Carcinogen Chemistry. 4. (Haloalkyl)oxonium and (Haloalkyl)carboxonium Ions. Preparation, Nuclear Magnetic Resonance Structural Study, and Alkylating Ability[1a]

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For exploration of the in vitro formation of the potential carcinogenic alkylating agents and particularly the reactive ionic intermediates derived from formaldehyde–hydrogen halides and haloalky ethers, their protolytic ionization under stable-ion conditions in low-nucleophilicity solutions was studied. The preparation, a NMR spectroscopic structural study, and the alkylating ability of a series of (haloalkyl)oxonium and (haloalkyl)-carboxonium ions, including the previously elusive (fluoromethyl)- and (chloromethyl)oxonium ions, are reported, indicating their potential bioalkylating ability.

Halomethyl ethers and their derivatives are recognized as extremely reactive carcinogens.[2,3] The mechanism whereby these precarcinogens are transformed into de facto active carcinogens is one of the challenging aspects of carcinogen chemistry. According to Miller's concept,[4] electrophilic alkylating agents are formed in the critical step of chemical carcinogenesis. Brookes and Dipple[5] also suggested that the most probable "ultimate carcinogen" formed from methyl- or halomethyl-substituted hydrocarbons would be of a *carbenium ion*[6] nature. This concept has also been recently tested by Hulbert in his study of carcinogenesis of polycyclic aromatic hydrocarbons.[7] It is, however, necessary to question the involvement of "free" carbocations, particularly that of the methyl cation (CH_3^+).[2,8] Although many carbocation salts have been prepared and even isolated from low nucleophilic solutions,[9] they are nonetheless by definition extremely reactive toward any nucleophiles present in the system. The methyl cation was only detectable in the gas phase as a highly energetic species.[10]

Haloalkyl derivatives (ethers, aldehydes, and alcohols) 1 were widely used in chemical industry. Increasing evidence suggests that these compounds are potential chemical carcinogens in that they can easily form some type of electrophilic species.[11] Low molecular weight haloalkyl ethers, as they are generally quite volatile liquids, are liable to cause occupational hazards both in direct skin contact and inhalation exposure.[12] Bis(chloromethyl) ether is one of the most active carcinogens. As it is known that DNA displays only moderate nucleophilic properties,[13] it seems to be indicated that the de facto alkylating metabolite would indeed react with appreciable carbocation character. The exact nature of these species is, however, still unknown and only speculated upon. In view of our previous studies of heteroatom-stabilized cations it is possible that carcinogenic activity of chloromethyl ethers 2 and related formaldehyde derivatives could be the result of their forming (haloalkyl)oxonium 3 or (haloalkyl)carboxonium ions 4 (eq 1).

$$\underset{\mathbf{3}}{ClCH_2O^+HR} + CH_2{=}\overset{+}{O}CHRCl \leftrightarrow \underset{\mathbf{4}}{{}^+CH_2OCHRCl} \quad (1)$$

R = H or alkyl

In order to study the possible in vitro formation and structure of potential ionic alkylating agents derived from haloalkyl ethers, we have carried out a study of the protolytic ionization of formaldehyde–hydrogen halides and haloalkyl ethers under "stable-ion conditions" and report now our findings. Whereas obviously no direct extrapolation can be made between stable-ion studies in highly acidic, low-nucleophilicity media and in vitro biological conditions, nevertheless the identification and study of reactive cationic alkylating intermediates under the former conditions can be of substantial significance for a better understanding of potentially carcinogenic alkylating systems.

Results and Discussion

I. Halomethyloxonium Ions. A. Chloromethyl Alcohol.[14] Although chloromethyl alcohol was suggested

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Table I. ^{1}H NMR Data of (Halomethyl)oxonium Ions[a]

	H^1	H^2	H^3	H^4	H^5	H^6	coupling const, Hz
$XC^2H_2O^+H^1_2$ (X = Cl)	11.67 (t)	6.40 (t)					J_{12} = 4.8
(X = F)	12.34 (td)	6.15 (dt)					J_{12} = 4.9, J_{1F} = 1.7, J_{2F} = 47.9
$ClC^2H_2O^+(H^1)C^6H_5$	11.40 (m)	6.38 (d)				4.82 (d)	J_{12} = 4.8, J_{16} = 3.3, J_{12} = 5.0
$ClC^2H_2O^+(H^1)C^3H_2C^6H_5$	11.00 (p)	6.40 (d)	5.37 (d, q)			1.90 (t)	J_{13} = 3.4, J_{36} = 7.4, J_{12} = 4.2
$ClC^2H_2O^+(H^1)C^3H_2C^4H_2Cl$	11.70 (p)	6.37 (d)	5.27 (d, t)	4.16 (t)			J_{34} = 4.2, J_{12} = 4.5
$ClC^2H_2O^+(H^1)C^3H_2C^5H_2$-$C^5H_2C^4H_2Cl$	11.17 (m)	6.37 (d)	5.27 (m)	3.90 (t)	2.26 (m)		J_{45} = 5.3
$ClC^2H_2O^+(H)C^3H_2C^5H_2$-$C^5H_2C^3H_2O^+(H^1)C^2H_2Cl$	11.83 (m)	6.43 (br s)	5.28 (m)		2.50 (m)		

[a] Spectra were obtained from a Varian A56/60A spectrometer at −80 °C in SO_2. Chemical shifts in δ units refer to a capillary of tube of Me_4Si, and the multiplicities are given in parentheses: s, singlet; d, doublet; t, triplet; q, quartet; p, quintet; m, multiplet; br, broad.

to be an elusive intermediate in chloromethylation with formaldehyde and hydrogen chloride,[15] it was not directly observed nor substantiated by physical measurements. Neither was the exact nature of the reactive chloromethylating agents in electrophilic aromatic chloromethylations clearly established. $CH_2{=}OH^+$ and $^+CH_2Cl$ are the species most frequently suggested. It is, however, highly improbable that the chloromethyl cation ($^+CH_2Cl$) would exist as the de facto reactive intermediate involved in chloromethylation. We now report the first direct evidence for the formation of chloromethyl alcohol and its direct observation in its protonated form.

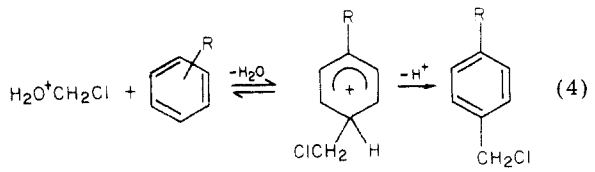
A solution of protonated chloromethyl alcohol **5** was obtained from protonated formaldehyde (the hydroxycarbenium ion) **6**[15d] and HCl in FSO_3H–SbF_5–SO_2 solution at −80 °C (eq 2).

$$\underset{\mathbf{6}}{CH_2{=}{}^+OH} + Cl^- \xrightarrow[-80\ °C]{SO_2} \underset{\mathbf{7}}{[ClCH_2OH]} \xrightarrow{FSO_3H\text{–}SbF_5} \underset{\mathbf{5}}{ClCH_2OH_2^+} \quad (2)$$

The ^{1}H NMR spectrum of **5** (Table I) shows the $^+OH_2$ triplet at δ 11.67 ($J_{H\text{-}H}$ = 4.8 Hz) and the methylene triplet at δ 6.40. There is no evidence of chloride-fluoride exchange which would show characteristic H–F coupling as found in $FCH_2OH_2^+$ (see subsequent discussion). The ^{13}C NMR spectrum (Table IV) shows a triplet at δ ^{13}C 71.8 ($J_{C\text{-}H}$ = 17 Hz).

Data can be best interpreted by the hydroxycarbenium ion **6** reacting with HCl to give chloromethyl alcohol **7**, which in the superacidic medium is observed in its stable, protonated form, i.e., the (chloromethyl)oxonium ion **5**. The observation of ion **5** suggests that it can be the de facto reactive alkylating agent in chloromethylation with formaldehyde–HCl systems (eq 3 and 4). This is in accord with

$$CH_2O + 2HCl + ZnCl_2 \rightleftharpoons ClCH_2O^+H_2,ZnCl_3^- \quad (3)$$



(4)

kinetic data of chloromethylations[14] showing first-order dependence in aromatics and formaldehyde, and would eliminate the need to suggest the involvment of the energentically less favorable chloromethyl cation ($^+CH_2Cl$) or hydroxycarbenium ion ($^+CH_2OH$).

We feel that these findings shed new light on the mechanistic aspects of chloromethylation and may also contribute to the understanding of the nature of the reactive alkylating species involved in the *in vitro* carcinogenic activity of chloromethyl ethers and related formaldehyde systems.[11]

B. Fluoromethyl Alcohol.[17] Formation of fluoromethyl alcohol (**8**, FCH_2OH), from ethyl fluoroformate or formyl fluoride was reported by Olah and Pavlath[18] in 1953. They were, however, unable to isolate and characterize the pure compound. Andreades and England[19] in 1961 prepared a number of highly fluorinated α-fluoro alcohols. Weinmayer[20] in 1963 studied the reaction of fluoro olefins with formaldehyde in hydrogen fluoride and suggested that a solution of paraformaldehyde in hydrogen fluoride contains an equilibrium on 25–30% fluoromethyl alcohol and 70–75% bis(fluoromethyl) ether. Olah and Tolgyesi[21] in 1964 reviewed the haloalkylation reactions and available information on α-halo alcohols. They also reported that trioxymethylene and HF forms a polymeric fluorohydrin [$HO(CH_2O)_nCH_2F$] which reacts similarly to fluoromethyl alcohol under acid-catalyzed conditions. German and Knunyantz in a more recent review article[22] discussed reactions of paraformaldehyde in hydrogen fluoride, with particular emphasis on their own earlier work in the field. Fluoromethyl alcohol recently aroused substantial theoretical interest as a model compound for ab initio calculations.[23] Finally, the elusive trifluoromethyl alcohol was recently obtained at −70 °C by the reaction of CF_3OCl and HCl.[24]

When monomeric formaldehyde (generated by thermal

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(24) Prepared by the metathetic reaction of $ClCH_2OCH_3$ with HgF_2: δ_{CH_2} 4.69, δ_{CH_2} 3.02; J_{HF}^{gem} = 57 Hz, J_{HF}^{vic} = 16 Hz.

Table II. Proton NMR Parameters of Halomethyl Haloalkyl Ethers in $CDCl_3$ at 25 °C

ether	X	Y	chemical shift, δ H¹	H²	H³	H⁴	H⁵
$XC^1H_2OC^2H_2C^3H_2Y$	Cl	Cl	5.62 (s)	3.90 (t)	3.90 (t)		
	Cl	Br	5.57 (s)	4.03 (t)	3.55 (t)		
	Cl	I	5.57 (s)	4.00 (t)	3.32 (t)		
$XC^1H_2OC^2H_2C^3H_2C^4H_2Y$	Cl	Cl	5.67 (s)	4.00 (t)	2.22 (p)	3.78 (t)	
	Cl	Br	5.53 (s)	3.85 (t)	2.17 (p)	3.50 (t)	
$XC^1H_2OC^2H_2C^3H_2C^4H_2C^5H_2Y$	Cl	Cl	5.57 (s)	3.75 (t)	1.83 (m)	1.83 (m)	3.36 (t)
	Br	Cl	5.82 (s)	3.73 (t)	1.85 (m)	1.85 (m)	3.65 (t)
	Br	Br	5.78 (s)	3.73 (t)	1.85 (m)	1.85 (m)	3.50 (t)

depolymerization of paraformaldehyde) is dissolved in 3:1 (v/v) HF–SbF_5 solution at −78 °C a white precipitate is formed (probably a polymeric formaldehyde product). This precipitate is partly dissolved when the temperature is increased to −40 °C. The clear supernatant consists of a saturated solution of fluoromethyl alcohol, **8**, in its stable protonated form **9** (eq 5).

$$CH_2O + HF \rightarrow \underset{\mathbf{8}}{[FCH_2OH]} \xrightarrow[SbF_6^-]{H^+} \underset{\mathbf{9}}{FCH_2{}^+OH_2,SbF_6^-} \quad (5)$$

The ^1H NMR spectrum of **9** clearly demonstrates its structure. The methylene signal appearing at δ 6.15 (from a capillary of Me_4Si) is a doublet (J_{HF}^{gem} = 47.9 Hz) of triplets (J_{HH}^{vic} = 4.9 Hz). The OH_2 triplet ($J_{CH_2OH_2}$ = 4.9 Hz) at δ 12.34 exhibits further splitting (1.7 Hz) due to the corresponding fluorine–proton vicinal coupling. The ^{19}F spectrum shows a triplet of triplets with the above-mentioned coupling constants. The fluorine chemical shift is φ 166.7 (from CCl_3F), a value comparable with that obtained for FCH_2OCH_3 (φ 163.7).[24] The ^{13}C NMR spectrum shows the carbon shift as a doublet of tripltes at $\delta_{^{13}C}$ 100, with a J_{C-F} of 248 Hz and a J_{C-H} of 192.2 Hz. The ^{13}C NMR data, together with those of model compounds are summarized in Table IV.

When formaldehyde is dissolved at −78 °C in 1:1 FSO_3H–SbF_5/SO_2ClF a stable solution of protonated formaldehyde **6** (the parent carboxonium ion)[25] is formed. Upon addition of fluoride ion (in the form of sodium fluoride or hydrogen fluoride) at −78 °C, protonated fluoromethyl alcohol **9** is obtained (eq 6).

$$CH_2O \xrightarrow[SO_2ClF,\ -78\ °C]{FSO_3H\text{–}SbF_5} \underset{\mathbf{6}}{[CH_2{=}OH^+ \leftrightarrow {}^+CH_2OH]} \xrightarrow[2.\ H^+]{1.\ F^-} \underset{\mathbf{9}}{FCH_2OH_2^+} \quad (6)$$

Ion **6** reacts through its hydroxycarbenium ion form with fluoride ion, giving fluoromethyl alcohol which then is protonated in the superacid medium (eq 7).

$$\underset{\mathbf{6}}{{}^+CH_2OH} + F^- \rightarrow \underset{\mathbf{8}}{FCH_2OH} \overset{H^+}{\rightleftharpoons} \underset{\mathbf{9}}{FCH_2OH_2^+} \quad (7)$$

The preparation of protonated fluoromethyl alcohol from protonated formaldehyde with fluoride ion seems to be direct experimental evidence of the stable protonated carbonyl intermediate reacting through its hydroxycarbonium ion nature and thus is in agreement with conclusions reached from ^1H, ^{13}C, and ^{19}F NMR studies of the contribution of the hydroxycarbenium ion form in protonated formaldehyde. Fluoromethyl alcohol also represents a molecule of substantial interest as the parent compound of α-halo alcohols.

Whereas in its protonated form fluoromethyl alcohol is stable, the free alcohol readily loses HF to form formaldehyde and has not been isolate so far in the pure state.

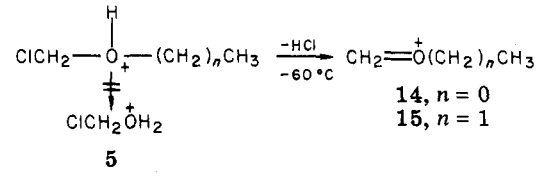
II. (Halomethylalkyl)oxonium Ions. The α-haloalkyl ethers such as chloromethyl methyl ether (**10**) that have found wide use in preparative chemistry are also potent alkylating agents and carcinogens. The corresponding β- and γ-haloalkyl ethers are, however, much less reactive. In order to understand more of their alkylating activity, a series of chloromethyl alkyl ethers was studied in superacidic systems.

Chloromethyl methyl ether (**10**) was protonated in FSO_3H–SbF_5–SO_2ClF solution at −78 °C and gave the (chloromethyl)methyloxonium ion **11** (eq 8). Chloromethyl ethyl ether **12** gave the corresponding oxonium ion **13**. The ^1H NMR data are summarized in Table II. Protonated chloromethyl alkyl ethers are much less stable than their parent analogues, i.e., protonated methylalkyl ethers,[27] and they slowly eliminate hydrogen chloride at around −60 °C to form the corresponding carboxonium ions, **14** and **15** (vide infra).[15d] There is, however, no cleavage reaction taking place to form protonated chloromethyl alcohol **5** (Scheme I).

$$\underset{\mathbf{10},\ n=0}{ClCH_2O(CH_2)_nCH_3} \xrightarrow[SO_2ClF,\ -78\ °C]{FSO_3H\text{–}SbF_5} \underset{\mathbf{11},\ n=0}{ClCH_2O^+H(CH_2)_nCH_3} \quad (8)$$
$$\underset{\mathbf{12},\ n=1}{} \qquad \underset{\mathbf{13},\ n=1}{}$$

III. (Haloalkyl)carboxonium Ions. A. (Chloromethyl)carboxonium Ion. Bis(chloromethyl)ether (**16**) has been recognized to possess carcinogenic activity when present at even very low concentration in the atmo-

Scheme I



Scheme II

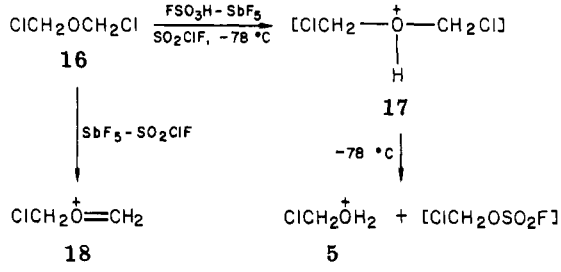


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Table III. Proton NMR Parameters of Alkyl- and (Haloalkyl)carboxonium Ions in SO_2 Solution at −60 °C

ion	X	chemical shift, δ H¹	H²	H³	H⁴	H⁵
$C^1H_2{=}O^+C^2H_2C^3H_2X$	Cl	9.97 (s)	6.00 (t)	4.34 (t)		
	Br	9.93 (s)	6.13 (t)	4.27 (t)		
	I	10.00 (s)	6.23 (b)	3.30 (b)		
$C^1H_2{=}O^+C^2H_2C^3H_2C^4H_2X$	Cl	9.98 (s)	6.03 (t)	2.85 (p)	4.03 (t)	
	Br	9.87 (s)	5.97 (t)	2.85 (p)	3.80 (t)	
$C^1H_2{=}O^+C^2H_2C^3H_2C^4H_2C^5H_2X$	Cl	10.13 (s)	6.10 (t)	2.48 (m)	2.48 (m)	4.02 (t)
	Br	9.83 (s)	5.83 (m)	2.43 (m)	2.43 (m)	3.83 (b)
$C^1H_2{=}O^+C^2H_2Cl$		9.82	6.76			

Table IV. ^{13}C NMR Parameters of (Halomethyl)oxonium and Alkyl- and (Chloroalkyl)carboxonium Ions in SO_2 Solution at −80 °C

ion	C¹	C²	C³
$FC^1H_2O^+H_2$	100.4 (d, J_{C-F} = 248.0 Hz; t, J_{C-H} = 192.2 Hz)		
$ClC^1H_2O^+H_2$	77.8 (t, J_{C-H} = 187.0 Hz)		
$C^1H_2{=}O^+{-}H$	223.7 (t, J_{C-H} = 204.4 Hz)		
$C^1H_2{=}O^+{-}C^2H_3$	220.3 (t, J_{C-H} = 204.1 Hz)	83.3 (br, J_{C-H} = 158.5 Hz)	
$C^1H_2{=}O^+{-}C^2H_2C^3H_3$	217.7 (t, J_{C-H} = 203.0 Hz)	98.2 (t, J_{C-H} = 159.5 Hz)	14.4 (br, J_{C-H} = 130.8 Hz)
$C^1H_2{=}O^+{-}C^2H_2Cl$	216.4 (t, J_{C-H} = 207.0 Hz)	96.0 (t, J_{C-H} = 190.6 Hz)	
$C^1H_2{=}O^+{-}C^2H_2C^3H_2Cl$	220.2 (t, J_{C-H} = 205.0 Hz)	97.4 (t, J_{C-H} = 161.7 Hz)	40.6 (t, J_{C-H} = 156.1 Hz)

sphere.[11,26] When **16** was dissolved in FSO_3H–SbF_5–SO_2ClF solution at −78 °C, the ^1H NMR spectrum (see Table III) showed the exclusive formation of the protonated chloromethyl alcohol **5** (Scheme II). In SbF_5–SO_2 solution at −78 °C, **16** gave only the (chloromethyl)carboxonium ion **18** (vide infra) which is very stable, and no dehydrochlorination took place.

When formaldehyde is dissolved in 1:1 HF–SO_2ClF solution at −78 °C, the ^1H and ^{19}F NMR spectra indicates presence of bis(fluoromethyl) ether (**19**), formed through the acid-catalyzed self-condensation of the initially produced fluoromethyl alcohol (**8**, eq 9).

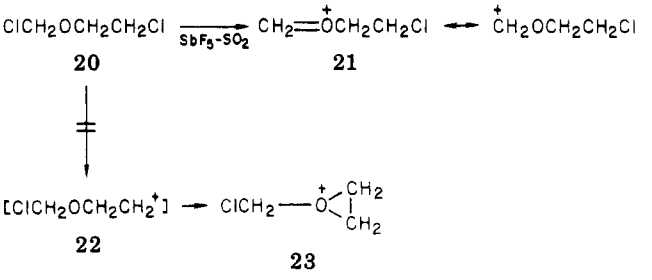
$$2CH_2O + 2HF \rightarrow \underset{\mathbf{8}}{[2FCH_2OH]} \rightarrow \underset{\mathbf{19}}{FCH_2OCH_2F} + H_2O \quad (9)$$

The self-condensation could involve the alkylation of fluoromethyl alcohol by the carboxonium ion **6**, and subsequent fluorination of the fluoromethyl hydroxymethyl ether by HF[28] (eq 10).

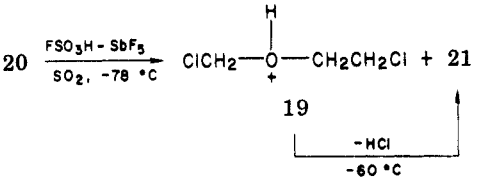
$$FCH_2OH + {}^+CH_2OH \rightarrow FCH_2OCH_2OH \xrightarrow{HF} FCH_2OCH_2F \quad (10)$$

B. (β-Haloalkyl)carboxonium Ions. Preferential ionization of the chloromethyl group adjacent to the oxygen atom in (chloromethyl)haloalkyl ethers to give the corresponding highly stabilized (haloalkyl)carboxonium ions, is observed in the present study in superacids. When a solution of chloromethyl β-chloroethyl ether (**20**) in SO_2 was slowly introduced into a well-stirred solution of SbF_5–SO_2 at −78 °C, the formation of the stable (β-chloroethyl)carboxonium ion **21**, is observed (see Scheme III). The proton NMR spectrum of ion **21** consists of three groups of proton absorptions at δ 9.97 (s, 2 H), 6.00 (t, 2 H), and 4.35 (t, 2 H) which assigned to $CH_2{=}O^+$, $=O^+{-}CH_2$, and CH_2Cl, respectively. Ionization occurs at the chloromethyl group of **20** as indicated by the proton NMR

Scheme III



Scheme IV



data, as the observed spectrum of **21** is in good accord with that of previously discussed ion **18**.[15d]

$CH_2{=}O^+CH_2CH_2Cl$
21, δ_{H^1} 9.96, δ_{H^2} 6.00, δ_{H^3} 4.35

$CH_2{=}O^+CH_2Cl$
18, δ_{H^1} 9.82, δ_{H^2} 6.76

When **20** was treated with FSO_3H–SbF_5–SO_2 under similar conditions a mixture of ions was obtained, i.e., (β-chloroethyl)carboxonium ion **21** and (chloromethyl)-(chloroethyl)oxonium ion **19**,[15d] as indicated by the proton NMR spectroscopic data. Ion **19**, which has been previously reported,[14,15] undergoes slow dehydrochlorination upon being warmed to −60 °C and yields exclusively ion **21** (Scheme IV).

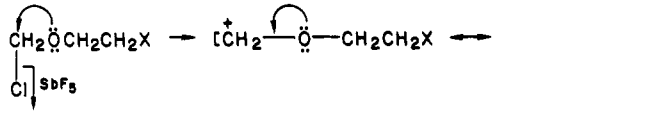
Ionization of the bromo (**24**) and iodo (**25**) analogues of **1** in SbF_5–SO_2 solution similarly yields the more stable carboxonium ions **26** and **27** (eq 11), respectively. The

$$\underset{\mathbf{24},\ X = Br}{\underset{\mathbf{25},\ X = I}{ClCH_2OCH_2CH_2X}} \xrightarrow{SbF_5\text{–}SO_2,\ -78\ °C} \underset{\mathbf{27},\ X = I}{\underset{\mathbf{26},\ X = Br}{CH_2{=}O^+CH_2CH_2X}} \quad (11)$$

(28) The zinc chloride catalyzed condensation reaction of fluoromethyl alcohol with aromatic hydrocarbons was previously observed to produce diphenylmethane derivatives. The reaction is also considered to involve hydroxymethylation of the aromatic compound followed by acid-catalyzed condensation of the benzyl alcohol.

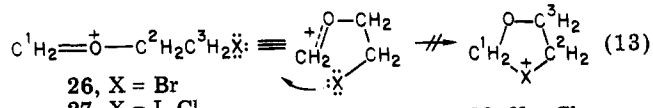
(29) G. A. Olah, Ed., "Halonium Ions", Wiley-Interscience, New York, 1975, and references therein.

proton NMR parameters and chemical shifts assignments for these ions and their corresponding precursors are summarized in Tables I and II, respectively. The preferential ionization of the chloride ion adjacent to the oxygen atom in chloromethyl haloalkyl ethers (eq 12) thus



(12)

demonstrates the ability of the oxygen heteroatom in stabilizing the neighboring carbenium ion center. Although ionization of the β carbon–halogen bond also would be possible via oxygen atom participation, forming the three-membered oxonium ion **23**, such reaction does not take place in the studied SbF_5-SO_2 system, as demonstrated by the NMR studies. It was also shown that the ionization of the chloromethyl group adjacent to the oxygen atom is preferred over that of β-bromoethyl or even β-iodoethyl groups. It is also interesting to note that halogen participation does not seem to be involved either in ions **21**, **26**, or **27**. 1,4-Halogen participation, forming five-membered-ring halonium ions, is well-known.[7] If halogen participation indeed would take place, cyclic ions **28** would be formed. However, the lack of deshielding of the methylene protons (H^3) and the fact that the H^1 methylene protons remain as singlet seems to exclude structure **28** (eq 13). The extremely deshielded H^1



(13)

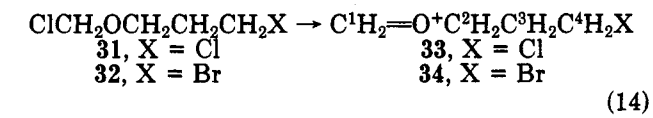
26, X = Br
27, X = I, Cl

28, X = Cl, Br, or I

methylene protons (δ_{H^1} about 10 ppm) seem to further support the linear rather than cyclic structures for the ions formed from the ionization of chloromethyl haloethyl ethers. The possibility of a cyclic structure can also be ruled out by the lack of coupling between the H^1 and H^3 methylene protons (through hetroatom couplings). It is also noticed that the H^2 methylene protons in the observed ions **21**, **26**, and **27** (Table I), are deshielded by about 2 ppm from that of their corresponding precursors. However, H^2 in structure **28** should not be so. This further eliminates cyclic halonium ions **28** as the observed ions.

The studied (β-haloethyl)carboxonium ions can also be formed by ionization of the chloromethyl haloethyl ethers in $SbCl_5$–SO_2 solution at −78 °C. When the precursor ethers were carefully added into FSO_3H–SO_2ClF–SO_2 solution at −78 °C, the corresponding protonated ethers **29** and **30** were formed (Scheme V). They subsequently slowly lose hydrogen chloride to give the (β-haloethyl)-carboxonium ions **26** or **27**.

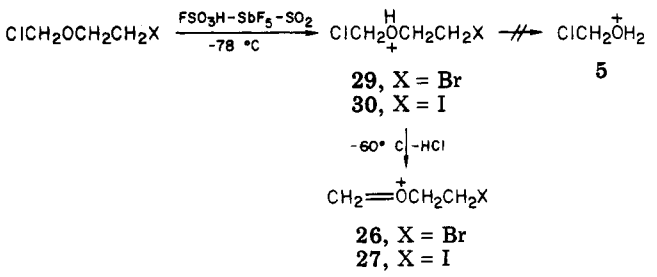
C. (γ-Halopropyl)carboxonium Ions. Chloromethyl γ-halopropyl ethers **31** and **32** were ionized in SbF_5(or $SbCl_5$)–SO_2 solution at −78 °C and gave the methylene-(γ-halopropyl)oxonium ions **33** and **34**, respectively (eq 14).



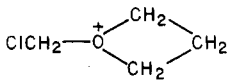
(14)

The ^1H NMR spectra of ions (Table I) show the terminal methylene singlets at about δ 5.6, close to those found in (β-haloethyl)carboxonium ions, discussed previously. Chemical shifts and assignments are summarized in Table I. The ^1H NMR spectroscopic data exclude a symmetrical

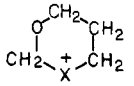
Scheme V



four-membered-ring (chloromethyl)trimethyleneoxonium ion **21** or the six-membered-ring halonium ions **36** and **37**.

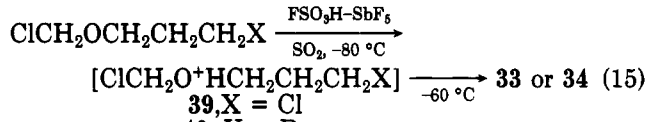


35



36, X = Cl
37, X = Br

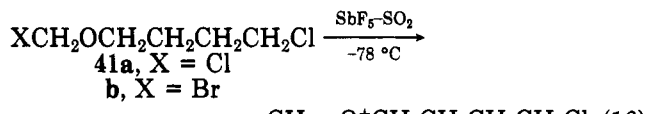
As mentioned, **33** and **34** are also the sole products observed to arise from the thermal dehydrochlorination of the corresponding protonated ethers **39** and **40**, respectively, in FSO_3H–SbF_5–SO_2 solution at ca. −60 °C (eq 15).



(15)

39, X = Cl
40, X = Br

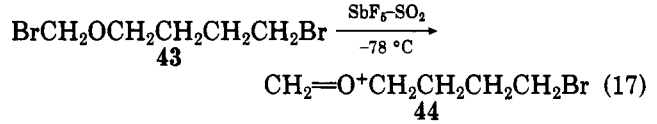
D. (δ-Halobutyl)carboxonium Ions. Both chloromethyl (**41a**) and bromomethyl (**41b**) δ-chlorobutyl ethers, when carefully added to a well-stirred solution of SbF_5 in SO_2 at −78 °C, quantitatively yielded the same (δ-chlorobutyl)carboxonium ion **42** (eq 16).



(16)

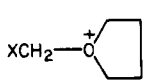
The H^1 methylene protons are a singlet at δ 10.13; the butyl group displays its absorptions at δ 6.10 (t), 4.02 (t), and 2.48 (m) in a ratio of 1:1:2. Assignments for proton shifts are given in Table I.

The (δ-bromobutyl)carboxonium ion **44** was obtained in a similar way from bromomethyl δ-bromobutyl ether **43** in SbF_5–SO_2 or $SbCl_5$–SO_2 solution at −78 °C (eq 17). No

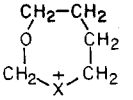


(17)

competing ionization of the δ-halogen atom to give the cyclic oxonium ions **45** and **46** nor competing ionization



45, X = Cl
46, X = Br



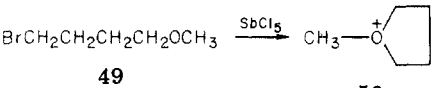
47, X = Cl
48, X = Br

of δ-halogen atom with halogen participation to give cyclic halonium ions **47** and **48** takes place. In the precursors, the central ethylenidene group (CH_2CH_2) shows a multiplet proton absorption at δ 1.85 for both **41a,b** and **43**. After ionization, they are deshielded by about 1 ppm but

remain unresolved multiplets. This agrees well with the formation of linear instead of cyclic oxonium ions. The H^1 methylenes of all the observed carboxonium ions show singlet proton NMR absorptions at about δ 10 ppm from an external Me_4Si signal (capillary), strongly indicating the contribution of the (haloalkoxy)carbenium ion forms (eq 18).

$$\underset{\textbf{42a or b}}{CH_2{=}O^+{-}(CH_2)_nX} \leftrightarrow {}^+CH_2O(CH_2)_nX \qquad (18)$$

It is interesting to mention that when **41** was treated with $SbCl_5$ in SO_2 solution, ion **45** was quantitatively formed.[30] Kirrmann and Wartski[31] also reported the formation of the similar ion **50** from **49** in $SbCl_5$–SO_2 solution via oxygen participation (eq 19). The selectivity



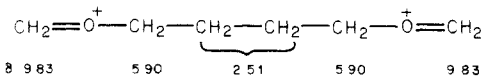
49 50 (19)

of ionization with SbF_5 and $SbCl_5$ in the same solvent (SO_2) is not yet fully understood at the present time but indicates varying degrees of oxygen participation.

IV. 1,4-Butylidenedicarboxonium Ion. The reaction of 1,4-bis[(chloromethyl)oxy]butane (**51**) with excess SbF_5 in SO_2 solution at −35 °C, resulted in ionization of both chlorine atoms, giving the dicarboxonium ion **52** (eq 20).

$$\underset{\textbf{51}}{ClCH_2OCH_2CH_2CH_2CH_2OCH_2Cl} \xrightarrow[SO_2]{SbF_5} \underset{\textbf{52}}{CH_2{=}O^+CH_2CH_2CH_2CH_2{-}O^+{=}CH_2} \qquad (20)$$

The ^1H NMR spectrum shows only three proton absorptions at δ 9.83 (s), 5.90 (br m), and 2.51 (br m) in a ratio of 1:1:1, corresponding to the assignment

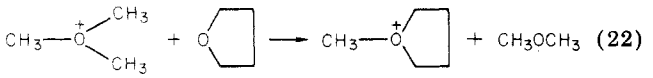


The two positive charges in **52** are well separated by the four-carbon chain, contributing to the stability of the ion.

Ion **52** can also be obtained via diprotonation of ether **51** in FSO_3H–SbF_5–SO_2 solution at −78 °C, followed by warming of the solution of 1,4-butylenedioxonium ion **53** to −35 °C, resulting in dehydrochlorination (eq 21).

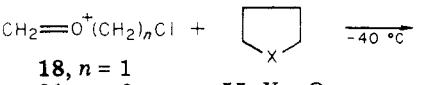
$$\textbf{51} \xrightarrow[SO_2,\ -78\ °C]{FSO_3H\text{–}SbF_5} \underset{\textbf{53}}{ClCH_2O^+HCH_2CH_2CH_2CH_2O^+HCH_2Cl} \xrightarrow[-35\ °C]{-2HCl} \textbf{52} \qquad (21)$$

V. Alkylation with (Haloalkyl)carboxonium Ions. Tertiary or secondary oxonium ions are known to also transfer their alkyl groups and act as alkylating agent toward nucleophiles. For instance, trimethyloxonium ion **54** readily alkylates cyclic ethers such as THF **55**, yielding **56**[9,10] (eq 22). The (haloalkyl)carboxonium ions studied



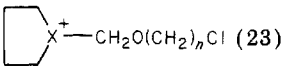
54 55 56 (22)

in the present work were found to act as (haloalkoxy)-methylating agents toward nucleophiles. The reaction between (δ-chloroalkyl)oxonium ions with tetrahydrofuran **55** and tetrahydrothiophene **57**, respectively, are illustrative (eq 23).



18, n = 1
21, n = 2
33, n = 3
43, n = 4

55, X = O
57, X = S

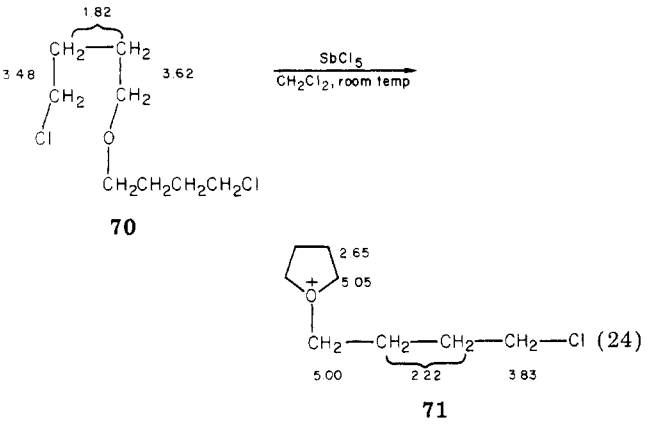


(23)

58, n = 1, X = O
59, n = 2, X = O
60, n = 3, X = O
61, n = 4, X = O
62, n = 1, X = S
63, n = 2, X = S
64, n = 3, X = S
65, n = 4, X = S

The reaction between (chloroalkyl)carboxonium ions and tetrahydrofuran (tetrahydrothiophene) was carried out by careful addition of 1 equiv of ether **55** or sulfide **57**, precooled at −60 °C, to the well-stirred solution of the carboxonium ions in SO_2 at −78 °C (dry ice–acetone bath temperature). O-Alkylations of acetone and methyl ethyl ketone were also carried out. Chemical shifts and assignments for obtained haloalkoxymethylated oxonium are given in Table V.

When the related system bis(δ-chlorobutyl) ether (**70**) was treated with $SbCl_5$ in methylene chloride solution at room temperature, it underwent cyclization via oxygen participation with the developing carbenium ion center to give (δ-chlorobutyl)tetramethyleneoxonium ion **71** (eq 24;



70 **71** (24)

δ_H values are given on the structures). In SO_2 solution at −50 °C, $SbCl_5$ was not able to induce ionization and cyclization but merely gave a stable complex with **70** whose ^1H NMR spectrum only shows slightly deshielded proton absorptions at δ_H 4.65 (t), 3.58 (t), and 1.80 (m) in a ratio of 1:1:2.

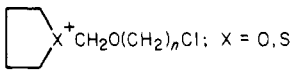
The same ion, **71**, interestingly, can also be formed by the reaction between tetrahydrofuran and the tetramethylenechloronium ion (**72**)[29] (Scheme VI). However, in THF, chemical shifts of ion **71** are slightly different from those generated in methylene chloride solution, presumably due to a bulk solvent effect. Quenching of the chloronium ion **72** with tetrahydrothiophene **57** gave S-alkylated ion **73**.

Preparational demonstration of the in vitro alkylating ability of (haloalkyl)oxonium and -carboxonium ions can be of significance, when considering possible pathways

(30) (a) G. A. Olah, D. A. Beal, S. H. Yu, and J. A. Olah, *Synthesis* 560 (1974); (b) G. A. Olah, D. W. Bernard, J. A. Olah, *J. Org. Chem.*, 41, 1627 (1967).

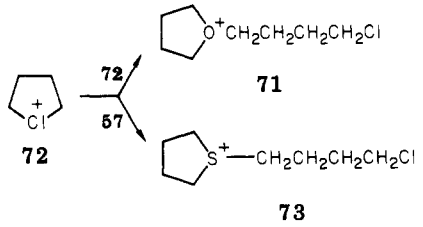
(31) A. Kirrmann and L. Wartski, *Bull. Soc. Chim.* Fr., 3825 (1956).

Table V. NMR Parameters of [(Chloroalkyoxy)methyl]tetramethylene Onium Ions in SO_2 Solution at −40 °C



n	$^+XCH_2O$	OCH_2	CH_2Cl	CH_2	CH_2CH_2	$^+XCH_2$	CH_2CH_2
				For X = O			
1	5.97 (s)	5.87 (s)				5.07 (m)	2.63 (m)
2	5.92 (s)	4.46 (t)	4.02 (t)			4.97 (m)	2.60 (m)
3	5.82 (s)	4.25 (t)	3.83 (t)	2.23 (m)		4.83 (m)	2.50 (m)
4	6.00 (s)	4.33 (t)	3.87 (t)		2.05 (m)	5.02 (m)	2.70 (m)
				For X = S			
1	5.33 (s)	5.80 (s)				3.74 (m)	2.52 (m)
2	5.37 (s)	4.23 (t)	4.00 (t)			3.73 (m)	2.60 (m)
3	5.17 (s)	4.07 (t)	3.77 (t)	2.15 (m)		3.50 (m)	2.40 (m)
4	5.33 (s)	4.10 (t)	3.65 (t)		1.98 (m)	3.82 (m)	2.57 (m)

Scheme VI



through which their neutral precursors can act as biological alkylating agents. Work is continuing with regard to alkylation of other substrates, including nucleic acid bases.

Experimental Section

Materials. All halo ethers were obtained from the corresponding alcohols according to previously described methods.[32]

Preparation of Carboxonium Ions. To SbF_5 (or $SbCl_5$) dissolved in about a twofold amount of SO_2 at dry ice/acetone temperature (ca. −78 °C) was slowly added, with vigorous stirring, a similarly cooled slurry or solution of the corresponding halo ethers in SO_2. When the temperature was raised to about −40 °C, dehydrohalogenation takes place, giving an approximately 10% solution of the corresponding carboxonium ion. The same procedure was employed in the case of obtaining the ions via protolysis with FSO_3H–SbF_5. ^1H and ^{13}C NMR spectra were obtained on Varian A56/60, XL-100, and FT-80 NMR spectrometers, respectively, equipped with multinuclei, broad-band, variable-temperature probes. Chemical shifts were referenced to an external (capillary) Me_4Si signal.

Alkylation with (Haloalkyl)carboxonium Ions. To the solution of the oxonium ions in SO_2 at dry ice/acetone temperature (ca. −78 °C) was slowly added a cooled slurry or solution of the corresponding substrate (THF or thiophene). The resulting alkylated products were analyzed by ^1H and ^{13}C NMR spectroscopy.

Preparation of Protonated Fluoromethyl Alcohol 9. Parafomaldehyde (0.1 g) was added to a rapidly stirred solution of FSO_3H–SbF_5 (1:1 mol, 10.0 g) in SO_2 (5 mL) at −78 °C. The resulting stock solution of protonated fomaldehyde 6 was used in the subsequent expeeriments.

An aliquot of the stock solution of protonated formaldehyde was transferred to an NMR tube and then cooled to −78 °C. With rapid stirring anhydrous HF, precooled to −78 °C, was added to this solution. The resulting solution of 9 was then analyzed by ^1H, ^{19}F, and ^{13}C NMR spectroscopy.

Preparation of Protonated Chloromethyl Alcohols 5. An aliquot of the stock solution of 6 was transferred to an NMR tube and cooled to −78 °C. Anhydrous HCl was slowly bubbled into this solution for 1 min. The resulting solution of 5 was then analyzed by ^1H and ^{13}C NMR spectroscopy.

Acknowledgment. Support of our work by the National Institute of Health is gratefully acknowledged.

Registry No. 5, 56003-53-3; **6**, 18682-95-6; **9**, 33010-92-3; **11**, 56003-54-4; **13**, 56003-55-5; **14**, 41879-84-9; **15**, 51624-52-3; **17**, 56003-56-6; **18** (n = 1), 71681-46-4; **20**, 1462-33-5; **21**, 75863-57-9; **24**, 1462-35-7; **26**, 75863-58-0; **27**, 75863-59-1; **31**, 3970-18-1; **32**, 54314-83-9; **33**, 75863-60-4; **34**, 75863-61-5; **41a**, 3970-17-0; **41b**, 53970-36-8; **42**, 75863-62-6; **43**, 51918-70-8; **44**, 75863-63-7; **52**, 75863-64-8; **58**, 75863-65-9; **59**, 75863-66-0; **60**, 75863-67-1; **61**, 75863-68-2; **62**, 75863-69-3; **63**, 75863-70-6; **64**, 75863-71-7; **65**, 75863-72-8; $ClCH_2O$-CH_2CH_2I, 56003-59-9; $ClCH_2O^+(H)CH_2CH_2CH_2CH_2Cl$, 56003-57-7.

(32) D. A. Beal, Ph.D. Dissertation, Case Western Reserve University, Cleveland, OH, 1973, and references given therein.

Synthesis and Configurational Assignment of Geiparvarin: A Novel Antitumor Agent

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Received July 14, 1980

This report presents the first total synthesis of geiparvarin as well as assignment of configuration of the previously undefined trisubstituted olefin. A central aspect of this synthetic adventure leading to this novel antitumor agent which possesses the 3(2*H*)-furanone ring system was the development of a viable general approach for the elaboration of 5-alkenyl-3(2*H*)-furanones. Configurational assignments were based on NMR correlations, NOE experiments, and completion of a single-crystal X-ray structure on synthetic geiparvarin.

During the past several years considerable effort in our laboratory has been directed toward the synthesis of jatrophone (**1**)[2] and the eremantholides (**2**),[3] naturally occurring antitumor agents which incorporate the 3(2*H*)-

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