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ACTION OF BORON TRIFLUORIDE ETHERATE ON UNSATURATED EPOXYCOMPOUNDS

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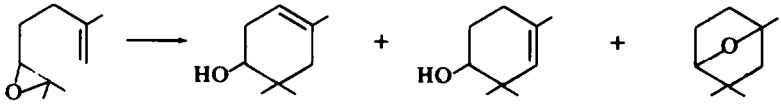
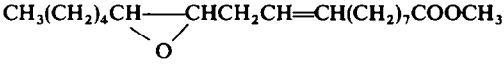
Abstract—The reaction of methyl 12,13-epoxyoctadec-9-enoate (VII) and methyl 9,10-epoxyoctadec-12-enoate (VIII) with BF_3-etherate yielded mixtures of cyclic and unsaturated acyclic compounds. The latter arise from usual reactions of epoxy compounds with Lewis acids. The main cyclic products were the *cis*- and *trans*-isomers of methyl 9-methylene-12-oxoheptadecanoate (V) and methyl 9-oxo-11-methylene-heptadecanoate (XX) obtained from the epoxy esters (VII) and (VIII) respectively. A minor quantity of the 2,4-disubstituted 3-oxabicyclo[3.1.0]hexane (XVI) was formed from each epoxy ester. The formation of the cyclic products is hypothesized as arising from cationic intermediates which are formed by the participation of the double bond in epoxide ring opening. The stereochemical course of the reaction is discussed.

THE reaction of epoxy olefins with Lewis acids yields alcohols or ethers of the cyclopentane, cyclohexane, and cycloheptane series via an intramolecular nucleophilic attack of the double bond on the incipient carbonium ion.[1] Thus, for example, the epoxy olefin I on treatment with BF_3-etherate is transformed into a mixture of products from which the two alcohols II and the ether III may be isolated.[2]

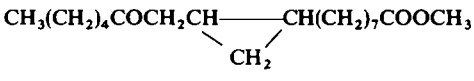


I II III

With one exception, in all examples reported the double bond and the oxirane system are separated by at least two C atoms. The exception is that described by Conacher and Gunstone[3] who reported an unusual rearrangement of methyl



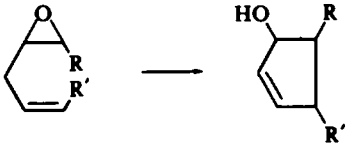
IV



V

vernolate (IV) on acid treatment. The reaction of IV with BF_3-etherate gives a mixture of the *cis*- and *trans*-ketocyclopropanes (V) as well as other acyclic products.

Assuming a mechanism similar to that which leads to the formation of the alcohols (II), the monoepoxides VII and VIII* were treated with BF_3-etherate in anticipating that products such as IX and structurally related to prostaglandins[4] could be obtained.



IX

An analogous mechanism for the biosynthesis of the prostaglandins from essential fatty acids has been suggested,[5] but subsequent biochemical studies[6] have not confirmed this.

The reaction of the monoepoxides VII and VIII with BF_3-etherate did not lead to the formation of compounds of type IX but yielded mixtures containing saturated cyclic and unsaturated acyclic products corresponding in part to those obtained by Conacher and Gunstone.[3]

A preliminary examination of the crude reaction mixture (GLC-MS) identified the products from VII as methyl 12- and 13-ketooctadec-9-enoate (X and XI) and methyl 12-hydroxyoctadecadienoate (XII) and the products from VIII as methyl 9- and 10-ketooctadec-12-enoate (XIII and XIV) and methyl 9-hydroxy-10-fluoro-octadecenoate XV.†

$$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOCH_3$$

VI

$$CH_3(CH_2)_4CH\!-\!\underset{\diagdown\,O\,\diagup}{}\!CHCH_2CH{=}CH(CH_2)_7COOCH_3$$

VII

$$CH_3(CH_2)_4CH{=}CHCH_2CH\!-\!\underset{\diagdown\,O\,\diagup}{}\!CH(CH_2)_7COOCH_3$$

VIII

$$CH_3(CH_2)_4CH_2COCH_2CH{=}CH(CH_2)_7COOCH_3$$

X

$$CH_3(CH_2)_4COCH_2CH_2CH{=}CH(CH_2)_7COOCH_3$$

XI

$$C_6H_{11}\underset{\displaystyle OH}{\underset{|}{CH}}(CH_2)_nCH{=}CH(CH_2)_mCOOCH_3 \qquad (n + m = 8)$$

XII

* The separation and characterization of the two monoepoxides will be described in a forthcoming publication in J.A.O.C.S.

† Mass spectrometric data are reported in the Experimental section; although MS data did not indicate the position of the double bond, it is assumed that it remains in position 9 or 12.

$CH_3(CH_2)_4CH{=}CHCH_2CH_2CO(CH_2)_7COOCH_3$

XIII

$CH_3(CH_2)_4CH{=}CHCH_2COCH_2(CH_2)_7COOCH_3$

XIV

$CH_3(CH_2)_nCH{=}CH(CH_2)_mCHCH(CH_2)_7COOCH_3 \quad (n + m = 5)$

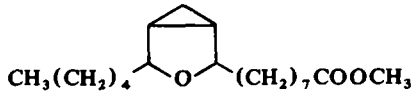
F OH

XV

As these unsaturated acyclic compounds result from the normal reactions of epoxides with acidic reagents, the saturated cyclic products present in these reaction mixtures were examined.

Treatment of the crude mixture from the reaction of methyl 12,13-epoxyoctadec-9-enoate (VII) with mercuric acetate, followed by column chromatography on alumina, resulted in the separation of the saturated esters from the considerable quantities of unsaturated esters.[7] The GLC of the saturated products indicated the presence of three compounds which were shown by GLC-MS data to be isomeric with the starting epoxy ester VII. After careful chromatography of the mixture on alumina one of these compounds appeared homogeneous in GLC and on TLC. The other two components could not be separated under preparative conditions.

On the basis of the following results the first compound was assigned the structure XVI.

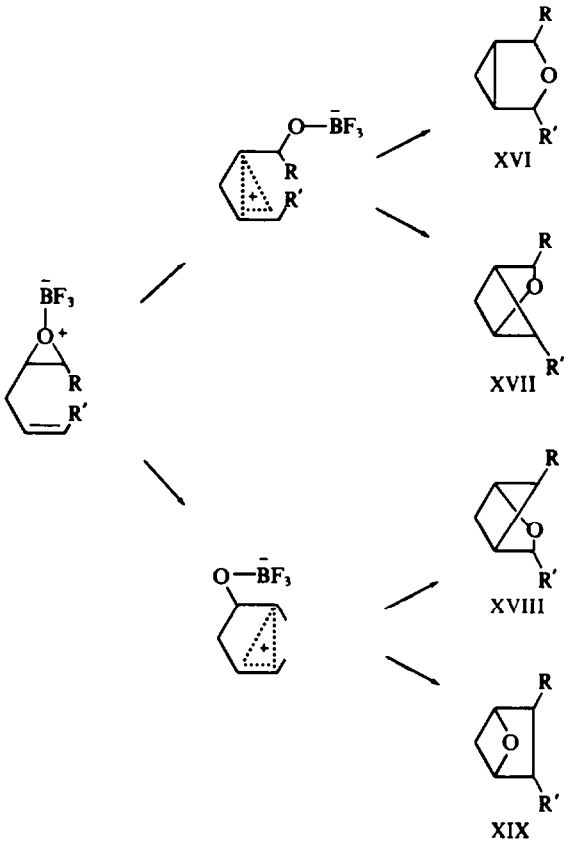


XVI

The IR spectrum of XVI lacked hydroxyl absorption but showed carbonyl absorption at 1740 cm^{-1}. The compound was recovered unchanged after treatment with acetic anhydride-pyridine, Jones' reagent, and sodium borohydride. Reduction of XVI with LAH gave a primary alcohol which on successive treatment with Jones' reagent and diazomethane reformed the starting ester XVI.

From a consideration of these results and the molecular formula of the compound ($C_{19}H_{34}O_3$), the ester XVI appeared to be a bicyclic compound which, besides the carbomethoxyl group, contained one ethereal oxygen. The mass spectrum of XVI shows intense peaks at *m/e* 239 and 153, corresponding to ions $[M{-}C_5H_{11}]^+$ and $[M{-}(CH_2)_7COOCH_3]^+$ respectively, attributed to the loss of $CH_3(CH_2)_4$— and —$(CH_2)_7COOCH_3$ chains from a ring.

On the basis of these fragmentations, one of the four structures XVI–XIX shown in Scheme 1 could be considered but structures XVIII and XIX, which arise via the mechanism illustrated in Scheme 1, are improbable according to the results obtained in other cases of intramolecular nucleophilic reactions.[8]



SCHEME 1

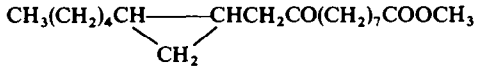
The NMR spectrum is in favour of structure XVI. The four proton multiplet between 8·6–10·5 τ is attributable to a disubstituted cyclopropane system, whereas a two proton multiplet centred at 6·2 τ is indicative of the protons at α,α'-positions of a tetrahydrofuran ring. Furthermore, the intense relative abundance of the peaks at *m/e* 239 and 153 in the mass spectrum of XVI agree with the type of fragmentation observed for the α-alkylderivatives of tetrahydrofurans and tetrahydropyrans.[9]

The other two isomers of the starting epoxy ester VII could not be separated preparatively but showed different retention times in GLC, thus allowing separate registration of their mass spectra. These proved to be identical indicating that the only difference between these two products must be of a steric nature. The spectroscopic properties and chemical behaviour of this mixture correspond with those of the *cis*- and *trans*-isomers of the ketocyclopropane (V) described by Conacher and Gunstone.[3]

The reaction mixture resulting from BF_3-etherate treatment of methyl 9,10-epoxyoctadec-12-enoate (VIII), after elimination of the unsaturated components as described above, consisted of three compounds. From this we isolated a product identical in all respects with XVI.

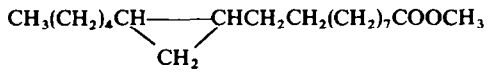
The mixture of the other two compounds, as in the case of the ketocyclopropane V, could not be separated, nevertheless GLC–MS data indicated that the two compounds are isomers of the starting epoxy ester and are stereoisomeric.

The physico-chemical data, the products of degradation, and analogy with the compounds obtained from the epoxy ester VII, indicated that these compounds are *cis*- and *trans*-ketocyclopropanes (XX).



XX

The mass spectra of XX, which shows fragments at *m/e* 185, 153, and 125, localizes the ketonic carbonyl (IR 1720 cm^{-1}) at position 9. The NMR spectrum shows a four proton signal between 9·6 and 10·6 τ, assigned to a cyclopropane system, as well as signals for six protons at 7·8 τ attributable to protons α- to carbonyl groups. Of these protons, four must be adjacent to a ketone group and consequently this cannot be conjugated with the cyclopropane ring. Since the physico-chemical results were not sufficient to establish the position of the cyclopropane ring, the desoxo derivatives XXI, obtained by reduction of the derived tosylhydrazones with sodium borohydride,[10] were degraded with chromic acid. This degradation yielded the monomethyl esters of C-9, C-10, and C-11 dicarboxylic acids, expected[3] if the cyclopropane ring is at position 11 (i.e. consisting of C-11, 12, 13).

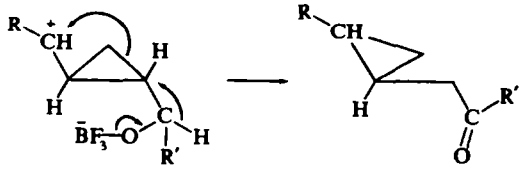


XXI

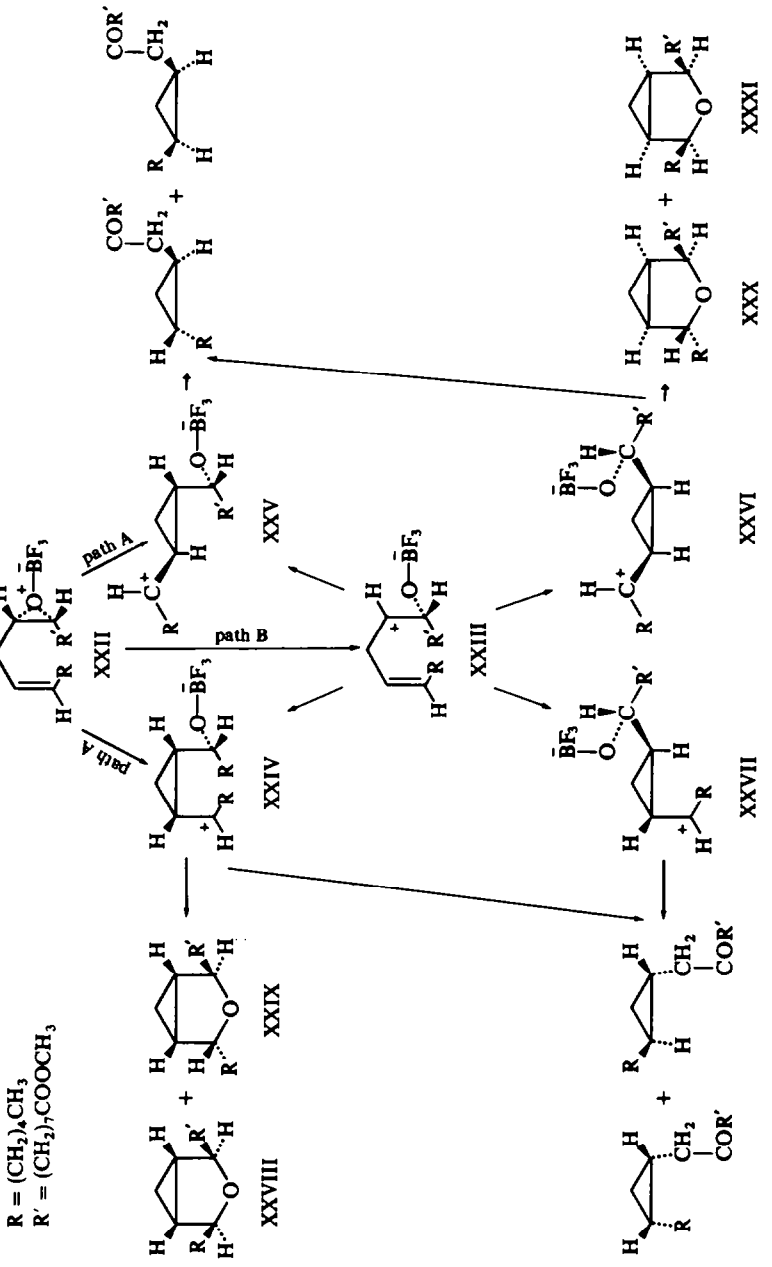
The mechanistic pathways which can be considered for the formation of the bicyclic compound XVI and of the ketocyclopropanes V and XX are shown in Scheme 2, taking for simplicity one of the antipodes of methyl 9,10-epoxyoctadec-12-enoate (VIII).*

The epoxy ester–BF_3 complex XXII can lead via a concerted process to the *cis*- and *trans*-carbonium ions XXIV and XXV respectively (path A). Alternatively (path B), the epoxide ring can open to give the ion XXIII, which can then act as precursor not only of XXIV and XXV, but also of the other *cis*- and *trans*-ions XXVI and XXVII.

From the two *trans*-intermediate ions XXV and XXVII it is possible to obtain only the ketocyclopropanes via the mechanism shown below.



* Although only one antipode is written for the compounds in Scheme 2, racemates are intended.


R = $(CH_2)_4CH_3$
R′ = $(CH_2)_7COOCH_3$
path A
path B
path A
XXII
XXIII
XXIV
XXV
XXVI
XXVII
XXVIII
XXIX
XXX
XXXI

SCHEME 2

The *cis*-intermediate ions XXIV and XXVI can lead not only to the ketocyclopropanes, but can also yield the bicyclic ethers XXVIII to XXXI. As can be seen in the scheme if the mechanism is concerted (path A) two diastereoisomeric bicyclic ethers XXVIII and XXIX can be obtained, whereas if the mechanism is not concerted (path B), beside XXVIII and XXIX, the other two isomers XXX and XXXI are possible.

The formation of a single bicyclic product can only occur if the mechanism is completely concerted, a possibility which appears highly improbable from an examination of molecular models.

A choice between path A and path B cannot be made on the basis of the results reported here. Actually the bicyclic ethers XVI appears homogeneous in GLC and on TLC, however the possibility that it is not a single compound cannot be excluded, particularly since the NMR does not indicate the stereochemistry involved. On the other hand, the configuration of the final product may be controlled by steric factors or by the deviation from planarity of the carbonium ion α- to the cyclopropane ring arising from the possible delocalization of the charge induced by that ring.[11]

EXPERIMENTAL

IR spectra were measured with a Perkin–Elmer 137 spectrophotometer. NMR spectra were measured with a Perkin–Elmer R20 spectrometer (60 Mc) in $CDCl_3$ solns containing TMS as internal standard. GLC analyses were carried out on a Perkin–Elmer F20 gàs chromatograph using a glass column packed with Chromosorb W-2·5% SE 30 at temps of 220° with a N_2 flow rate of 25 ml/min. GLC–MS analyses were conducted with an LKB 9000, using for the gas-chromatograph the conditions described above.

Reaction of methyl 9,10-*epoxyoctadec*-12-*enoate* (VIII) *with* $BF_3 \cdot Et_2O$. A soln of VIII (2·0 g; 7 mmoles) in dry benzene (125 ml) was added dropwise to a soln of freshly distilled $BF_3 \cdot Et_2O$ (0·8 ml; 6·9 mmoles) in dry benzene (200 ml), and the mixture was stirred for 2 hr at room temp. The mixture was poured into water and the organic layer was separated, washed with 8% $NaHCO_3$ aq, water and dried. Evaporation

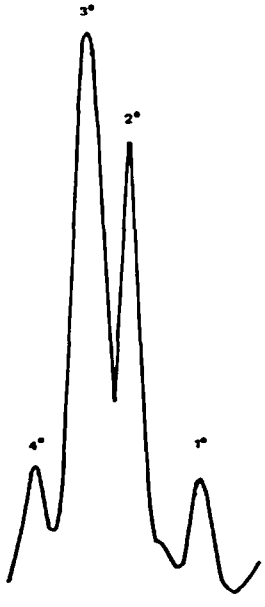


FIG. 1

of the solvent gave a product (1·98 g) which resulted a mixture of 5 compounds from an examination in GLC (Fig. 1) and GLC–MS (Table 1).

TABLE 1

Peaks (GLC)	Compounds	M.W.; fragments (MS)
1°	bicyclic ether XVI	310; 239, 153
2°	ketocyclopropane XX	310; 185, 153, 125
3°	(a) ketocyclopropane XX	310; 185, 153, 125
	(b) methyl 9-ketooctadec-12-enoate (XIII)	310; 185, 125
	(c) methyl 10-ketooctadec-12-enoate (XIV)	310; 199, 139
4°	methyl 9-hydroxy-10-fluorooctadecenoate XV	330; 219, 181, 155

Isolation of the bicyclic ether XVI. The crude reaction mixture (1·98 g) was treated with a soln of mercuric acetate in AcOH–MeOH–water.[7] After 36 hr the mixture was poured into water and extracted with ether. Evaporation of the solvent gave a product (3·2 g) which was adsorbed on Woelm alumina (Act. III; 120 g). Elution with pet ether and pet ether–3% ether gave fractions (490 mg) of the saturated cyclic products which were analysed in GLC (Fig. 2). Repeated chromatography of the mixture allowed the separation of

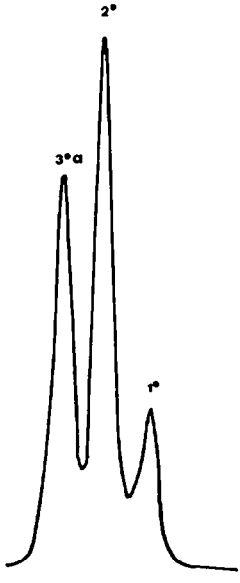


FIG. 2

the cyclic ether XVI (93 mg) from the mixture of the ketocyclopropanes XX (359 mg). The former appeared homogeneous in GLC and on TLC, IR 1740 cm^{-1} (ester). The NMR showed resonances at 8·6–10·5 τ (cyclopropane protons), 9·1 τ (3 protons triplet; secondary Me), 8·6 τ (paraffinic methylenes), 7·7 τ (2 protons; protons α- to the carbomethoxyl group), 6·3 τ (3 protons; carbomethoxy), and at 6·2 τ (2 protons; α- and α′-protons of a tetrahydrofuran).

The bicyclic ether was recovered unchanged after treatment with $NaBH_4$ in isopropylic alcohol or on treatment with Ac_2O-pyridine.

LAH *reduction of the bicyclic ether* XVI. Compound XVI (80 mg) in ether (3 ml) was treated with LAH (700 mg) in ether (5 ml) and then heated under reflux for 5 hr the mixture was carefully poured into water,

filtered and extracted with ether. Evaporation of the solvent gave a product (54 mg) homogeneous in TLC and GLC (its R_f and T_r respectively indicated it to be more polar than the starting ester). The IR spectrum ($CHCl_3$) shows absorption bands at 3600 and 3450 cm^{-1} (OH group).

A stirred soln of the alcohol (18 mg) in acetone (8 ml) was treated with Jones' reagent (0·065 ml) for 0·6 hr. The excess reagent was destroyed with isopropylic alcohol and the soln was extracted with ether. Recovery of the product gave an acid (17 mg) which on treatment with diazomethane yielded an ester identical in all respects with the bicyclic ether XVI.

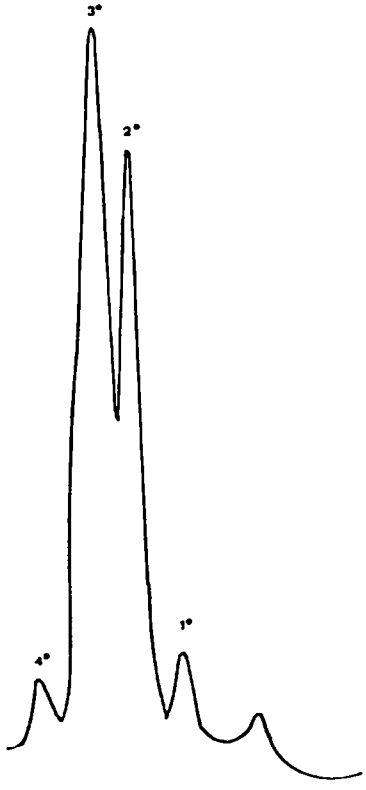


FIG. 3

9-*Ketocyclopropanes* XX. The mixture of the two ketones XX appeared homogeneous in TLC, but GLC analysis shows two distinct peaks (second and third peak; Fig. 2). The IR spectrum of the mixture shows absorption at 3050 cm^{-1} (cyclopropane), at 1740 cm^{-1} (ester) and 1720 cm^{-1} (ketone). The NMR shows resonances at 9·2–10·5 τ (4 protons; cyclopropane), 9·12 τ (3 protons-triplet; secondary Me), 8·62 τ (paraffinic methylenes), 7·8 τ (6 protons α- to carbonyl groups), and 6·3 τ (3 protons-singlet; carbomethoxy). The mixture of the ketocyclopropanes XX was treated with tosylhydrazide (400 mg) in MeOH (10 ml) and heated under reflux for 2 hr. After addition of a further quantity of MeOH (10 ml), $NaBH_4$ (400 mg) was added and the mixture was heated under reflux for a further 10 hr. The mixture was poured into water and then extracted with pet ether. Evaporation of the solvent gave a product (104 mg) which was absorbed on Woelm alumina (Act. III). Elution with pet ether gave fractions of the desoxo derivatives XXI (40 mg) (IR: 3050, 1740 cm^{-1}).

Methyl azelate, sebacate, and undecandioate. The desoxo derivatives XXI (40 mg) were treated with a soln (2·3 ml) of a mixture of CrO_3 (3·0 g), AcOH (20 ml), and water (2·4 ml). The soln was stirred at room temp for 2 hr, poured into ice and then extracted with ether. The organic layer was washed with water and the solvent was evaporated. The product isolated was esterified with diazomethane and the resulting

product examined in GLC–MS which showed it to be a mixture of esters of C-9, C-10, and C-11 dicarboxylic acids. Comparison with authentic samples of methyl azelate, sebacate, and undecandioate respectively, showed them to be identical.

Reaction of methyl 12,13-*epoxyoctadec-9-enoate* (VII) *with* $BF_3 \cdot Et_2O$. The reaction performed as described for the epoxide VIII, yielded products which were analyzed by GLC (Fig. 3) and GLC–MS (Table 2).

TABLE 2

Peaks (GLC)	Compounds	M.W.; fragments (MS)
1°	bicyclic ether XVI	310; 239, 153
2°	ketocyclopropane V	310; 99, 71
3°	(a) ketocyclopropane V	310; 99, 71
	(b) methyl 12-ketooctadec-9-enoate (X)	310; 113, 85
	(c) methyl 13-ketooctadec-9-enoate (XI)	310; 99, 71
4°	methyl 12-hydroxyoctadecadienoate XII	310; 227, 198, 195, 166

Separation of the saturated cyclic products. The crude reaction mixture was treated with mercuric acetate and then chromatographed on alumina as described. The saturated cyclic products (obtained in 30% yield) were analyzed by GLC (Fig. 4). The bicyclic ether XVI was obtained pure after repeated chromatography and was identical with that isolated from the reaction of epoxy ester VIII with $BF_3 \cdot Et_2O$.

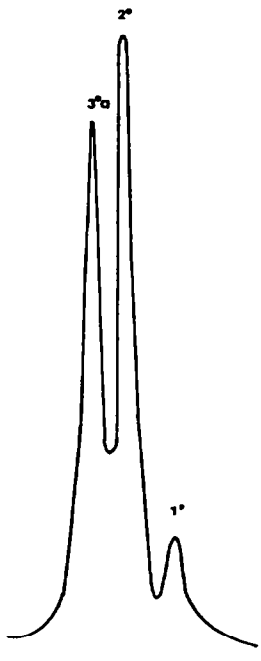


FIG. 4

Methyl pimelate, suberate, and azelate. The mixture of the ketocyclopropanes V was converted into the desoxo derivatives using the procedure of Caglioti and Grasselli[10] and as described for XX. Degradation of the desoxo derivatives with CrO_3–AcOH–water, as described for XXI, gave a mixture of acids whose methyl esters were identical by GLC–MS with authentic samples of methyl pimelate, suberate, and azelate.

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