Hypohalogenation of β-Hydroxy Olefinic Fatty Acid

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ABSTRACT

The reactions of hypohalous acids with β-hydroxy olefinic (ricinoleic) acid have been examined. The hypobromination and hypoiodination reactions gave the expected halogen-containing cyclic ether resulting from neighboring group participation between the hydroxyl group and the reaction occurring at the unsaturated center. A similar hypochlorination reaction did not furnish any cyclic ether. The structures of individual products were characterized by spectral methods. The mechanism of the cyclization reactions is discussed.

INTRODUCTION

Studies of long chain hydroxy alkenes containing the unit $-CH = CH-(CH_2)_n\ CH(OH)-$ have shown that neighboring group participation may occur between the hydroxyl group and a reaction taking place at the double bond depending particularly on the value of *n* and to a lesser extent the configuration of the double bond. The reaction in which this neighboring group participation has been observed was during epoxidation (1), oxymercuration-demercuration (2), and halogenation (3) of long chain hydroxy alkenes. The present work on the hypohalogenation of β-hydroxy olefinic (ricinoleic) acid was undertaken for two reasons. First, there appeared to be no mention in the literature of the reactions of hypohalous acids on this compound. Second, as the olefinic bond is close to the hydroxyl function, the influence of hydroxyl on the halohydroxy groups of the halohydrins would affect their polarity, thereby enabling them to be separable chromatographically. In this paper we report our experiments on the hypohalogenation of ricinoleic acid. The structures of individual reaction products were characterized by spectral methods.

EXPERIMENTAL PROCEDURES

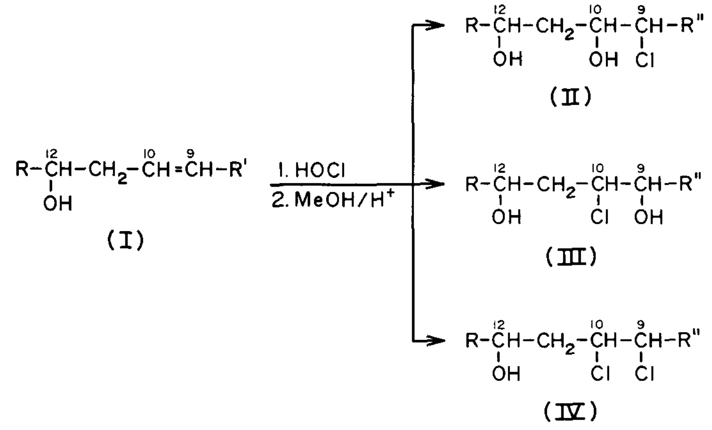
Infrared (IR) spectra were obtained with a Perkin-Elmer 621 spectrophotometer (liquid film or 1% solutions in carbon tetrachloride). Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ using a Varian A60 NMR spectrometer. Chemical shifts were measured in ppm downfield from internal tetramethylsilane ($\delta = 0$). The abbreviations "s, d, m, um, br, q and t" denote "singlet, doublet, multiplet, unresolved multiplet, broad, quartet and triplet," respectively. Only diagnostic and structure specific signals are discussed in Results and Discussion. Thin layer chromatographic (TLC) plates were coated with Silica Gel G (0.25 mm wet thickness), and a mixture of petroleum ether/diethyl ether/acetic acid (70:30:1; v/v/v) was used as developing solvent. The spots were visualized by charring after spraying with a 20% aqueous solution of perchloric acid. Petroleum ether refers to a fraction of bp. 40-60C.

MATERIALS AND METHODS

The ricinoleic (12-hydroxy-*cis*-9-octadecenoic) acid (I) was isolated from castor oil following Gunstone's partition method (4), and the structure was established by spectral methods (5).

Hypochlorination of I

Hypochlorination of ricinoleic acid (I) was carried out according to the procedure of King (6). A 2% aqueous solution of the potassium salt of I (5.5 g) containing a 4% solution of potassium carbonate (145 ml) was cooled below 10 C and chlorine gas passed into the solution for 6 hr with occasional shaking. Excess of hypochlorous acid, formed in situ, was destroyed with 10% aqueous sodium thiosulphate solution and then acidified with 50% hydrochloric acid. The resulting product was extracted with diethylether, washed, dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The crude reaction product showed 3 distinct spots on TLC in addition to the unreacted acid. The crude acids (5.24 g) were methylated by heating for 2 hr with anhydrous methanol (80 ml) in the presence of a catalytic amount of sulphuric acid. After the usual work-up, the mixture of methyl chloro-hydroxy esters was passed over a column of Silica Gel G (80 g), and 3 products (II, 46%; III, 6%; and IV, 3%) (see Scheme 1) were eluted successively with a mixture of petroleum ether/diethyl ether (93:7, 93:7 and 90:10, v/v), respectively. Fractions of 15 ml were collected. The TLC monitored fractions were combined and rechromatographed to give pure TLC homogenous samples of the individual isomers of chlorohydroxy esters (positive Beilstein test).



where; $R = CH_3(CH_2)_5$; $R' = (CH_2)_7COOH$; $R'' = (CH_2)_7COOCH_3$

SCHEME 1

Methyl 9-chloro-10,12-dihydroxy octadecanoate (II). Analysis: Calc. for $C_{19}H_{37}O_4Cl$:C, 62.55; H, 10.15; Cl, 9.74. Found: C, 62.51; H, 10.14: Cl, 9.71%. IR: 3300 (C—OH), 1740 (COOCH$_3$), and 720 (C—Cl) cm^{-1}.

Methyl 10-Chloro-9,12-dihydroxy octadecanoate (III). Analysis: Calc. for $C_{19}H_{37}O_4$ Cl: C, 62.55; H, 10.15; Cl, 9.74. Found: C, 62.52; H, 10.11; Cl, 9.69%. IR: 3300 (C—OH), 1740 (COOCH$_3$), and 720 (C—Cl) cm^{-1}.

Methyl 9,10-dichloro-12-hydroxy octadecanoate IV). Analysis: Calc. for $C_{19}H_{36}O_3Cl_2$: C, 56.92; H, 9.39; Cl, 18.53. Found: C, 56.88; H, 9.36; Cl, 18.49%. IR: 3400 (C—OH), 1740 (COOCH$_3$), and 720 (C—Cl) cm^{-1}.

Hypobromination of I

Hypobromination of ricinoleic acid (I) was carried out with 0.35 M sodium hypobromite as described in the case of α,β-unsaturated acid (7). The potassium salt of ricinoleic

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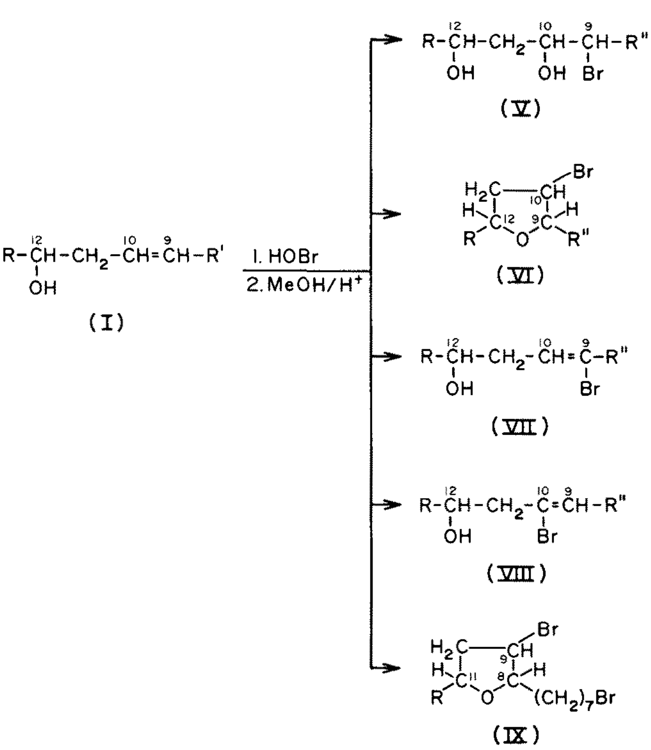
acid (5.0 g) in water (200 ml) was reacted with sodium hypobromite (100 ml) at room temperature. The reaction mixture was allowed to stand at room temperature for 2 hr with occasional shaking. It was acidified with dilute sulphuric acid, any excess of bromine was destroyed with sodium sulphite solution and the product was extracted with diethyl ether. The ethereal layer was washed with water and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude reaction products (4.52 g) showed 5 components on TLC and were chromatographed over a column of Silica Gel G (75 g) after methylation with acidic methanol. Five components (V, 30%; VI, 25%; VII, 4%; VIII, 4%, and IX, 3%) (see Scheme 2) were eluted successively with a mixture of petroleum ether/diethyl ether (93:7, 91:9, 86:14, 86:14, and 83:17, v/v), respectively. Each individual component gave a positive Beilstein test.



where; R = $CH_3(CH_2)_5$; R' = $(CH_2)_7COOH$; R" = $(CH_2)_7COOCH_3$

SCHEME 2

Methyl 9-bromo-10,12-dihydroxy octadecanoate (V). Analysis: Calc. for $C_{19}H_{37}O_4$ Br: C, 55.88; H, 9.06; Br, 19.36. Found: C, 55.87; H, 9.02; Br, 19.33%. IR: 3300 (C—OH), 1740 ($COOCH_3$), and 720 (C—Br) cm^{-1}.

Methyl 10-bromo-9,12 epoxy octadecanoate (VI). Analysis: Calc. for $C_{19}H_{35}O_3$ Br: C, 55.89; H, 8.97; Br, 20.26. Found: C, 55.85; H, 8.95; Br, 20.23%. IR: 1740 ($COOCH_3$), 1215, 1110, 1000 (C—O—C, epoxide ring), and 720 (C—Br) cm^{-1}.

Methyl 9-bromo-12-hydroxy octadec-9-enoate (VII). Analysis: Calc. for $C_{19}H_{35}O_3$ Br: C, 55.89; H, 8.97; Br, 20.26. Found: C, 55.83; H, 8.93; Br, 20.22%. IR: 3460 (C-OH), 1660, 1645 (trisubstituted alkene), and 720 (C—Br) cm^{-1}.

Methyl 10-bromo-12-hydroxy octadec-9-enoate (VIII). Analysis: Calc. for $C_{19}H_{35}O_3$ Br: C, 55.89; H, 8.97; Br, 20.26. Found: C, 55.86; H, 8.95; Br, 20.24%. IR: 3460 (C—OH), 1660, 1645 (trisubstituted alkene), and 720 (C—Br) cm^{-1}.

8,11-Epoxy heptadec-1,9-dibromide (IX). Analysis: Calc. for $C_{17}H_{32}O$ Br_2: C, 49.75; H, 7.80; Br, 38.50. Found: C, 49.73; H, 7.76; Br, 38.48%. IR: 1215, 1110, 1000 (C—O—C, epoxide ring), and 720 (C—Br) cm^{-1}.

Hypoiodination of I

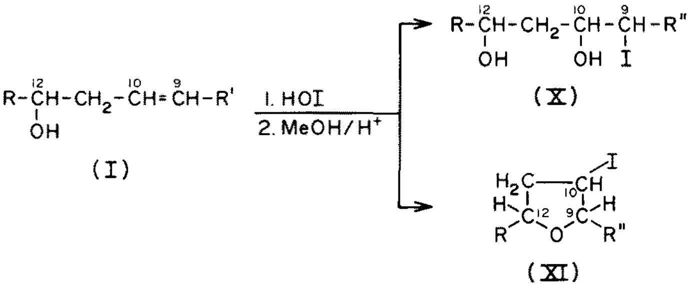
Hypoiodination of ricinoleic acid (I) was carried out following the procedure of Conforth and Green (8). The acid (I, 4.0 g) was dissolved in ethanol (50 ml) and treated with iodine (2.6 g), potassium iodate (1.0 g), water (75 ml), and concentrated sulphuric acid (1 ml). After keeping for 8 hr at room temperature, the mixture was extracted with diethyl ether, washed, and dried over anhydrous sodium sulfate. After evaporation of the solvent, the crude reaction product (3.53 g) showed 2 distinct spots on TLC. It was methylated with acidic methanol and passed over a column of Silica Gel G (60 g). Two products (X, 35% and XI, 35%) (see Scheme 3) were eluted successively with a mixture of petroleum ether-diethyl ether (99:1 and 93:7, v/v), respectively. Each fraction showed a positive test for halogen.

Methyl 9-iodo-10,12-dihydroxy octadecanoate (X). Analysis: Calc. for $C_{19}H_{37}O_4I$: C, 50.0; H, 8.11, I, 27.87. Found: C, 49.95; H, 8.08; I, 27.85%. IR: 3300 (C—OH), 1740 ($COOCH_3$), and 720 (C—I) cm^{-1}.

Methyl 10-iodo-9,12-epoxy octadecanoate (XI). Analysis: Calc. for $C_{19}H_{35}O_3I$: C, 50.06; H, 7.99; I, 28.99. Found: C, 50.03; H, 7.97; I, 28.97%. IR: 1740 ($COOCH_3$), 1215, 1110, 1000 (C—O—C, epoxide ring), and 720 (C—I) cm^{-1}.

RESULTS AND DISCUSSION

In continuation of our earlier study on the hypohalogenation of long chain α,β-unsaturated acid (7), the present work describes the results (Scheme 1-3) of the reaction of hypohalous acids with ricinoleic acid (I), and a proof of structure of the products by spectroscopic data discussed below.



where; R = $CH_3(CH_2)_5$; R' = $(CH_2)_7COOH$; R" = $(CH_2)_7COOCH_3$

SCHEME 3

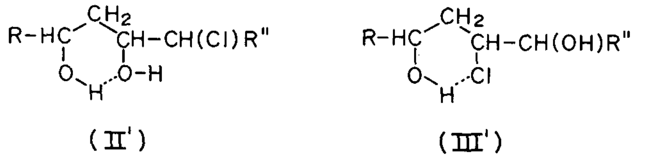
Hypochlorination of I

Hypochlorination of ricinoleic acid (I) was carried out according to the procedure of King (6). The reaction product showed the presence of three components on TLC (Scheme 1). A column separation of its methyl ester yielded methyl 9-chloro-10,12-dihydroxy octadecanoate (II), methyl 10-chloro-9,12-dihydroxy octadecanoate (III), and methyl 9,10-dichloro-12-hydroxy octadecanoate (IV).

Compound II (positive Beilstein test) analyzed for $C_{19}H_{37}O_4Cl$. The IR spectrum showed, besides the usual bands, absorptions at 3300 (C–OH), 1740 ($COOCH_3$), and 720 (C–Cl) cm^{-1}, indicative of the chlorohydroxyl functions. NMR signals were observed at δ4.0 m (1H,–CH (Cl)–), 3.85 br, s (2H,–CH(OH)–CH_2–CH(OH)–), 3.6 s (3H, $COOCH_3$), 2.55 br, s (2H,–CH(OH)–CH_2–CH(OH)–, disappeared on addition of D_2O), 2.25 t (2H,–CH_2COOCH_3), and 1.9 um (2H,–CH(OH)–CH_2–CH(OH)–). From these evidences, the structure of II was formulated as methyl 9-chloro-10,12-dihydroxy octadecanoate.

Compound III (positive Beilstein test) exactly corresponded to formula $C_{19}H_{37}O_4Cl$. In its IR spectrum, bands at 3300 (C–OH), 1740 ($COOCH_3$), and 720 (C–Cl) cm^{-1} were observed. The NMR spectrum was the main source to reach the structure of this compound. It gave signals at δ4.2-3.85 br, m (3H,–CH(OH)–CH_2–CH(Cl)–CH(OH)–), 3.6 s (3H, $COOCH_3$), 2.55 br, s (2H,–CH(OH)–CH_2–CH(Cl)–CH(OH)–, disappeared on addition of D_2O), 2.25 t (2H,–CH_2COOCH_3), and 1.9 um (2H,–CH(OH)–CH_2–CH(Cl)–). From these data, the structure of III was formulated as methyl 10-chloro-9,12-dihydroxy octadecanoate.

Theoretically hypochlorination of I would have given rise to a mixture of two isomers (II and III) in an equal amount. In the present study, however, it was observed that hypochlorination of I did not afford equal amounts of isomers, and the isomeric mixtures II and III were separated in pure form. There was no evidence of cyclized product by neighboring group participation, but the hydroxyl group had a considerable influence on the relative amount of the isomers II and III, and their separation. These isomers can take configurations (II' and III') in which there is an intramolecular hydrogen bonding through the 6-membered ring structure, shown in Scheme 4. The hydrogen bonding in II' will be stronger due to the higher electronegativity of oxygen than of chlorine. The greater hydrogen bonding accounted for the greater stability of product II in comparison to product III. Therefore, it is thought that II is formed quantitatively and preferentially to III on the ground of neighboring group participation.



where; R = $CH_3(CH_2)_5$; R' = $(CH_2)_7COOCH_3$

SCHEME 4

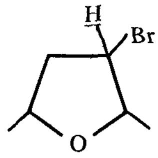
The minor product methyl 9,10-dichloro-12-hydroxy octadecanoate (IV) (positive Beilstein test) supported the formula $C_{19}H_{36}O_3Cl_2$. Its IR spectrum gave peaks at 3400 (C–OH), 1740 ($COOCH_3$), and 720 (C–Cl) cm^{-1}. The structure of IV finds further support from its NMR spectrum. It gave signals at δ4.6-3.7 br, m (3H,–CH(OH)–CH_2–CH(Cl)–CH(Cl)–), 3.6 s (3H, $COOCH_3$), 2.55 br, s (1H,–CH(OH)–, disappeared on addition of D_2O), 2.25 t (2H,–CH_2COOCH_3), and 1.9 um (2H,–CH(OH)–CH_2–CH(Cl)–).

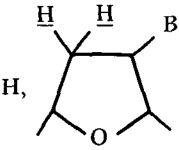
Hypobromination of I

Hypobromination of ricinoleic acid (I) was carried out according to the procedure of King (6). The reaction resulted in the formation of 5 distinct products (V-IX) as evidenced by TLC (Scheme 2). The resulting product after methylation was separated chromatographically to furnish methyl 9-bromo-10,12-dihydroxy octadecanoate (V), methyl 10-bromo-9,12-epoxy octadecanoate (VI), methyl 9-bromo-12-hydroxy octadec-9-enoate (VII), methyl 10-bromo-12-hydroxy octadec-9-enoate (VIII), and 8,11-epoxy heptadec-1,9-dibromide (IX).

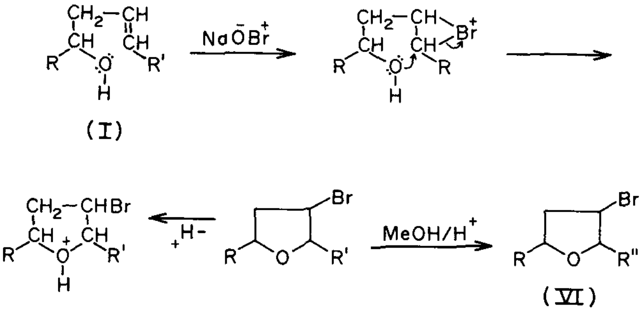
Compound V (positive Beilstein test) analyzed for $C_{19}H_{37}O_4Br$. The IR spectrum showed absorptions at 3300 (C–OH), 1740 ($COOCH_3$), and 720 (C–Br) cm^{-1} indicative of bromohydroxyl functions. The NMR spectrum gave signals at δ3.9 um (1H,–CH(Br)–), 3.8 br, s (2H,–CH(OH)–CH_2–CH(OH)–), 3.6 s (3H, $COOCH_3$), 2.55 br, s (2H,–CH(OH)–CH_2–CH(OH)–, disappeared on addition of D_2O), 2.25 t (2H,–CH_2COOCH_3), and 1.9 um (2H, –CH(OH)–CH_2–CH(OH)–). On the basis of these data, compound V was formulated as methyl 9-bromo-10,12-dihydroxy octadecanoate.

Compound VI (positive Beilstein test) corresponded to formula $C_{19}H_{35}O_3$ Br. This compound showed IR bands at 1740 ($COOCH_3$), 1215, 1110, 1000 (C–O–C, epoxide ring), and 720 (C–Br) cm^{-1}. The NMR spectrum was very informative in establishing the structure of VI. It gave signals at

δ4.5-4.0 um (3H, ), 3.6 s (3H, $COOCH_3$),

2.2 t (2H,–CH_2COOCH_3), and 1.6 um (2H, ).

From these data, VI was characterized as methyl 10-bromo-9,12-epoxy octadecanoate. The formation of halogen-containing cyclic ether (VI) resulting from neighboring group participation between the hydroxyl group and the reaction occurring at the unsaturated center can be rationalized in terms of the mechanistic sequence (Scheme 5).

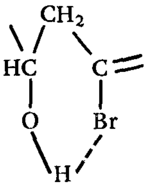


where; R = $CH_3(CH_2)_5$; R' = $(CH_2)_7COOH$; R'' = $(CH_2)_7COOCH_3$

SCHEME 5

Microanalysis of products VII and VIII (positive Beilstein test) gave composition $C_{19}H_{35}O_3$ Br with characteristic IR bands at 3460 (C–OH), 1660, 1645 (substituted alkene), and 720 (C–Br) cm^{-1}. NMR spectrum established the structure of VII and VIII as methyl 9-bromo-12-hydroxy octadec-9-enoate and methyl 10-bromo-12-hydroxy octadec-9-enoate, respectively. The NMR of VII had signals at δ6.2-5.7 m (1H,–CH_2–CH=C(Br)–), 3.9 um (1H,–CH(OH)–CH_2–CH=C(Br)–), 3.35 s (1H, –CH(OH)–, disappeared on addition of D_2O), 2.42 t (2H,–CH=C(Br)–CH_2–), and 2.25 t, t (4H,–CH(OH)–CH_2–CH=C(Br)– + CH_2 $COOCH_3$). The NMR of VIII exhibited signals at δ5.8 m (1H,–CH_2–C(Br)=CH–), 3.9 m (1H,–CH(OH)–CH_2–C(Br)=), 3.35 s (1H,–CH(OH)–, disappeared on addition of D_2O), 2.44 d (2H,–CH(OH)–CH_2–C(Br)=CH CH_2), and 2.25 t, t (4H,–CH(OH)–CH_2–C(Br)=CH– + CH_2-$COOCH_3$).

The separability of these 2 isomeric vinyl halides (VII and VIII) may be explained on the basis of their polarity. They were identified by NMR spectra. The less polar of the 2 isomers is considered to be the 10-bromo isomer since it, and not the 9-bromo isomer, can take up a configuration in which there is intramolecular hydrogen bonding through a 6-membered ring structure.

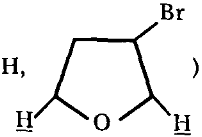


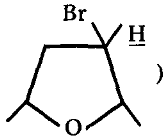
This conclusion is confirmed by the observation that in the NMR spectrum of the 10-bromo isomer (VIII) there is a doublet at δ2.44 and the 9-bromo isomer (VII) shows a triplet at δ2.42 arising from the protons underlined in the following structures.

$-CH(OH)CH_2CBr{=}CHC\underline{H}_2-$ $-CH(OH)CH_2CH{=}CBrC\underline{H}_2-$
10-bromo isomer 9-bromo isomer

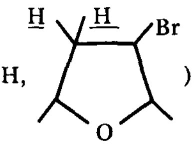
The formation of these vinyl bromides can be explained via bromination and dehydrobromination reaction. The excess of bromine present in situ may react with olefinic double bond by electrophilic addition to yield dibromo compound. The base catalyzed dehydrobromination of the dibromo compound at C9 and C10 yielded the vinyl bromides VII and VIII, respectively. In open chain systems the HBr elimination is regiospecific leading to vinyl bromides rather than to allyl bromides. This probably reflects a lower energy transition state leading to the substituted olefin.

Another product, 8,11-epoxy heptadec-1,9-dibromide (IX), exactly corresponded to formula $C_{17}H_{32}OBr_2$ by its combustion data. Its IR spectrum gave peaks at 1215, 1110, 1000 (C–O–C, epoxide ring) and 720 (C–Br) cm^{-1}. The structure IX finds further support from its NMR spectrum. It displayed signals at

δ4.5 br,m (2H, 

), 4.0 q (1H, 

),

3.8 t like (2H, $-C\underline{H}_2Br$), and 1.75 um (2H, 

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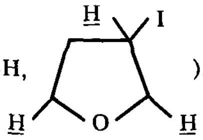
The formation of this unusual product can be rationalized on the basis of Hunsdiecker reaction, i.e. decarboxlative halogenation of fatty acid salts (9). The reaction proceeds through homolytic cleavage as shown in Scheme 6.

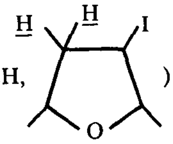
Hypoiodination of I

Following the procedure of Conforth and Green (8), the hypoiodination of ricinoleic acid (I) resulted in the formation of 2 distinct products (X and XI) as evidenced by TLC (Scheme 3). These products were separated by column chromatography after methylation with acidic methanol. Each gave positive Beilstein test. The structure of X was established as methyl 9-iodo-10,12-dihydroxy octadecanoate. The elemental analysis corresponded to the formula $C_{19}H_{37}O_4I$. Its IR spectrum gave bands at 3300 ($C-\underline{OH}$), 1740 ($\underline{CO}OCH_3$), and 720 (C–I) cm^{-1}. The NMR signals at δ3.95 m ($1H,-C\underline{H}(I)-$), 3.75 br,s ($2H,-C\underline{H}(OH)-CH_2-C\underline{H}(OH)-$), 3.6 s ($3H,COOC\underline{H}_3$), 2.55 br, s ($2H,-CH(O\underline{H})-CH_2-CH(O\underline{H})-$, disappeared on addition of D_2O), 2.25 t like ($2H,-C\underline{H}_2COOCH_3$), and 1.9 um ($2H,-CH(OH)-C\underline{H}_2-CH(OH)-$) support its structure.

Another product, methyl 10-iodo-9,12-epoxy octadecanoate (XI), exactly corresponded to formula $C_{19}H_{35}O_3I$ by its combustion data. Its IR spectrum gave peaks at 1740 ($\underline{CO}OCH_3$), 1215, 1110, 1000 (C–O–C, epoxide ring), and 720 (C–I) cm^{-1}. The structure (XI) finds further support from its NMR spectrum. It gave signals at

δ4.1-3.8 um (3H, 

), 3.6 s ($3H, COOC\underline{H}_3$),

2.2 t ($2H,-C\underline{H}_2$ $COOCH_3$), and 1.6 um (2H, 

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The formation of iodo cyclic ether (XI) follows the same mechanistic path as the bromo cyclic ether (VI), discussed above (Scheme 5).

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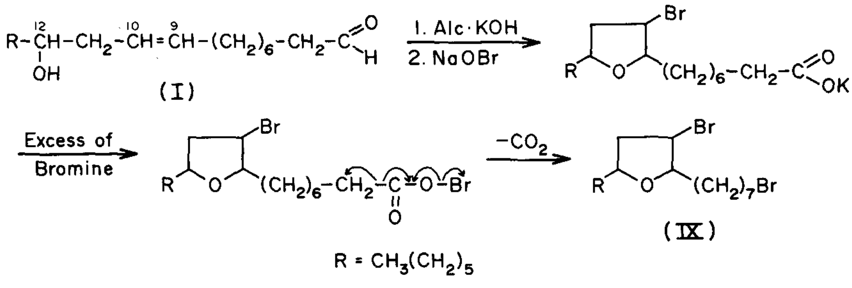

SCHEME 6