grade H alumina) in hexane. Elution with 2% benzene in hexane gave 1.8 g. of *trans*-2-(1′-bromopentadecyl)-5-benzyloxy-1,3-dioxane (IIa), m.p. 40–42°, which after crystallization from ether–ethanol had m.p. 46–47°.

*Anal.* Calcd. for $C_{26}H_{43}BrO_3$: C, 64.65; H, 8.93; Br, 16.55. Found: C, 64.55; H, 9.02; Br, 16.36.

Further elution with 10% benzene in hexane afforded 3.7 g. of *cis*-2-(1′-bromopentadecyl)-5-benzyloxy-1,3-dioxane (IIIa), m.p. 62–64°, which crystallized from ether–ethanol, m.p. 66–68°.

*Anal.* Found: C, 64.82; H, 9.00; Br, 16.39.

**Hydrogenolysis of Benzyl Ethers IIa and IIIa.**—A solution of 1.1 g. of *cis*-2-(1′-bromopentadecyl)-5-benzyloxy-1,3-dioxane (IIIa) in 15 ml. of ethyl acetate was hydrogenolyzed at 55° over 147 mg. of palladium oxide under hydrogen at atmospheric pressure for 3 hr. The catalyst was removed by filtration and the solvent was evaporated to yield 1.01 g. of *cis*-2-(1′-bromopentadecyl)-5-hydroxy-1,3-dioxane (IIIb), m.p. 80–82°, which after recrystallization from hexane had m.p. 81–82°.

*Anal.* Calcd. for $C_{19}H_{37}BrO_3$: C, 58.02; H, 9.51; Br, 20.28. Found: C, 58.27; H, 9.46; Br, 19.98.

In the same way, the *trans* epimer IIa gave *trans*-2-(1′-bromopentadecyl)-5-hydroxy-1,3-dioxane (IIb), m.p. 74–75°.

*Anal.* Found: C, 58.24; H, 9.43; Br, 20.04.

**5-Acetoxy-2-(1′-bromopentadecyl)-1,3-dioxane Epimers (IIc and IIIc).**—Acetylation of *trans*-2-(1′-bromopentadecyl)-5-hydroxy-1,3-dioxane (IIb) with acetic anhydride in pyridine at room temperature 16 hr. gave the *trans*-acetoxy compound IIc, m.p. 47–49° from ethanol.

*Anal.* Calcd. for $C_{21}H_{39}BrO_4$: C, 57.88; H, 9.04; Br, 18.32. Found: C, 57.78; H, 8.84; Br, 18.34.

Acetylation of IIIb in the same manner afforded the *cis*-acetoxy epimer IIIc as crystals, m.p. 95–96° from ethanol.

*Anal.* Found: C, 57.64; H, 8.95; Br, 18.54.

**Debromination of 2-(1′-Bromopentadecyl)-5-hydroxy-1,3-dioxane Epimers (IIb and IIIb) with Lithium. A.**—Dry 1,2-dimethoxyethane (75 ml.) was stirred at 65° with 1.0 g. of finely chopped lithium metal. After addition of 0.9 g. of *cis* epimer IIIa, the mixture was stirred at 65–70° for 24 hr. Excess lithium was filtered off; the solution was poured into water, extracted with ether, washed with water, dried over magnesium sulfate, and evaporated to yield 0.71 g. of waxy solid, which was immediately acetylated with acetic anhydride in pyridine at room temperature for 16 hr. Working up gave 0.84 g. of a mixture of *cis*- and *trans*-hexadec-1-enyl 2,3-diacetoxy-*n*-propyl ethers VIIc and VIId which crystallized on standing at 0°. The infrared spectrum showed bands at 1739 (-OCOMe), 1678, 1667 (-O—C=C), and 930 cm.$^{-1}$ (*trans* —C=C); the n.m.r. spectrum had doublets at $\delta$ = 6.16 ($J$ = 12.5 c.p.s.) and 5.84 p.p.m. ($J$ = 6.5 c.p.s.). The ratio of the integrated intensities of the two doublets was *cis*:*trans* = 20:80.

Vapor phase chromatography was carried out using a 5 ft. × 0.25 in. column of 30% QF1 fluorosilicone on Celite at 238° with 15 p.s.i. of helium as carrier gas. Only two components were present: the *cis* isomer VIIc, retention time 30 min., and the *trans* isomer VIId, retention time 39 min. The ratio *cis*:*trans* was 1:4, and the ratio of the retention times was 1.30.

**B.**—Identical treatment of *trans*-2-(1′-bromopentadecyl)-5-hydroxy-1,3-dioxane (IIa) gave a mixture of VIIc and VIId with the same infrared spectrum as that obtained in A above. The n.m.r. spectrum was also identical, except that the ratio of the integrated intensities of the two doublets was *cis*:*trans* = 34:66. This was confirmed by vapor phase chromatography which gave VIIc and VIId in the ratio *cis*:*trans* = 1:2.

**Separation of *cis*- and *trans*-Hexadec-1′-enyl 2,3-Diacetoxy-*n*-propyl Ethers (VIIc and VIId).**—Vapor phase chromatography using the same conditions as described above gave two fractions. (1) The *cis* isomer VIIc was a colorless liquid: infrared spectrum 1739 (-OCOMe), 1677 (*cis* O—C=C), and 735 cm.$^{-1}$ (*cis* CH=CH); n.m.r. spectrum doublet at $\delta$ = 5.87 p.p.m. ($J$ = 6.5 c.p.s.) (olefinic H on C-1′), pair of triplets at $\delta$ = 5.13 p.p.m. ($J$ = 6.5 c.p.s.) (olefinic H on C-2′).

(2) The *trans* isomer VIId crystallized on standing: m.p. 39–41°; infrared spectrum 1739 (-OCOMe), 1677, 1655 (*trans* O—C=C), 930 cm.$^{-1}$ (*trans* CH=CH); n.m.r. spectrum doublet at $\delta$ = 6.20 p.p.m. ($J$ = 12.5 c.p.s.) (olefinic H on C-1′), pair of triplets at $\delta$ = 4.78 p.p.m. ($J$ = 12.5 c.p.s.) (olefinic H on C-2′).

*Anal.* Calcd. for $C_{23}H_{42}O_5$: C, 69.31; H, 10.62. Found: C, 69.67; H, 10.68.

***cis*- and *trans*-3-(Hexadec-1′-enyloxy)-1,2-propanediol (VIIa and VIIb). A.**—Alkaline hydrolysis[10a] of *cis*-hexadec-1′-enyl 2,3-diacetoxypropyl ether (VIIc), followed by chromatography on silicic acid,[11] was carried out as described for the isolation of the natural product. Low-temperature crystallization from pentane gave *cis*-3-(1′-hexadecenyloxy)-1,2-propanediol (VIIa) as crystals: m.p. 45–47°; infrared spectrum 3356 (-OH), 1680 (*cis* O—C=C), and 740 cm.$^{-1}$ (*cis* CH=CH). Its n.m.r. spectrum is shown in Figure 2A, and its mass spectrum in Figure 3A.

*Anal.* Calcd. for $C_{19}H_{38}O_3$: C, 72.50; H, 12.18. Found: C, 72.12; H, 11.97.

**B.**—In the same way, *trans*-3-(hexadec-1-enyloxy)-1,2-propanediol (VIIb) was obtained as crystals from pentane: m.p. 59–61°; infrared spectrum 3367 (-OH), 1680, 1656 (*trans* O—C=C), and 930 cm.$^{-1}$ (*trans* CH=CH). Its n.m.r. spectrum is shown in Figure 2B, and its mass spectrum in Figure 3B.

*Anal.* Found: C, 72.28; H, 11.85.

**Hydrogenation of *cis*- and *trans*-Hexadec-1′-enylglycerol.**—Both isomers were hydrogenated in the same manner. The diol (1 mg.) was dissolved in 0.5 ml. of ethyl acetate and hydrogenated over 1 mg. of platinum oxide at 30 p.s.i. of hydrogen for 4 hr. The catalyst was filtered off, the solvent was evaporated, and the residue was filtered through a short silicic acid column.

The *cis* isomer gave crystals, m.p. 59–62°, while the *trans* isomer gave crystals, m.p. 60–63°. Both were identical in their infrared spectra, melting point, and mixture melting point with synthetic (±)-chimyl alcohol, m.p. 61–63° (see below).

**4-(*n*-Hexadecyloxymethyl)-2,2-dimethyldioxolane (VIII).**—A mixture of 507 mg. of 1-hexadecanol and 212 mg. of sodium hydride in 10 ml. of 1,2-dimethoxyethane was heated under reflux until evolution of hydrogen ceased. A solution of 550 mg. of 2,2-dimethyl-4-*p*-toluenesulfonyloxymethyldioxolane[14] in 5 ml. of 1,2-dimethoxyethane was added, and the mixture was heated under reflux for 24 hr. It was then cooled, poured into water, and extracted with ether, giving 750 mg. of 4-(hexadecyloxymethyl)-2,2-dimethyldioxolane as crystals from aqueous ethanol, m.p. 50–52°. The infrared spectrum showed that the bands due to sulfonate ester (1355 and 1167 cm.$^{-1}$) had disappeared. The material was used immediately for the next step.

**(±)-Chimyl Alcohol.**—A solution of 500 mg. of the preceding dioxolane, 50 ml. of ethanol, and 25 ml. of 2 *N* hydrochloric acid was heated under reflux for 4 hr. It was poured into water and extracted with ether, giving 450 mg. of (±)-chimyl alcohol, purified by chromatography on silicic acid. Elution with ether and recrystallization from hexane gave crystals, m.p. 61–63° (lit.[15] m.p. 62–63°), showing infrared absorption at 3350 cm.$^{-1}$ (OH).

**2,3-Dimethyl-4-(allyloxymethyl)dioxolane (Xa).**—Sodium methoxide (5.4 g., 0.1 mole) was added to 40 ml. of 2,2-dimethyl-4-hydroxymethyldioxolane, and the mixture was heated to 150° until all methanol had distilled off. The cooled mixture was treated with 6.0 g. of allyl bromide and stirred at room temperature for 20 hr. Ether was added, the solid filtered off, and the

ethereal layer was washed (water) and dried (magnesium sulfate). Distillation gave the dioxolane, b.p. 76–78° (20 mm.), $n^{24}D$ 1.4307 [lit.[17] b.p. 87° (22 mm.), $n^{19}D$ 1.4326], $\nu_{max}$ 1640 (w) (–C=C–) and 926 cm.$^{-1}$ (–CH=$CH_2$).

**Rearrangement of 2,2-Dimethyl-4-(allyloxymethyl)dioxolane.**—A mixture of 0.3 ml. of the dioxolane Xa and 117 mg. of potassium *t*-butoxide in 4 ml. of dry dimethyl sulfoxide was left at room temperature for 3 days. The mixture was poured into water and extracted with ether, and the ethereal extracts were washed with water and dried over anhydrous magnesium sulfate. Evaporation gave 2,2-dimethyl-4-(prop-1′-enyloxymethyl)dioxolane (XIa) as an oil showing infrared absorption bands at 1666 (s) (*cis* O—C=C–) and 723 cm.$^{-1}$ (*cis* CH=CH), and no absorption at 1640 or 926 cm.$^{-1}$.

**2,2-Dimethyl-4-(2′-butenyloxymethyl)dioxolane (Xb).**—Prepared in the same manner as Xa using 6.8 g. of 1-bromo-2-butene, the dioxolane was obtained (5 g., 53% yield) as an oil, b.p. 95° (20 mm.), $n^{23}D$ 1.4362, showing infrared absorption bands at 1660 (w) and 967 cm.$^{-1}$ (*trans* CH=CH bending).

The compound was recovered unchanged after attempted rearrangement with potassium *t*-butoxide in dimethyl sulfoxide.

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# Ketenes. V. Reactions of Ketenes with Dienes and Olefins[1]

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Butylethylketene undergoes 1,2 cycloadditions with 1,3-butadiene, alkyl-substituted butadienes, and 1,3-butadienyl methyl ether to give substituted cyclobutanones. Methyl 1-methyleneallyl ether combines with ketoketenes in a 1,4 addition to give 5,6-dihydro-4-methoxy-2H-pyrans. Cyclopentadiene and indene add 1,2 to dimethylketene. 2,4-Dimethyl-2,3-pentadiene reacts very readily with ketenes to give cyclobutanones. Butylethylketene undergoes 1,2 cycloadditions with nonactivated cyclic and acyclic olefins at elevated temperatures to give cyclobutanones.

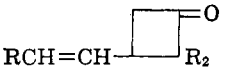
Ketenes usually add to monoolefinic compounds by 1,2 cycloaddition. Where the evidence is well documented, the tendency for 1,2 cycloaddition also applies in the reaction of ketenes with conjugated dienes. Staudinger and Suter noted the ready reaction of diphenylketene with isoprene and with 2,3-dimethyl-1,3-butadiene, but they isolated no crystalline products, and only surmised that 1,4 cycloaddition took place to form cyclohexenones.[2] Later studies showed, through definite structural assignments, that diphenylketene formed 1,2 cycloadducts with cyclic dienes[3–8]; by analogy, and with good evidence against 1,4 cycloaddition, the reaction with acyclic dienes was formulated in the same way.[3,5,9]

Similar studies with ketene and the higher aliphatic ketenes have been limited chiefly to adducts with cyclopentadiene,[10–19] and here 1,2 cycloaddition is also firmly established. A low yield of 1,2-cycloadduct was obtained from the reaction of 1,3-butadiene with ketene.[20] Isoprene[21] and 2,3-dimethyl-1,3-butadiene[22] did not react with ketene at low to moderate temperatures, but at 600° some 1,4 cycloaddition to the latter diene was suggested.[22] Only one addition of higher aliphatic ketenes to acyclic dienes has been reported.[23] Bestian and Günther generated dimethylketene at 140° in the presence of excess 1,3-butadiene to give a 1,2-cycloadduct.

After a thorough consideration of prior work in the field, the following generalizations can be made: (1) diphenylketene is very reactive with dienes even at room temperature; (2) dimethylketene is less reactive than diphenylketene and dimerizes rapidly, so that cycloadditions are possible only at moderate temperatures and with fairly nucleophilic olefins (except when the dimethylketene is generated *in situ* at elevated temperatures in the presence of a diene); (3) butylethylketene is less reactive than dimethylketene, but because of its slow rate of dimerization, cycloadditions have been forced with various olefins by use of higher temperatures[24]; and (4) ketene is even less reactive than butylethylketene in 1,2 cycloaddition reactions and generally must be heated, even with such active dienes as cyclopentadiene.

This paper describes our work concerning the cycloaddition of a variety of dienes to ketenes. We observed that dialkylketenes undergo 1,2 cycloaddition with dienes to give 3-vinylcyclobutanones, according to the general equation

$$R_2C{=}C{=}O + RCH{=}CHCH{=}CH_2 \longrightarrow$$

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