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Preparation and Etherification Reaction of Fatty Dichlorocyclopropanes[1]

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Abstract

Dichlorocarbene was added to *cis*-9-octadecene, methyl oleate, methyl elaidate, and methyl linoleate to form the corresponding mono- or bis-dichlorocyclopropanes in yields of 75–88%. The dichlorocyclopropanes underwent ring-opening substitution on heating with alcohols (or water) to form β-chlorallylic ethers (or alcohols). The ethers were obtained in yields of 46 to 84%. Tetraethylene glycol and methyl lactate, as hydroxyl compounds, gave a polyethenoxy ester and an ether-linked diester, respectively.

Introduction

During the 1950's, the fundamental chemistry of dihalocarbenes was elucidated. Proof was given of their existence (1a,2), their electrophilic character (1b,3b,5), and their *cis*-addition to isomeric 2-butenes (3a,4).

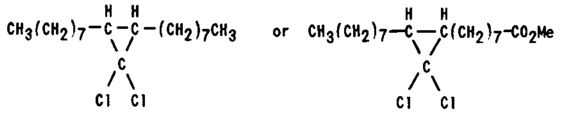
It was desired in the present study to extend the carbene addition reaction, originated with small molecules, to the field of fat chemistry. Dichlorocarbene was chosen as the first carbene to study in this way, and it was added to *cis*-9-octadecene, as a model, and to methyl oleate, methyl elaidate, and methyl linoleate, selected as olefinic fatty esters. These unsaturated compounds were prepared in better than 99% purity by published methods (6,7,8,9).

Procedures

The generation of dichlorocarbene is usually accomplished by the action of an alkoxide on either chloroform (2) or on ethyl trichloroacetate (10), according to the equations:

$$HCCl_3 + R'O^- \rightarrow R'OH + CCl_3^- \quad (1a)$$
$$Cl_3C{-}CO_2R + R'O^- \rightarrow R'OCO_2R + CCl_3^- \quad (1b)$$
$$CCl_3^- \rightarrow Cl^- + :CCl_2 \quad (2)$$

As applied to *cis*-9-octadecene and to methyl oleate, the formation of dichlorocyclopropanes is described by the following equation:


(3)

To methyl linoleate two moles of the carbene were attached. Since in these substrates, the double bonds are all *cis*, and since the mode of addition is *cis* (3a,4), each resultant cyclopropane ring must also have the *cis* structure. The dichlorocyclopropane from methyl elaidate must similarly be *trans*. In assigning product structures any isomerization of the parent olefin by the alkaline conditions has been neglected.

In initial experiments with *cis*-9-octadecene, the ethyl trichloroacetate method (Equations 1b,2,3) gave better results than the chloroform procedure. Yields, however, were still much lower with octadecene than in repetitions of Parham's addition of dichlorocarbene to cyclohexene (10). The yield of *1,1-dichloro-2,3-dioctylcyclopropane* (I) was improved by several techniques. A high speed stirrer with cruciform impeller improved reaction rate, and the ethyl trichloroacetate was added at rates causing substantial but controllable evolution of heat. The exothermicity was accommodated by the use of n-heptane instead of n-pentane as solvent, by large reaction flasks, and by a cooling bath applied as needed. The procedure developed was also applied in the additions to methyl oleate, methyl elaidate, and methyl linoleate. Two typical preparations are described below, while yield and analytical data for products are listed in Table I.

1,1-Dichloro-2-octyl-3-(7-Carbomethoxyheptyl)-Cyclopropane. (II). Methyl oleate, 15g (0.05 mole), was placed with 30 ml of n-heptane and 15g (0.28 mole) of sodium methoxide in a four-necked, round-bottomed 1-liter flask fitted with a thermometer, a by-pass addition funnel, and a condenser protected with a drying tube. Nitrogen was introduced through the addition funnel. The reaction mixture was cooled to 2C with an ice-salt bath and stirred at high speed while 30 ml (0.22 mole) of ethyl trichloroacetate were added dropwise. Heat of reaction caused refluxing of solvent. Upon completion of the addition (1 hr) the mixture was removed from the cooling bath, stirred for 4 hr, and allowed to stand overnight at room temp. After addition of water, the mixture was extracted by shaking with three 100-ml portions of diethyl ether. The ether layer was washed with five 75-ml portions of water and dried over sodium sulfate. Excess ether was removed under vacuum in a rotating evaporator. The product was purified by column chromatography using a Florisil:sample ratio of 20:1. Fractions eluted with hexane afforded the desired dichlorocyclopropane, 15.1g.

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TABLE I
Dichlorocyclopropane Preparations

Parent Olefin	Dichlorocyclopropanes	Yield %	n_D^{25}	Carbon		Hydrogen		Chlorine	
				Calc.	Found	Calc.	Found	Calc.	Found
9-Octadecene	*cis*-1,1-dichloro-2,3-dioctylcyclopropane (I)[a]	75	1.4658	68.04	68.21	10.82	11.07	21.14	20.96
Methyl Oleate	*cis*-1,1-dichloro-2-octyl-3-(7-carbomethoxyheptyl) cyclopropane (II)	80	1.4661	63.31	63.10	9.56	9.80	18.69	19.05
Methyl Elaidate	*trans*-1,1-dichloro-2-octyl-3-(7-carbomethoxyheptyl) cyclopropane (III)	80	1.4646	63.31	62.86	9.56	9.58	18.69	18.68
Methyl Linoleate	*cis,cis*-(2,2-dichloro-3-pentyl) cyclopropyl-(2,2-dichloro-3-(7-carbomethoxyheptyl) cyclopropyl) methane (IV)	88	1.4828	54.79	55.27	7.44	7.45	30.81	30.87

[a] Purified either by chromatography on Florasil or by distillation; bp 170C at 0.4 mm.

(2,2-Dichloro-3-pentyl) cyclopropyl-(2,2-dichloro-3-(7-carbomethoxyheptyl)-cyclopropyl)-Methane. (IV). In the apparatus described for the previous preparation, 10g (0.034 mole) methyl linoleate, 20 ml n-heptane, and 10g (0.185 mole) of sodium methoxide were stirred at 2C. Within 20 min 20 ml (0.144 mole) of ethyl trichloroacetate was added. The ice bath was removed; the mixture warmed gradually for ½ hr, when it refluxed violently for several minutes. Stirring was continued at room temp; the mixture was briefly cooled to 2C (after 2 hr and 5 hr reaction) for two additions of 2g of sodium methoxide and 3.7 ml of ethyl trichloroacetate. Maximum temp reached after these additions were 30 and 60C respectively. After 6½ hr stirring, at room temp except as noted, the mixture was worked up as before, affording 13.6g of compound IV.

Properties. The dichlorocyclopropane from *cis*-9-octadecene was stable to distillation, but those from methyl oleate and elaidate were not, and had to be purified by chromatography. The bis-dichlorocyclopropane from methyl linoleate was, in addition, unstable to prolonged contact with Florisil, so that its chromatography had to be accomplished very rapidly (15 min).

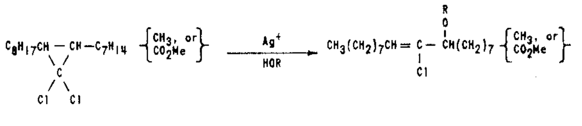
Dilute sulfuric acid did not affect the ring of 1,1-dichloro-2,3-dioctylcyclopropane (I), but sodium in refluxing ethanol removed both chlorine atoms hydrogenolytically. Magnesium in refluxing ether did not react, nor did aqueous alcoholic silver nitrate, in eight hours at room temp.

Etherification Reaction

Dihalocyclopropanes differ in their reactivity toward silver nitrate. In the experience of Doering and Hoffmann (2), dichloro- and dibromonorcarane were unaffected by aqueous silver nitrate at room temp, and the former also resisted refluxing with silver oxide in alcohol. On the other hand, Skell and Sandler (11), reported that shaking with aqueous silver nitrate converted dihalocyclopropanes made from cyclopentene to monohalocyclohexenols; with aqueous alcoholic reagent evidence for a mixture of a bromoalcohol and a bromoether was obtained.

The adaptation of this reaction to fatty compounds was explored, with emphasis on its etherification possibilities. The present dichlorocyclopropanes were, like their counterparts from cyclohexene, virtually inert to aqueous and alcoholic silver nitrate solutions at room temp. At temp ranging 70–130C, however, it was possible to bring about reaction. Treating the octadecene derivative (I), with silver nitrate in refluxing 99% ethanol afforded a mixture of an ether and an alcohol, while in hot anhydrous alcohols ethers alone were produced. Analytical and IR data supported β-chlorallylic structures.

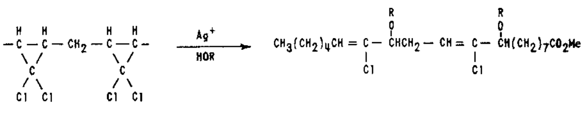
The outcome of these probing reactions, together with similar ones on the cyclopropane derived from methyl oleate, suggested the feasibility of syntheses using various alcohols (or water) in decycloetherification (or hydroxylation) of the dichlorocyclopropanes made from 9-octadecene, and methyl oleate, methyl elaidate, and methyl linoleate. These syntheses are formulated in Equations 4 and 5 and summarized in Table II. Since the rings can open in two ways, the substituents and double bonds are considered to be located in the alternate positions as well as those shown in the equations. Typical ether preparations are detailed in the next section.



(4)

I, II, or III

V, VI, or VII



(5)

IV

VIII

In the β-chlorallylic products the simplicity or complexity of structure is determined both by the functionality of the original unsaturated compound and by that of the hydroxylic reactant. In the methyl oleate series, e.g., water yielded a hydroxyester, ethanol and hexadecanol yielded ether esters, butanediol a hydroxyether monoester, tetraethylene glycol, a polyethenoxy monoester, and methyl lactate an ether-linked diester. The last two products were also converted to the corresponding polyethenoxy soaps. When ethanol was used, alcoholysis of ester occurred during etherification, so that the product was the ethyl rather than the methyl ester.

The bis-dichlorocyclopropane from methyl linoleate was converted to a methyl ester with two tetraethylene glycol side chains, attached by β-chlorallylic ether links.

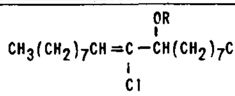
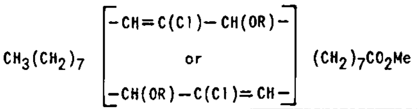
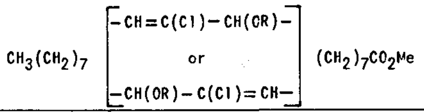
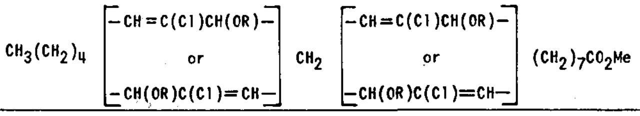
Since the ring-opening effects overall insertion (11), the monocyclic intermediates give rise to products with one extra carbon atom in the backbone, and the bicyclic intermediates to products with two.

Preparation of β-Chlorallylic Ethers (and Alcohols)

The procedures below were used in the preparation of typical products. Variations made in syntheses of other members are noted in Table II.

10-Chloro-11-ethoxy-nonadec-9-ene (V-B). Ten g (0.03 moles) of 1,1-dichloro-2,3-dioctylcyclopropane (I) and 100 ml of an ethanolic silver nitrate solution containing 1% water were mixed. No precipitate of silver chloride was noted. The mixture was stirred

TABLE II
Ether (or Alcohol) Preparations

Alcohol Etherified, ROH	Product No.	Reaction Temp., C	Reaction Time, Hrs.	Yield, %	n_D^{25}	Carbon, %		Hydrogen, %		Chlorine, %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
cis-9-Octadecene product type:	 $CH_3(CH_2)_7CH{=}\underset{\displaystyle Cl}{C}{-}\overset{\displaystyle OR}{CH}(CH_2)_7CH_3$										
Ethanol	V-B	reflux	24	68	1.4548	73.10	72.55	11.98	11.97	10.28	10.19
Water	V-A			29		72.00	72.23	11.77	11.71	11.19	10.86
Tetraethylene Glycol	V-D	130	6[b]	74	1.4650	65.75	65.56	10.83	10.67	7.19	7.52
Methyl Lactate	V-E[a]	80	4[c]	69		68.54	68.27	10.75	10.97	8.80	8.97
2-Methoxyethanol	V-F	reflux	2	76	1.4578	70.45	70.70	11.56	11.54	9.46	9.58
Methyl oleate product type:	 $CH_3(CH_2)_7\left[\begin{array}{c}-CH{=}C(Cl){-}CH(OR){-}\\ \text{or}\\ -CH(OR){-}C(Cl){=}CH{-}\end{array}\right](CH_2)_7CO_2Me$										
H_2O	VI-A	100	8[f]	33[e]		66.55	66.58	10.33	10.37	9.82	9.90
Ethanol	VI-B	reflux	9[c,g]	79[d]	1.4584	68.54	68.67	10.75	10.73	8.80	8.83
Cetyl Alcohol	VI-C	130	13[h]	46	1.4622	73.86	74.28	11.88	11.80	6.06	6.18
Tetraethylene Glycol	VI-D	110	6[h]	84		62.74	62.72	9.96	9.91	6.62	6.53
Methyl Lactate	VI-E	112	6[b]	69	1.4625	64.48	64.53	9.69	9.81	7.93	7.99
1,4-Butanediol	VI-G	105	6	75	1.4690	66.56	66.76	10.47	10.63	8.19	8.13
Methyl elaidate product type:	 $CH_3(CH_2)_7\left[\begin{array}{c}-CH{=}C(Cl){-}CH(OR){-}\\ \text{or}\\ -CH(OR){-}C(Cl){=}CH{-}\end{array}\right](CH_2)_7CO_2Me$										
1,4-Butanediol	VII-G	106	4	73	1.4677	66.56	66.85	10.47	10.55	8.19	8.53
Methyl linoleate product type:	 $CH_3(CH_2)_4\left[\begin{array}{c}-CH{=}C(Cl)CH(OR){-}\\ \text{or}\\ -CH(OR)C(Cl){=}CH{-}\end{array}\right]CH_2\left[\begin{array}{c}-CH{=}C(Cl)CH(OR){-}\\ \text{or}\\ -CH(OR)C(Cl){=}CH{-}\end{array}\right](CH_2)_7CO_2Me$										
Tetraethylene Glycol	VIII-D	110	6	55		57.28	56.95	8.84	8.66	9.14	8.49

[a] From this product the free acid was later obtained by saponification at 40C with 10% methanolic NaOH, and acidification.

[b] Molecular sieves 4A used to assure anhydrous conditions.

[c] U.V. irradiation for 1 hr.

[d] Ethyl ester.

[e] After allowance for recovered cyclopropane.

[f] U.V. irradiation for 4 hrs.

[g] 10% acetonitrile present

[h] U.V. irradiation for 2 hrs.

[i] As a second product the corresponding butanediol monoester was formed in 20% yield.

and refluxed 24 hr. On cooling, an oily layer was observed floating on the ethanolic solution. The total mixture was extracted with diethyl ether, and the ether layer was washed with water and dried over sodium sulfate. Solvent was removed at room temp using a rotating evaporator. The product was purified on a chromatography column with 30:1 Florisil to sample. The n-hexane eluant gave a 6.9 g fraction identified by IR spectrum as the ethyl ether (V-B). A benzene fraction, 2.9 g, was identified as the hydroxyl derivative (V-A).

Methyl 10-chloro-9(11)-(1,4,7,10-Tetraoxa-12-hydroxydodec-1-yl)-nonadec-10(9)-enoate (VI-D). The dichlorocyclopropane from methyl oleate (II), 3.4 g (0.009 mole), was placed with 25 g (0.116 mole) of tetraethylene glycol in an oven-dried round-bottomed flask, provided with a nitrogen inlet, condenser with drying tube, and magnetic stirrer. Finely ground silver nitrate, 2 g (0 011 mole), was also charged to the reaction flask. With the flask immersed in an oil bath maintained at 110C, the mixture was stirred for 6 hr; during the third and fourth hours it was irradiated with a 3-watt UV lamp (germicidal type) at 6 inches from the flask. The mixture was allowed to stand at room temp overnight under nitrogen. The product was extracted with diethyl ether, and the ether layer washed with water. After drying with sodium sulfate the solvent was removed in a rotatory vacuum evaporator. The crude substitution product was purified on a chromatography column with 30:1 Florisil to product, using benzene to elute the main product. Evaporation of solvent afforded 3.94 g of the pure tetraethylene glycol monoether (VI-D).

Modified Procedures. It was found that even with elevated temp and prolonged reaction times some of the substitution products could be obtained only in low yields. In such cases, irradiation of the reaction flasks with UV light caused silver chloride to be precipitated in a reasonable time, and the products could be obtained in good yield.

In several cases a reduction of reaction time was accomplished by addition of acetonitrile to the reaction system to increase the solubility of silver nitrate in the alcohol.

Chromatographic Purification. Reaction mixtures were purified by column chromatography using Florisil adsorbent and hydrocarbon eluants. This removed resinous impurities and provided separation into fractions of different polarities, which were examined by analytical-scale TLC, and IR spectrophotometry.

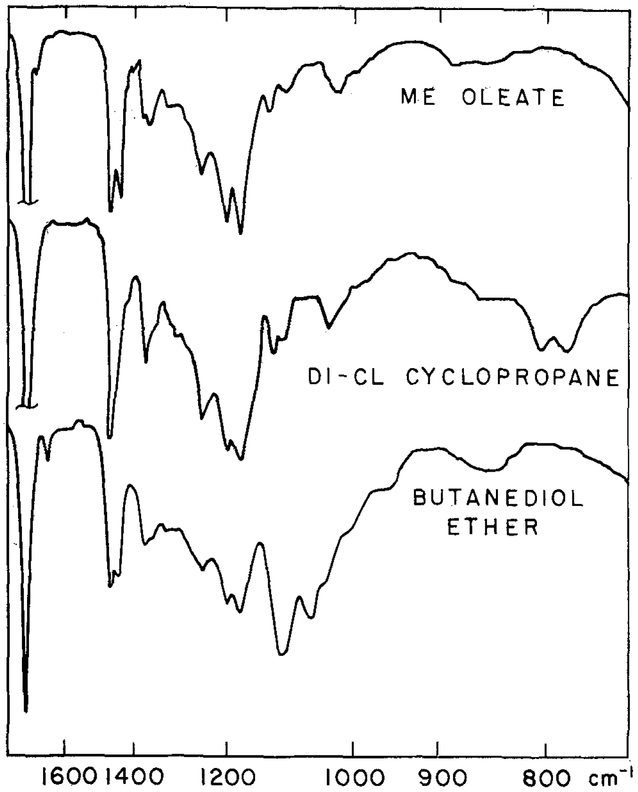


FIG. 1. Section of infrared spectra: methyl oleate, the corresponding dichlorocyclopropane, and the 1,4-butanediol monoether derivative of the latter.

Usually this procedure identified fractions affording the substitution products in good yield and purity. A few products prepared on micro scale, or more difficult to purify, were also submitted to preparative-scale TLC.

Infrared Spectra

Infrared data, obtained with Perkin-Elmer Infracord 137, accorded well with the expected structures of the present compounds. The spectra of the fatty dichlorocyclopropanes resembled that of dichloronorcarane (2) but with less distinct peaks in the 1050–1000 cm^{-1} region. Figures 1 and 2 show corresponding sections of the spectra in a methyl oleate and a methyl elaidate series.

The dichlorocyclopropane derivatives of the *cis*-unsaturated ester (or of *cis*-octadecene) showed a doublet at 805 and 780 cm^{-1}, attributable to the two chlorine atoms. On etherification the first peak disappeared and only a trace of the second was left. The presence of an ether linkage after reaction with 1,4-butanediol is suggested by strong absorbance at about 1110 cm^{-1}. An allylic double bond is reported to have little effect on the C-O-C frequency (12a); similarly β-chloroethers are reported to behave normally in this respect.

A peak at 1655 cm^{-1} in the ether suggests a double bond (12b), shifted to lower frequency by halogen. The broad band near 840 cm^{-1} is further indication of a trisubstituted ethylenic structure in the final product.

In the methyl elaidate series, addition of dichlorocarbene caused disappearance of the *trans* band at 970 cm^{-1} and appearance of a single strong peak at 800 cm^{-1}. Etherification with butanediol resulted in a trace band at 780 and bands at 1110,1655, and 840 similar to those in the corresponding β-chlorallylic ether from methyl oleate. Indeed, superimposability of spectra suggests possible identity of these two final products.

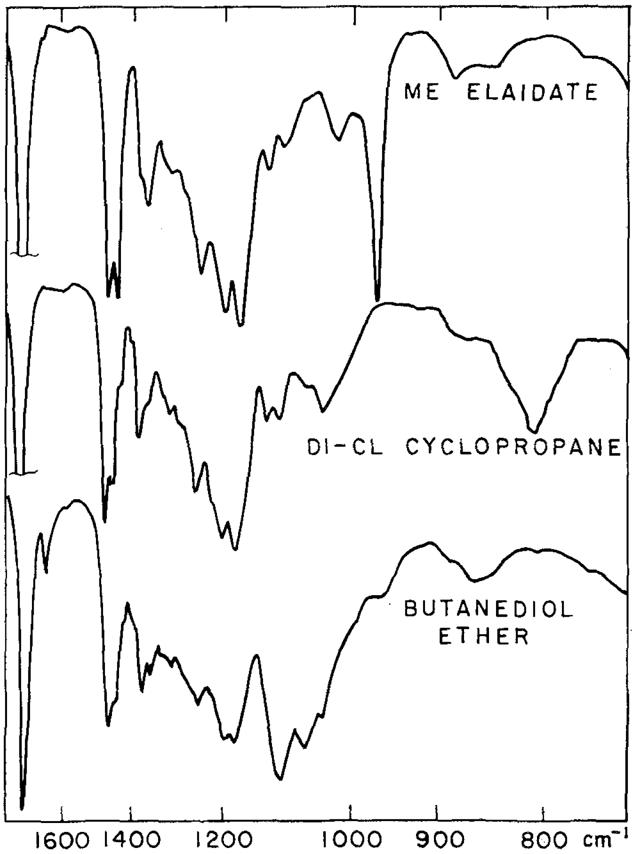


FIG. 2. Section of infrared spectra: methyl elaidate, the corresponding dichlorocyclopropane, and the 1,4-butanediol monoether derivative of the latter.

The spectra of the other compounds were similar, with occasional exceptions. The bis-dichlorocyclopropane from methyl linoleate showed one broad, flat peak from 805 to 780 cm^{-1}, which after etherification with tetraethylene glycol was replaced with a small peak at 810 cm^{-1}. When the cyclopropanes from octadecene and methyl oleate were reacted with the large tetraethylene glycol molecule, both the 805 and 780 cm^{-1} bands gave way to a new one at 800 cm^{-1}.

All alcohols and hydroxyethers prepared showed OH peaks at 3500 to 3600 cm^{-1}.

ACKNOWLEDGMENTS

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