Mode of attack of hydriodic acid on unsaturated glyceryl ethers

DONALD J. HANAHAN

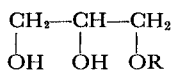
Department of Biochemistry, University of Washington, Seattle, Washington

SUMMARY The mode of action of hydriodic acid (HI) on a sample rich in selachyl alcohol [1-*O*-9(*cis*)-octadecenyl glycerol] has been studied. HI attacked the olefinic bonds as well as the ether bonds, with the formation of at least two diiodides as well as the expected primary iodide. Subsequent conversion of these iodides to the acetates yielded a mixture of saturated diacetates and monounsaturated monoacetates. The unsaturated acetates consisted of a mixture of positional isomers and showed the presence of a *trans* double bond. On the basis of these results it was concluded that HI can attack on either side of the double bond, with the resultant formation of isomeric products in the subsequent dehydrohalogenation reaction.

A reaction scheme for formation of these products is presented. The use of HI in studies of the structure of unsaturated glyceryl ethers is not recommended.

KEY WORDS glyceryl ethers · unsaturated ethers · hydriodic acid attack · gas–liquid chromatography · long-chain iodides · ether cleavage · bond migration

A CLASSICALLY IMPORTANT and useful approach to the cleavage of aliphatic ethers, ROR′, has been to use the nucleophilic reagents hydriodic acid or hydrobromic acid to form alkyl halides, which can be used for further characterization. This reaction has been utilized in structural studies on the glyceryl ethers, i.e.,



but the application has been restricted primarily to those compounds with saturated alkyl side chains. Recently, Guyer, Hoffman, Horrocks, and Cornwell (1) reported the use of hydriodic acid in analyzing naturally occurring glyceryl ethers of different degrees of unsaturation.

The results of the present study show that hydriodic acid readily attacks olefinic bonds as well as the ether bond in unsaturated glyceryl ethers. This behavior, in addition to the formation of multiple products on conversion of the iodides to acetates, renders this approach equivocal as a route to analysis or structure proof of the unsaturated glyceryl ethers.

MATERIALS AND METHODS

A fraction rich in selachyl alcohol (1-*O*-9-octadecenyl glycerol) was obtained from a dogfish liver oil preparation (generously supplied by the Western Chemical Co., Vancouver, B.C., Canada) by a combination of low temperature precipitation and silicic acid chromatography (2). This ether sample migrated as a single spot on thin-layer chromatography (TLC), had the expected infrared spectrum, and consumed 1 mole of periodate per mole of substance. This material, which is referred to as I (see diagram below) was analyzed by gas–liquid chromatography (GLC) of its isopropylidene derivative and its composition is reported in Table 1. Batyl alcohol (1-*O*-octadecyl glycerol) was prepared by synthesis (3) or was purchased from Aldrich Chemical Co., Milwaukee, Wis. The batyl alcohol from the latter source was purified further by recrystallization three times from acetone before use. Each of the batyl alcohol samples melted at 70–71°, consumed one mole of periodate per mole of substance, yielded correct analysis figures for carbon and hydrogen, and showed the expected infrared spectrum (2). On GLC of the isopropylidene derivative (2), the batyl alcohol samples all had a similar retention time and showed a single, symmetrical peak. In addition the iso-

propylidene derivative was optically active, $[\alpha]_D^{25} = -17.5°$ (c, 3% in hexane), and migrated as a single discrete spot on TLC.

GLC was carried out on a 6 ft x 1/4 inch column of 15% ethylene glycol succinate polyester on Anakrom AK 60–70 mesh (Analab, Hamden, Conn.) in a Barber-Colman Model 10 Argon chromatograph, with the column at 178°, flash heater at 225°, detector at 250°, and an inlet pressure of 10–12 psi. Methyl esters were prepared from free fatty acids using boron trifluoride in methanol (obtained from Applied Sciences Laboratory, State College, Pa.), as described by Metcalfe and Schmitz (4). Carbon, hydrogen, and iodine analyses were performed by Dr. Alfred Bernhardt (Mülheim, Germany). Infrared spectra were obtained on a Perkin-Elmer Model 21 infrared spectrometer with sodium chloride optics; in nearly all instances samples were in chloroform solution in 1 mm Irtran cells (Connecticut Instrument Corp., Wilton, Conn.). TLC on Silica Gel G was performed essentially as described by Stahl (5). The compounds were located by spraying the air-dried plates with concd H_2SO_4 and heating. Unsaturated compounds were detected with iodine vapor. Column chromatography with silicic acid (Mallinckrodt, 100 mesh, suitable for chromatography) was carried out essentially as described previously (2).

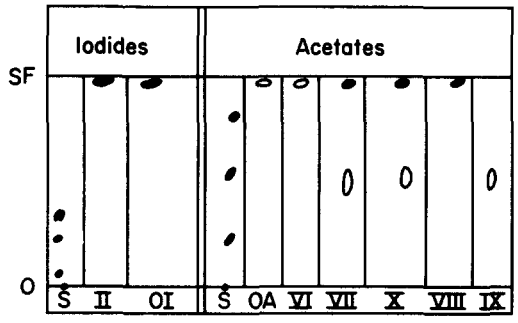


FIG. 1. Thin-layer chromatograms of iodides derived from hydriodic acid attack on glyceryl ethers and of acetates prepared from these iodides.

The samples applied to each channel were as follows. Iodides: *S*, standard consisting in ascending order from origin (*O*) to solvent front (*SF*) of selachyl alcohol, cholesterol, palmitic acid, and triolein; *II*, iodides prepared from selachyl alcohol; *OI*, pure octadecyl iodide. Solvent system: petroleum ether–diethyl ether–glacial acetic acid 200:1:1 (v/v).

Acetates: *S*, standard (the same as on iodide plate); *OA*, pure octadecyl acetate: *VI*, acetates derived from iodides of hydrogenated selachyl alcohol; *VII*, acetates prepared from iodides of selachyl alcohol; *X*, acetates derived from hydrogenated *II*; *VIII* and *IX*, silicic acid column fractions from *VII*. Solvent system: petroleum ether–diethyl ether–glacial acetic acid 90:10:1 (v/v).

Open circles indicate no reaction with iodine vapor; closed circles, positive reaction to iodine vapor.

Iodine numbers were obtained by a modified Wijs method. Unsaturated samples were also hydrogenated at atmospheric pressure over PtO_2 as catalyst. Similar products were obtained upon hydrogenation of samples in a Parr apparatus at 40 psi with PtO_2 as catalyst. Glacial acetic acid, C.P., was a product of Merck, Inc. Silver acetate, purified, was obtained from the Fischer Chemical Co., Fairlawn, N.J. Hydriodic acid, sp gr 1.7, 55–58% HI, was purchased from Merck, Inc. Periodic acid was a product of the G. F. Smith and Co., Columbus, Ohio. Tertiary butanol was a product of Matheson, Coleman and Bell, Norwood, Ohio. All other solvents were reagent grade.

The procedure of Guyer et al. (1) for the cleavage of glyceryl ethers by hydriodic acid was followed, except that the reflux reaction time was reduced from 24 to 3 hr. In all cases this time period gave yields, on a weight basis, of 90–95%. Octadecyl iodide was prepared from synthetic DL-batyl alcohol under the above conditions. This product was crystallized from acetone: mp 32–33°.

Calculated for $C_{18}H_{37}I$: C, 56.8; H, 9.7; I, 33.4.
Found: C, 56.8; H, 9.7; I, 33.4.

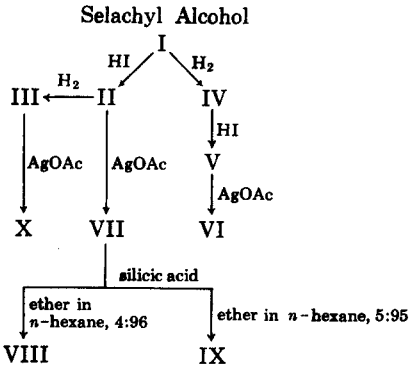
The iodides were converted to acetates under conditions similar to those described by Guyer et al. (1), namely, reaction with silver acetate in glacial acetic acid at reflux temperature for 24 hr. Octadecyl acetate was prepared from pure octadecyl iodide. It showed a single spot on TLC (Fig. 1) and a single, symmetrical peak (not shown) with a retention time identical with that of octadecyl iodide on GLC. The following absorption bands were observed in the infrared: 3.47 (shoulder), 3.53 (sharp, deep), 5.80 (sharp, deep), 6.90 (shallow, broad), 7.35 (sharp). This pure octadecyl acetate was used as the standard in the estimation of the acetyl content of the acetates derived from glycerol ethers, by measurement of the absorbance at 5.75 μ. A linear response was found in the range 0.5–4.0 mg octadecyl acetate per ml of chloroform, with absorbance values from 0.05 to 0.50.

RESULTS

Reaction of Hydriodic Acid on Glyceryl Ethers

The action of hydriodic acid on pure batyl alcohol gave in good yield octadecyl iodide, which behaved on TLC (Fig. 1) as a single component and gave a single sharp peak on GLC (OI, Fig. 2). The infrared spectrum showed the absence of any ether (—C—O—C—) band at 9.0 μ (1100 cm^{-1}) but gave the following absorption bands: 3.47 (shoulder), 3.53 (sharp, deep), 6.90 (sharp), 7.30 (sharp, shallow). On the other hand

a sample rich in selachyl alcohol, I (see reaction scheme) containing only unsaturated (olefinic) glyceryl ethers



(Table 1), reacted with hydriodic acid to yield an iodide, II, which behaved on TLC as a single component and had an infrared spectrum similar to pure octadecyl iodide, but trailed very severely on GLC (II, Fig. 2). This latter behavior was always encountered with various unsaturated samples and it was not possible to quantify any of the gas–liquid chromatographic patterns of "unsaturated" iodides. If I was hydrogenated prior to the hydriodic acid treatment, the iodide derivative, V, chromatographed as a symmetrical sharp peak (V, Fig. 2), the major component being identical with authentic octadecyl iodide. The composition of these iodides, as obtained by GLC, is given in Table 1. Interestingly, hydrogenation of the iodide II yielded a derivative, III, which showed only 10% of a component behaving as an 18:0 iodide, the remainder appearing as a reasonably symmetrical peak having a longer retention time (III, Fig. 2). Evidently, in addition to attacking the ether bond, HI has added to the olefinic linkages to produce one or more diiodides.

Conversion of Iodides to Acetates

The conversion of alkyl iodides to the acetates proceeded smoothly and in good yields. The acetates VII obtained from II yielded two spots on thin-layer chromatograms (Fig. 1), the upper one of which consisted of unsaturated monoacetates (positive reaction with iodine vapor), the lower consisting of saturated diacetates (not responsive to iodine vapor). On the other hand the saturated monoacetates, OA and VI, prepared via the iodides from pure batyl alcohol or hydrogenated selachyl alcohol, IV, gave a single spot, unreactive with iodine, almost at the solvent front (Fig. 1). Gas–liquid chromatography of VII gave several peaks, two of which represented over 80% of the material (Fig. 3). Neither of these two peaks corresponded to the 18:0 peak obtained in the GLC of

TABLE 1 GLC OF IODIDES AND ACETATES DERIVED FROM SELACHYL ALCOHOL

		Iodides			Acetates			VII (Acetates) after Silicic Acid Chromatography			
								VIII		IX	
Chain	I*	V	II	III	VI	VII	X	As Isolated	Hydrogenated	As Isolated	Hydrogenated
15:0		Tr.					3.0				
15:1											
?									Tr.		
16:0		6.0			6.0				7.0		
				7.0	Tr.						
16:1	5.0					3.0	2.0	6.0	Tr.	Tr.	
17:0		Tr.		Tr.	Tr.		Tr.	Tr.	Tr.		
17:1	Tr.					Tr.		Tr.			
18:0		91.1		10.0	92.0		4.0		87.0		6.0
18:1	93.0		Severe ↑ Trailing ↓			41.0	51.0	89.0		2.0	
?				84.0							
19:0											
19:1											
20:0		4.0			4.0				7.0		0.5
20:1	2					10.0	Tr.	5.0			
21:0†				Tr.							
21:1†											
22:0†						6.0					
22:1†										7.0	5.0
?										1.0	0.5
23:1†											2.0
24:1†						40.0	39.0			91.0	87.0

* Analyzed as the isopropylidene derivative.

† These are equivalent chain lengths based on the retention times for the emerging peaks and do not necessarily reflect the presence of a real chain of this composition.

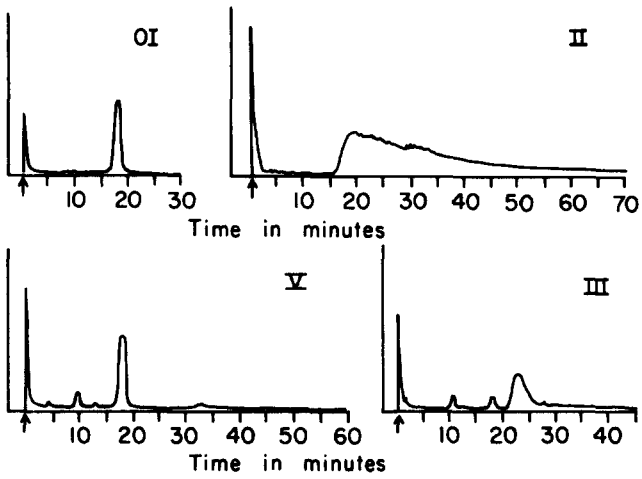


FIG. 2. Gas-liquid chromatogram of iodides derived from action of hydriodic acid on glyceryl ethers.

OI, pure octadecyl iodide; *II*, iodides prepared from selachyl alcohol; *V*, iodides prepared from hydrogenated selachyl alcohol; *III*, iodides of *II* after hydrogenation. Conditions: 15% ethylene glycol succinate polyester on Anakrom AK, 60–70 mesh, at 178° with inlet pressure of 12 psi; flash heater, 225°, detector, 225°.

octadecyl acetate, OA (not given; similar retention time to OI, Fig. 2), or of VI (Fig. 3). VI also contained minor components migrating as 16:0 and 20:0 acetates.

Derivative VII was chromatographed on silicic acid with ether–hexane 4:96, which eluted the first major component, VIII, and then ether–hexane 5:95, which eluted a second major component, IX, the two components corresponding to the two spots noted above on TLC. The progress of this separation was followed by the response of aliquots of the eluate dried on glass fiber paper to charring with sulfuric acid. VIII and IX were analyzed further by TLC, GLC (Table 1), and other analytical procedures.

VIII had an iodine uptake value of 81.5 and an acetyl content of 12.9% (theoretical for an 18:1 acetate, 82.7 and 13.6%). VIII migrated to the solvent front in the system shown in Fig. 1, was reactive to iodine vapor, and had a retention time (Fig. 3) similar to that of the first peak in VII. Its infrared spectrum had the following absorption bands: 3.47 (shoulder), 3.53 (sharp), 5.80 (deep), 6.90 (deep), 7.30, 8.0–8.5 (broad), 10.35 (sharp, deep). This last peak clearly showed the presence of a *trans* double bond. The band at 10.35 μ was not present in the parent sample of selachyl alcohol. After hydrogenation, VIII showed a major component with a retention time on GLC equal to that of pure octadecyl acetate. This evidence supports the conclusion that VIII consisted mainly of monounsaturated monoacetates.

IX migrated with an R_F near 0.5 on TLC, showed no reaction with iodine vapor and had a retention time fairly close to that of the second peak obtained on GLC of VII (Fig. 3). It had an insignificant iodine uptake and hydrogenation did not affect its retention time, as would be expected from its negligible unsaturation. IX had an acetyl content of 18.2% (theory for 18:0 diacetate, 23.2%). Further, IX showed the following absorption bands in the infrared: 3.47 (shoulder), 3.53 (sharp), 5.80 (deep), 6.90, 7.30, 8.0–8.5 (broad), 9.9 (shallow), 10.35 (trace). A portion of IX was refluxed in 1 N KOH in 95% ethanol for 3–4 hr, evaporated to small volume, acidified in the cold, and extracted with diethyl ether. The ether-soluble extract was washed several times with water, dried over sodium sulfate, and evaporated to dryness.

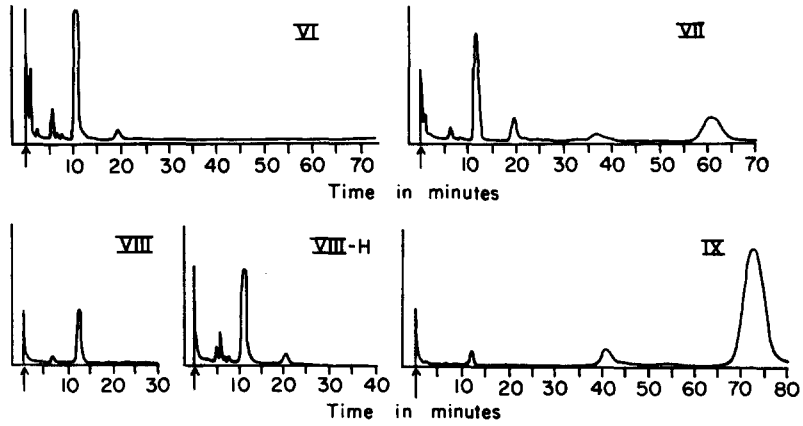


FIG. 3. Gas–liquid chromatograms of acetates derived from iodides.

These samples, prepared from iodides shown in Fig. 2, are identified as follows: *VI*, acetates from V iodides; *VII*, acetates from II iodides; *VIII*, fraction from silicic acid chromatography of VII acetates; *VIII-H*, hydrogenated VIII; *IX*, fraction from silicic acid chromatography of VII acetates. Conditions were the same as given under Fig. 2.

The residue was dissolved by warming in petroleum ether (bp 30–60°). A white solid separated on cooling which was filtered and air-dried. It was dissolved in methanol, and water was added to the point of turbidity. The mixture was warmed until clear and then allowed to cool to room temperature and placed at 4° overnight. The large sheaf-like white crystals were filtered, washed well with water, and recrystallized once more under the same conditions. The final colorless product, which was dried over P_2O_5 in vacuo for 6 hr, melted at 60–61° (Fisher-John's melting point block). Analysis: calculated for dihydroxy octadecane, $C_{18}H_{38}O_2$ (286): C, 75.5; H, 13.30; found: C, 75.39; H, 13.14. The following infrared absorption bands were observed: 2.94 (sharp, deep), 3.53 (sharp, deep), 6.90 (sharp), 7.30 (sharp), 10.15 (shallow). These results were considered to support a diacetate structure for IX.

Finally, III was converted in good yield to its corresponding acetate derivative, X. As shown in Table 1, the composition (and gas–liquid chromatographic pattern) of X was very similar to that of VII, the observed differences probably being due to by-products of the hydrogenation process. TLC of X with the solvent system shown in the legend to Fig. 1 for the acetates showed exactly the same pattern (and reaction to iodine vapor) as that obtained with VII (Fig. 1).

Structure of Unsaturated Acetate, VIII

A further insight into the possible isomers in VIII, obtained in silicic acid chromatography of VII (see above), was afforded by permanganate–periodate oxidation of this fraction, essentially as described by von Rudloff (6), and an examination of the resulting products. The reaction was allowed to continue at room temperature for 18 hr and the reaction mixture was then treated as described previously (2). The final extract, which contained the cleavage products and possibly some unreacted starting material, was chromatographed on silicic acid with the eluents hexane and ether–hexane 1:9, 2:8, and 7:3. The progress of the elution was followed by the response of aliquots of the eluate, dried on glass fiber filter paper, to bromothymol blue and to charring with sulfuric acid. The first fraction, eluted with ether–hexane 1:9, gave a single spot on TLC and had a neutralization equivalent of 141 (theory for octanoic acid, 143) and an infrared spectrum similar to that of octanoic acid. Another run yielded a similar fraction with a neutralization equivalent value of 148. This fraction was considered to consist of monocarboxylic acids and was esterified with BF_3–methanol and assayed by GLC. The results are presented in Table 2. The second component, which was eluted with ether–hexane 7:3, was not analyzed further, except for a total weight measurement. The over-all yields in this reaction and subsequent separation were 80–85% of theory.

TABLE 2 COMPOSITION OF MONOCARBOXYLIC ACIDS ISOLATED FROM PERIODATE–PERMANGANATE CLEAVAGE OF UNSATURATED ACETATE

Experiment	Methyl Esters*	
	Chain	Mole %
A	8:0	17
	9:0	32
	10:0	35
	11:0	11
	12:0	—
B	8:0	Tr.
	9:0	27
	10:0	47
	11:0	19
	12:0	8

Product VIII (Table 1 and text) was subjected to periodate–permanganate oxidation. The monocarboxylic acid fraction was isolated by silicic acid chromatography and analyzed as methyl esters by GLC.

* The neutralization equivalents of the free fatty acids obtained in A and B were 141 and 149, respectively.

Thus, permanganate–periodate cleavage of VIII yielded two main fractions, one of which was composed of monocarboxylic acids, C_8 to C_{11}; the other was also acidic. These data suggest that the unsaturated acetate VIII is, unlike the starting material I, a mixture of positional isomers rather than a single substance.

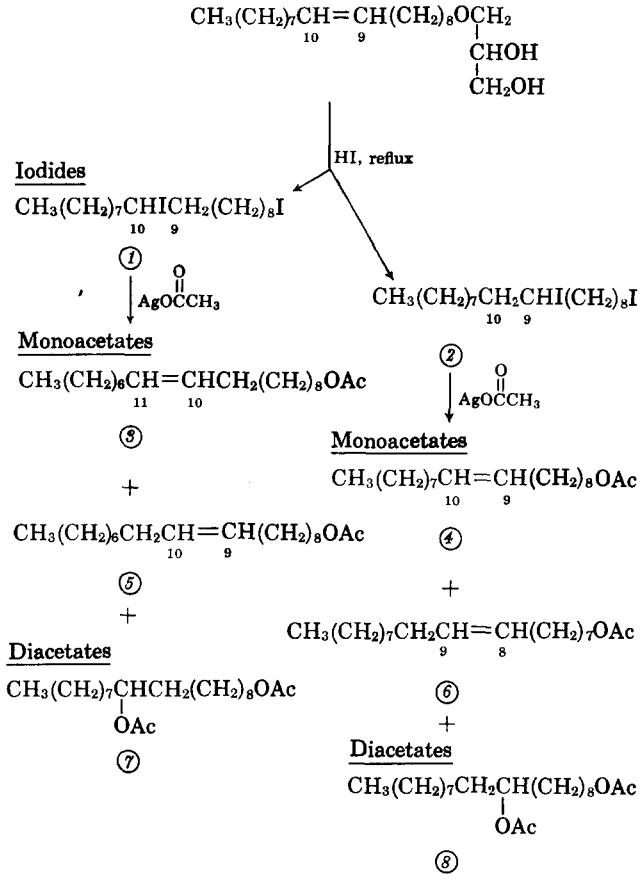
DISCUSSION

The data presented in this paper show conclusively that hydriodic acid attacks unsaturated glyceryl ethers at the olefinic bonds as well as at the ether bonds. The ether bond is cleaved with the formation of a primary iodide, whereas at least two different secondary iodides result from hydriodic acid attack at or contiguous to the olefinic bonds.

The iodides from unsaturated glyceryl ethers were unstable under the conditions used for GLC, as indicated by severe trailing of the peaks, and could not be assayed qualitatively or quantitatively by this technique. This behavior was attributed to the presence of secondary iodides, since the primary iodides, at least saturated ones such as octadecyl iodide, gave smooth, symmetrical GLC peaks. The instability of secondary iodides was noted by Guyer et al. (1). On the other hand, chromatographically stable products could be obtained by conversion of the iodides to acetates. However, this reaction resulted in the formation of saturated diacetates and monounsaturated monoacetates. The ratio of diacetates to monoacetates, on a weight basis, was close to one, and the infrared spectrum of the unsaturated acetates showed the presence of a *trans* bond. Only *cis* double bonds were present

in the unsaturated glyceryl ethers used as starting material.

The results of these experiments can be explained by the following series of reactions starting from selachyl alcohol:



Over 90% of the iodides formed in this reaction can be represented by structures *1* and *2*, since hydrogenation yielded only 9–10% of an 18:0 monoiodide component, as assayed by GLC. Subsequent conversion of these iodides to the acetates resulted in the formation of monoolefinic monoacetates, structures *3–6*, and saturated diacetates, structures *7* and *8*. The two major components separated by silicic acid chromatography gave analyses closely corresponding to the mono- and diacetates. The unsaturated monoacetates comprised a mixture of positional isomers, and it was evident that the dehydrohalogenation with silver acetate occurred not only at the 9:10 position, but also on either side of this bond, i.e., 8:9 and 10:11, for the monocarboxylic acids obtained from a periodate–permanganate oxidation of the unsaturated acetates contained a mixture of 8:0 through 11:0 acids. In addition, the presence of a 10.35 μ (966 cm^{-1}) band in the infrared spectrum of the unsaturated acetates showed the formation of a *trans* olefinic bond, whereas a *cis* bond existed in the starting material.

The mechanism of hydriodic acid attack on an unsaturated glyceryl ether is interesting in that it represents a nucleophilic attack at the ether bond as well as an electrophilic attack on an olefinic bond. It is probable that in the experiments described, the (polar) addition of hydrogen iodide to the olefinic bonds of selachyl alcohol proceeds, as suggested by Dewar and Fahey (7), via a classical carbonium ion intermediate, which could occur as an undissociated ion pair. The polarity of the solvent in the present case would tend to favor *trans* addition to the double bond.

The ease with which hydriodic acid can add to olefinic bonds in unsaturated glyceryl ethers, together with the apparent nonspecificity of the addition (at one carbon or the other), and the heterogeneity of the products obtained by conversion of the iodides to the acetates, makes it evident that this reagent must be used with caution in the identification of unsaturated glyceryl ethers.

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