

THE α -HALOALKYL ETHERS

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I. SCOPE OF THE REVIEW

This review deals with the chemistry of α -haloalkyl alkyl and aryl ethers in which the halogen on the α -carbon atom is chlorine, bromine, or iodine, and in which the ether oxygen atom is not included in a ring. α -Fluoroalkyl ethers, of which many examples are known, are not discussed here. α -Halovinyl ethers are included. The literature has been surveyed to the early part of 1954.

Tables of the known α -haloalkyl ethers of these types are included. For each compound in these tables, all literature references of which the author is aware are listed.

II. NOMENCLATURE

In this review and in the tables the compounds dealt with are named as ethers, essentially as in the *Chemical Abstracts* index names. Such nomenclature places on the ether function an emphasis which is undesirable, since the close chemical relationships of these compounds are not with the alkyl ethers (see Section III below). However, these names do make apparent immediately the nature of the two structures from which the substance was derived or to which it will hydrolyze. Since in this nomenclature the two groups are named as separate words, prime symbols (') are not employed in numbering. The group named first is always the α -haloalkyl group, and within that group the halogen attached to the α -carbon atom is always the first-named substituent. This practice serves to keep the chemical relationships obvious, but it sometimes leads to a departure from the usual order of naming substituents. In a few cases, also, the principle of "smallest numbers" is violated, in order that the same number may be used for like groups in the same positions in related compounds.

III. GENERAL CHEMICAL CHARACTERISTICS AND RELATIONSHIPS

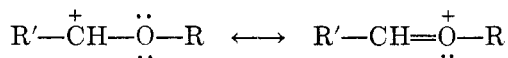
α -Haloalkyl ethers of the type R'CHXOR (where X is halogen and R and R' are organic groups) are rather highly reactive substances of limited thermal stability. The reactivity of the halogen atom in displacement reactions is considerably greater than in a simple alkyl halide, but not as great as in an acyl halide. Displacement of halogen by a wide variety of nucleophilic reagents is perhaps the most characteristic chemical property of these substances. Because of the ease of hydrolysis, these compounds cannot usually be employed in aqueous systems. Another characteristic property is thermal decomposition, which involves, as the initial step, dehydrohalogenation to a correspondingly substituted vinyl ether. This decomposition occurs at relatively low temperatures and in some cases at room temperature.

Compounds with the structure indicated above might be regarded formally as halogen-substituted alkyl ethers, as alkoxy- or aryloxyalkyl halides, as being related to hemiacetals in the way in which acyl halides are related to carboxylic acids, or as hydrogen halide adducts of vinyl ethers. Consideration of the chemical properties indicates that the compounds are best regarded as activated alkyl halides. Displacement reactions involving basic reagents proceed uniformly by

displacement of halogen. Acid-catalyzed displacements, also, usually involve the halogen atom rather than the ether linkage. For example, alcoholysis (which is acid-catalyzed) produces acetals rather than ethers; and reaction of α -haloalkyl ethers with hydrogen bromide gives α -bromoalkyl ethers. These reactions and others are discussed in Section VI, where it is shown that hydrolysis may also follow the same pattern. The outstanding apparent exception to this generalization is that α -haloalkylation gives a product in which the alkoxy group, rather than halogen, has been displaced (see Section VI,A,3,(g) for further comment on this reaction). In displacements such as these, halomethyl ethers behave similarly to other α -haloalkyl ethers.

The conclusion stated above was reached by Straus and Heinze (382), who stated in 1932 that α -haloalkyl ethers should be regarded as alkoxyalkyl halides. In a sense, this may be equivalent to considering them as halides derived from hemiacetals by replacement of OH, which consideration points out that the same products (for example, acetals) may often be obtained from an α -haloalkyl ether as from the corresponding aldehyde. However, the analogy with acyl halides which is suggested by this point of view is not valid. For example, the hydrolysis of α -haloalkyl ethers is acid-catalyzed, and alcoholysis also differs kinetically from alcoholysis of acyl chlorides (40).

Cocker, Lapworth, and Walton (69) attributed the reactivity of the halogen atom in displacement to the possibility of resonance involving an oxonium form.



This concept has been employed by others (274) in recent investigations.

The relationship of the α -haloalkyl ethers to vinyl ethers has been emphasized by Shostakovskii (337, 338, 339) in his researches on these compounds. This relationship is of importance in such reactions as thermal decomposition or halogenation (see Sections VI,C and VI,D). In these reactions halomethyl ethers behave differently from α -haloalkyl ethers having hydrogen on the β -carbon atom. In such reactions as hydrolysis, alcoholysis, and displacements by basic reagents, however, the halomethyl ethers react in the same fashion as other α -haloalkyl ethers. It is difficult to see how the relationship with vinyl ethers can apply to halomethyl ethers. Thus these numerous displacement reactions of α -haloalkyl ethers apparently do not depend on such a relationship.

IV. PREPARATION

A. GENERAL DISCUSSION

For the preparation of α -chloroalkyl alkyl ethers, the procedures which are of practical value are the reaction of an acetal or hemiacetal with an inorganic acid chloride, the reaction of an aldehyde-alcohol mixture with hydrogen chloride, the addition of hydrogen chloride to a vinyl alkyl ether, or the chlorination of a dialkyl ether. The first-named procedure is rather generally useful, and has produced types of α -chloroalkyl ethers which have not been made otherwise (see Section IV,B,3). In many cases the second procedure is equally good, and it has

TABLE 1
Chloromethyl alkyl ethers hydrolyzable to formaldehyde and a primary alcohol

Ether	Boiling Point	n_D^{20}	References
	°C.		
Chloromethyl methyl.....	59.1/766 mm.	1.39737	(3, 9, 10, 13, 14, 24, 30, 32, 40, 41, 43, 44, 46, 47, 54, 68, 69, 70, 72, 74, 80, 81, 82, 87, 89, 94, 95, 96, 101, 102, 106, 117, 118, 136, 146, 150, 157, 163, 174, 175, 177, 183, 192, 196, 198, 205, 207, 210, 214, 222, 223, 224, 226, 228, 229, 241, 242, 243, 245, 246, 248, 249, 251, 257, 258, 259, 271, 274, 276, 280, 303, 305, 312, 313, 315, 316, 318, 319, 331, 356, 357, 358, 359, 369, 370, 371, 374, 378, 379, 382, 383, 392, 393, 394, 406, 407, 410, 415, 416)
Chloromethyl ethyl.....	84	1.4040 (18°C.)	(10, 14, 20, 40, 94, 97, 105, 115, 117, 135, 136, 137, 163, 174, 182, 185, 206, 222, 229, 244, 246, 251, 257, 260, 265, 274, 303, 305, 366, 369, 370, 393, 408, 415, 416)
Chloromethyl 2-fluoroethyl.....	42-43/60 mm.	1.4120	(213)
Chloromethyl 2-chloroethyl.....	145-147	1.4578	(94, 97, 160, 240, 244, 326, 393)
Chloromethyl 2-[<i>p</i> -(α , α -dimethylpropyl)-phenoxy]ethyl.....	150-155/2.5 mm.		(77)
Chloromethyl propyl.....	109	1.4106	(14, 94, 101, 117, 136, 165, 205, 229, 260, 305, 369, 370, 415)
Chloromethyl 3-chloropropyl.....	60/8 mm.	1.45614	(160, 326)
Chloromethyl 3-dichloroarsinopropyl.....	136-137/5 mm.		(18)
Chloromethyl butyl.....	134	1.4208	(3, 94, 136, 168, 185, 192, 220, 260, 305, 344, 345, 393, 416, 423)
Chloromethyl 4-chlorobutyl.....	68-76/2.5 mm.		(413)
Chloromethyl 2-nitrobutyl.....	95 d./1 mm.	1.4510	(172, 173)
Chloromethyl 2-methylpropyl.....	120-121	1.410 (temperature not given)	(36, 101, 117, 168, 185, 305, 367, 376)
Chloromethyl 2-methyl-2-nitropropyl.....	85/4 mm.	1.4498	(172, 173)
Chloromethyl pentyl.....			(94, 294)
Chloromethyl 2-methyl-2-nitrobutyl.....	98/3 mm.	1.4548	(172, 173)
Chloromethyl 3-methylbutyl.....	55.6/24 mm.	1.4223	(94, 101, 117, 369, 414)
Chloromethyl octyl.....	217-218		(12, 220, 412)
Chloromethyl 2-ethylhexyl.....			(94, 393)
Chloromethyl decyl.....	124-125/10 mm.		(220)
Chloromethyl dodecyl.....	162-163/18 mm.		(79, 220, 393)
Chloromethyl tetradecyl.....	171-172/5 mm.		(220)
Chloromethyl hexadecyl.....	158/1-2 mm.		(60, 220, 258, 364, 393)
	29-30 (m. p.)		
Chloromethyl octadecyl.....	27 (m. p.)		(79, 364, 401)
Chloromethyl docosyl.....	197-211/2.5 mm.		(220)
Chloromethyl benzyl.....	102/14.5 mm.	1.5270 (17°C.)	(4, 57, 168, 185, 325)
Chloromethyl <i>m</i> -nitrobenzyl.....	147.5-148.5/0.6 mm.		(221)
Chloromethyl <i>m</i> -(phenylazo)benzyl.....	181-184/1.6-1.8 mm.		(221)
	34.5-36 (m. p.)		
Chloromethyl 2-phenylethyl.....	119-121.5/16 mm.	1.5227	(325)
Chloromethyl 3-phenylpropyl.....	130.5/13 mm.	1.5190 (18.5°C.)	(325)
Chloromethyl 2-methyl-3-(<i>p</i> -isopropyl-phenyl)propyl.....	160-161/13 mm.	1.5070 (15.6°C.)	(291)
Chloromethyl allyl.....	108	1.4340	(24, 134, 185)
Bis(chloromethyl) ethylene.....	97-99/13 mm.		(411)
Bis(chloromethyl) tetramethylene.....			(91)
Bis(chloromethyl) hexamethylene.....			(209)

TABLE 2

Bromomethyl and iodomethyl alkyl ethers hydrolyzable to formaldehyde and a primary alcohol

Ether	Boiling Point	n_D^{20}	References
	°C.		
Bromomethyl methyl	86-87		(3, 5, 70, 146, 155, 156, 157, 171, 205, 257, 315, 407)
Bromomethyl ethyl	109.2/745.7 mm.		(3, 5, 14, 205, 206)
Bromomethyl propyl	133.3/747.5 mm.	1.4515	(3, 5, 14, 33, 205, 206)
Bromomethyl butyl	159/749.5 mm.	1.4514	(33)
Bromomethyl 2-methylpropyl	52-53/30 mm.	1.4400 (25°C.)	(250)
Bromomethyl pentyl	178-180 d./748.3 mm.	1.4512	(33)
Bromomethyl 2-methylbutyl	67-68/16 mm.	1.4671 (25°C.)	(250)
Bromomethyl 3-methylbutyl	128-129/247 mm.	1.4489 (25°C.)	(250)
Bromomethyl benzyl			(4)
Bromomethyl allyl	45/21 mm.	1.4752	(134)
Iodomethyl methyl	123-125		(157, 205, 223, 251, 257)
Iodomethyl ethyl	31/11 mm.		(205, 251)
Iodomethyl propyl	39/5 mm.		(205, 251)

TABLE 3

Halomethyl alkyl ethers hydrolyzable to formaldehyde and a secondary alcohol

Ether	Boiling Point	n_D^{20}	References
	°C.		
Chloromethyl 1-methylethyl	101/758 mm.	1.4095	(97, 165, 185, 229, 242, 274, 377)
Chloromethyl 2-chloro-1-methylethyl	160-161/747 mm.	1.4528	(375, 377)
Chloromethyl 2-chloro-1-(chloromethyl)-ethyl	95-96/17 mm.		(37)
Chloromethyl 1-methylpropyl	121-123	1.4205 (16°C.)	(97)
Chloromethyl cyclohexyl	183-185	1.4713 (9°C.)	(94, 97)
Chloromethyl 4-chlorocyclohexyl	117.5/15 mm.	1.4942	(324)
Chloromethyl 4-propylcyclohexyl	105-110/11 mm.	1.4687 (16.5°C.)	(116)
Chloromethyl 3-(2', 2', 6'-trimethylcyclohexyl)-1-methylpropyl	150-151/15 mm.	1.4703 (24°C.)	(203, 204)
Bromomethyl 1-methylethyl	75-76/196 mm.	1.4251	(250)
Bromomethyl 1-methylpropyl	106-108/357 mm.	1.4453 (25°C.)	(250)
Bromomethyl 1-methylhexyl	68-69/4 mm.	1.4537 (25°C.)	(250)
Bromomethyl 1-methylheptyl	71-72/3 mm.	1.4562 (25°C.)	(250)
Iodomethyl 1-methylethyl			(251)

TABLE 4

Dihalomethyl alkyl ethers hydrolyzable to formic acid and a primary alcohol

Ether	Boiling Point	Reference
	°C.	
Dichloromethyl methyl	82-84	(327)
Dichloromethyl ethyl		(103)

been the method most commonly used. The organic starting material for these preparations is an aldehyde, of which a large number are available. The preparation from vinyl ethers is of limited utility because variously substituted vinyl ethers are not commercially available. Chlorination of dialkyl ethers can produce

TABLE 5

α-Chloroalkyl alkyl ethers hydrolyzable to an aldehyde (other than formaldehyde) and a primary alcohol

Ether	Boiling Point °C.	n_D^{20}	References
1-Chloroethyl methyl	72-73/751 mm.	1.4004	(17, 129, 164, 166, 223, 257, 296, 302, 317, 334, 390)
1-Chloroethyl ethyl	97.5/750 mm.	1.3950	(42, 89, 90, 93, 94, 107, 124, 128, 133, 145, 166, 179, 184, 195, 215, 217, 223, 228, 260, 268, 269, 300, 302, 317, 334, 341, 391, 414, 421, 422)
1-Chloroethyl 2-chloroethyl	51/10 mm.	1.4473	(73, 141, 201, 240, 385)
1-Chloroethyl 2-bromoethyl			(67)
1-Chloroethyl propyl	47.5/40 mm.	1.4013	(90, 117, 166)
1-Chloroethyl butyl	48.9-50.3/11 mm.	1.4155	(89, 90, 94, 166, 184, 260, 339, 340, 341, 404)
1-Chloroethyl 2-methylpropyl	132-138		(94, 117)
1-Chloroethyl pentyl	63.3-66.3/8 mm.	1.4218	(166)
1-Chloroethyl 3-methylbutyl	162-165		(117)
1-Chloroethyl dodecyl	148-153/15 mm.		(79)
1-Chloroethyl allyl	112/770 mm.	1.4260	(134)
Bis(1-chloroethyl) ethylene	92-94/15 mm.	1.4498	(179)
Bis(1-chloroethyl) ether of diethylene glycol	d.		(179)
1,2-Dichloroethyl methyl	24.5-24.7/11 mm.	1.4480	(275, 315, 346, 352, 353)
1,2-Dichloroethyl ethyl	42.3-43.5/12 mm.	1.4435	(1, 26, 27, 28, 39, 112, 128, 131, 145, 147, 149, 195, 197, 202, 230, 231, 236, 237, 238, 268, 269, 301, 351, 353, 388, 390, 391, 399, 400, 402, 419, 420, 422)
1,2-Dichloroethyl butyl	50/6 mm.	1.4473	(299, 340, 349, 351, 353)
1,2-Dichloroethyl 2-methylpropyl	85/43 mm.	1.642 (21°C.)	(197)
1,2-Dichloroethyl 3-methylbutyl	81/16 mm.	1.4450	(299, 349, 351)
1-Chloro-2-bromoethyl methyl			(See 391)
1-Chloro-2-bromoethyl ethyl			(See 391)
1-Chloro-2-bromoethyl allyl			(180)
1,2,2-Trichloroethyl methyl	50.5/9 mm.	1.4722	(353)
1,2,2-Trichloroethyl ethyl	174	1.4680	(131, 195, 277, 286, 289, 290, 353)
1,2,2,2-Tetrachloroethyl methyl	72-75/22 mm.	1.4820 (25°C.)	(154, 254, 263)
1,2,2,2-Tetrachloroethyl ethyl	188/740 mm.	1.4735 (25°C.)	(52, 122, 131, 152, 153, 154, 254, 263, 277, 278, 279)
1,2,2,2-Tetrachloroethyl 2-chloroethyl			(120, 121)
1,2,2,2-Tetrachloroethyl 2-(<i>o</i> -chlorophenoxy)ethyl			(121)
1,2,2,2-Tetrachloroethyl benzyl			(120, 121)
Bis(1,2,2,2-tetrachloroethyl) ethylene			(121)
1-Chloro-2,2,2-tribromoethyl ethyl	120-121.5/14 mm.		(277)
1-Chloropropyl methyl	78-80/550 mm.		(133, 156, 164, 317)
1-Chloropropyl ethyl	34-36/25 mm.	1.4120	(334, 335)
1-Chloropropyl 2-chloroethyl	60/10 mm.	1.4496	(240)
1-Chloropropyl propyl			(411)
1,2-Dichloropropyl propyl			(49, 285, 286, 288, 289; see 267)
1,2-Dichloropropyl 2-chloropropyl	115-120/5-10 mm.		(286, 288, 289)
1,3-Dichloropropyl methyl	45/12 mm.	1.44777	(85, 86, 133, 208, 296, 409)
1,3-Dichloropropyl ethyl	56/12 mm.	1.44235	(85, 86, 296)
1,3-Dichloropropyl propyl	65/12 mm.	1.44576	(85, 86)
1,3-Dichloropropyl 2-methylpropyl	89/21 mm.	1.44305	(85, 86)
1,3-Dichloropropyl 3-methylbutyl	103/20 mm.		(85, 86)
1,3-Dichloropropyl allyl	79/20 mm.	1.4649	(134)
1,2,2-Trichloropropyl propyl	74.2-74.4/10 mm.	1.4575	(267)
1,3,3,3-Tetrachloropropyl ethyl	79-80/11 mm.	1.4695 (25°C.)	(130)
1,3,3,3-Tetrachloropropyl butyl	51-52/0.23 mm.	1.4706	(130, 232)

TABLE 5—*Concluded*

Ether	Boiling Point	n_D^{20}	References
	°C.		
1-Chlorobutyl methyl	29/12 mm.		(257, 384)
1-Chlorobutyl ethyl	49-51/25 mm.	1.4168	(274, 334, 335, 384)
1-Chlorobutyl 2-chloroethyl	71/10 mm.	1.4471	(240)
1,2,2,3-Tetrachlorobutyl ethyl	84-86/4 mm.	1.4899	(148, 149)
1,2,2,3-Tetrachlorobutyl 2-chloroethyl	80-108/2.5 mm.	1.5050	(148, 149)
1,2,2,3-Tetrachlorobutyl 2-methylpropyl	85-92/2.2 mm.	1.4782	(148, 149)
1,2,2,3-Tetrachlorobutyl benzyl	145-150/3 mm.	1.5426	(148)
1,2,2,3-Tetrachlorobutyl allyl	78-81/2.5 mm.	1.4958	(148, 149)
1-Chloro-2-methylpropyl ethyl	43/24 mm.	1.4130	(117, 329)
1,2-Dichloro-2-methylpropyl ethyl	192.5		(49, 162)
1-Chloro-3-methylbutyl ethyl	54-55/20 mm.		(252, 334)
1-Chloro-2-bromo-3-methylbutyl ethyl	94-96/15 mm.		(See 391)
α -Chlorobenzyl methyl	71-72/0.1 mm. -24 (m. p.)		(39, 382, 383, 384)
α -Chlorobenzyl ethyl	52-54/0.05 mm.		(178, 384)
α , <i>p</i> -Dichlorobenzyl methyl	80-82/0.15 mm.		(384)
α -Chloro- <i>p</i> -nitrobenzyl methyl	109/2 mm.		(384)
1-Chloro-2-phenylethyl ethyl			(181)
1,3,3-Trichloroallyl butyl	97-98/11 mm.	1.475 (17.5°C.)	(232)
1-Chloro-3-phenylallyl methyl			(382)

only certain types of substituted ethers (see Sections IV,B,1 and VI,D). For such types (for instance, for 1,2-dichloroethyl ethyl ether or bis(1-chloroethyl) ether) this may be a convenient preparation if the dialkyl ether is available.

For α -bromoalkyl ethers, analogous preparations may be used. Also, such ethers may be obtained in good yield by reaction of hydrogen bromide with the α -chloroalkyl ether. Similarly, α -iodoalkyl ethers result from reaction of the α -chloroalkyl ether with sodium or potassium iodide. 1,2-Dibromoalkyl ethers are usually prepared by the reaction of bromine with an α -monochloroalkyl ether (see Section VI,D).

For halomethyl aryl ethers, the only general preparation is the reaction of aryloxymethanesulfonates with an inorganic acid halide (see Section IV,B,4). Other types of α -haloalkyl aryl ethers may be obtained by reaction of an inorganic acid halide with an acetal, or by addition of hydrogen halide to the vinyl aryl ether.

Bis(α -haloalkyl) ethers are prepared by methods analogous to those used for α -haloalkyl alkyl ethers.

B. METHODS OF PREPARATION

1. Halogenation of alkyl ethers

The products obtained by the chlorination of diethyl ether were the first known examples of α -haloalkyl ethers. The reaction was first studied by Malaguti (255) and by Regnault (314); d'Arcet (15) had previously isolated one of the products. Lieben (238) and Jacobsen (195) summarized the early researches. Chlorination occurs first on an α -carbon atom (107), so that the substance being halogenated in succeeding steps is an α -chloroalkyl ether. (Therefore the chlorination reaction

TABLE 6

α-Bromoalkyl alkyl ethers hydrolyzable to an aldehyde (other than formaldehyde) and a primary alcohol

Ether	Boiling Point	n_D^{20}	References
	°C.		
1-Bromoethyl methyl	56.5-57.0/153 mm.	1.4486	(340, 342, 347)
1-Bromoethyl ethyl	40-41/42 mm.	1.4465	(306, 342, 347)
1-Bromoethyl butyl	63.0-63.8/21 mm.	1.4483	(339, 341, 342, 347)
1-Bromoethyl allyl	50/22 mm.	1.4719	(134)
1,2-Dibromoethyl methyl	56-58/20 mm.	1.5130	(17, 100, 296, 307, 308, 315, 322, 334, 340)
1,2-Dibromoethyl ethyl	62-65/12 mm.	1.5044	(90, 93, 98, 100, 133, 143, 169, 225, 300, 308, 332, 334, 391, 420)
1,2-Dibromoethyl 2-chloroethyl	108/12 mm.		(73, 385)
1,2-Dibromoethyl propyl	86-87/16 mm.	1.4975	(90, 98, 308)
1,2-Dibromoethyl 2,3-dibromopropyl	137/4 mm.	1.5662	(134)
1,2-Dibromoethyl butyl	103-104/16 mm.	1.4967	(90, 98, 281, 338)
1,2-Dibromoethyl 2-methylpropyl	86-86.3/0.8 mm.	1.5490	(337, 338)
1,2-Dibromoethyl 3-methylbutyl	91/3 mm.	1.4922	(338)
Tris(1,2-dibromoethyl) glyceryl			(100)
1,2-Dibromo-2-chloroethyl ethyl			(131)
1,2,2,2-Tetrabromoethyl methyl	Boils above 180, violent decomposition		(315)
1,2,2,2-Tetrabromoethyl ethyl	130-140 d./16 mm.		(277)
1,2-Dibromo-2,2-dichloroethyl ethyl	106.5-107/16 mm.		(277)
1,2-Dibromo-2-(<i>p</i> -nitrophenylthio)ethyl ethyl	d. 52-56		(191)
1,2-Dibromopropyl methyl	66-67/13 mm.		(133, 225, 372)
1,2-Dibromopropyl ethyl	79-82/30 mm.	1.5000	(334, 335)
1,3-Dibromopropyl methyl	75/15 mm.	1.463	(133, 208, 296)
1,3-Dibromopropyl allyl	97/19 mm.	1.5129	(134)
1,2-Dibromo-2-chloropropyl propyl	140-142		(288)
1,2-Dibromo-3-chloropropyl methyl	104/19 mm.	1.5338	(133, 296, 309)
1,2-Dibromobutyl methyl			(225)
1,2-Dibromobutyl ethyl	79-81/12 mm.	1.4700	(169, 332, 334, 335, 418)
1,2-Dibromo-2-methylpropyl ethyl	73-75/8 mm.	1.4730	(53, 169, 329, 332)
1,2,3,4-Tetrabromobutyl ethyl	> 30 (m. p.)		(104)
1,2-Dibromopentyl methyl			(332)
1,2-Dibromopentyl ethyl	90/12 mm.		(332)
1,2-Dibromo-3-methylbutyl ethyl	92-93/10 mm.	1.5012	(332, 334)
1,2-Dibromoheptyl ethyl	114-116/18 mm.	1.4790	(169, 332)
1,2-Dibromo-9-chlorononyl methyl			(283)
α -Bromobenzyl methyl			(384)
α -Bromo- <i>p</i> -nitrobenzyl methyl	59-60 (m. p.)		(384)
1,2-Dibromo-2-phenylethyl ethyl	Solid		(181)

is discussed in Section VI,D.) Direct chlorination is useful for the preparation of only certain types of α -chloroalkyl ethers. After the initial reaction, the succeeding steps involve the β -carbon atom. For example, 1-chloroethyl ethyl and particularly 1,2-dichloroethyl ethyl ethers (419) can be prepared conveniently in this way. The photochlorination of dipropyl ether proceeds similarly (285, 287; see 267). 1,2-Dibromoalkyl ethers are readily obtained from an α -chloroalkyl ether and bromine (391). They are not obtained by the bromination of dialkyl ethers, which gives acetals (219).

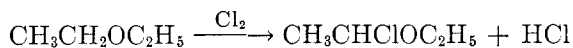


TABLE 7

 α -Haloalkyl alkyl ethers hydrolyzable to an aldehyde (other than formaldehyde) and a secondary alcohol

Ether	Boiling Point	n_D^{20}	References
	°C.		
1-Chloroethyl 1-methylpropyl.....	38-39/20 mm., d. slightly	1.4149	(373)
1-Chloroethyl 2-chloro-1-(chloromethyl)- propyl.....	89-90/18 mm.	1.4711	(11)
1,2-Dichloroethyl 1-methylethyl.....	34-34.5/9 mm.	1.4430	(351, 353)
1,2,2-Trichloroethyl 1-methylethyl.....	63-64/11 mm.	1.4640	(353)
1,2,2,2-Tetrachloroethyl cyclohexyl.....			(120, 121)
1,2,2,3-Tetrachlorobutyl cyclohexyl.....	118-121/2.2 mm.	1.5061	(148, 149)
1,2-Dibromoethyl 1-methylethyl.....	78-80/16 mm.	1.4990	(98, 337)
1,2,2-Tribromoethyl 1-methylethyl.....	118/14 mm.	1.5332	(98)

TABLE 8

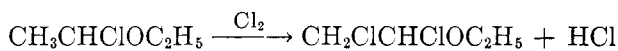
 α -Haloalkyl alkyl ethers hydrolyzable to a ketone and an alcohol

Ether	Boiling Point	n_D^{20}	References
	°C.		
1-Chloro-1-methylethyl methyl.....	14-15/88 mm.		(384)
1-Chloro-1-methylpropyl methyl.....			(59)
1-Chloro-1-methylpropyl ethyl.....			(59)
1-Chloro-1-(acetylmethyl)propyl methyl.....	43/3 mm.	1.441	(296)
Chlorodiphenylmethyl methyl.....			(382, 384)
1-Chloro-1,3-bis(p-chlorophenyl)allyl methyl.....	Liquid		(381)
1-Bromo-1-(bromomethyl)propyl methyl.....	65/81 mm.	1.5144	(296)

TABLE 9

 α,α -Dihaloalkyl alkyl ethers hydrolyzable to a carboxylic acid and a primary alcohol

Ether	Melting Point	n_D	References
	°C.		
Pentachloroethyl ethyl.....	190-210 (b. p.)		(52, 131, 195)
1,2-Dichloro-1,2,2-tribromoethyl ethyl.....	28-29	1.56833 (34°C.)	(360)
1,2-Dibromo-1,2,2-trichloroethyl ethyl.....	17		(52)



The low-temperature procedure of Hall and Ubertini (145) is perhaps the best method for the preparation of bis(1-chloroethyl) ether. This method did not give α -chloroisopropyl ethers (144).

Dimethyl ether was chlorinated photochemically by Friedel (106) to chloromethyl methyl ether. If, as in this case, there is no β -carbon atom, halogenation affects next the α -position in the other group (243, 244, 314, 371). Continued chlorination produces bis(chloromethyl) ether (314), chloromethyl dichloro-

TABLE 10
Halomethyl aryl ethers hydrolyzable to formaldehyde and a phenolic compound

Ether	Boiling Point	Melting Point	References
	°C.	°C.	
Chloromethyl phenyl.....	88-90/15 mm.	-3 to -4	(21, 388, 389, 417)
Chloromethyl 2-chlorophenyl.....	101-103/18 mm.	1-2	(19, 20, 21)
Chloromethyl 3-chlorophenyl.....	112-113/18 mm.	10	(21)
Chloromethyl 4-chlorophenyl.....	120-124/18 mm.	29-30	(19, 20, 21)
Chloromethyl 4-bromophenyl.....		54-56	(21)
Chloromethyl 2,4-dichlorophenyl.....	137-138/18 mm.	55-56	(19, 20, 21)
Chloromethyl 2,5-dichlorophenyl.....	128-129/18 mm.	52.5-54.5	(20, 21)
Chloromethyl 2,6-dichlorophenyl.....	131-132/20 mm.	6-7	(21)
Chloromethyl 3,4-dichlorophenyl.....	141-142/20 mm.	33-34	(21)
Chloromethyl 3,5-dichlorophenyl.....		38.5-40.5	(21)
Chloromethyl 2,3,4-trichlorophenyl.....		61-62	(21)
Chloromethyl 2,4,5-trichlorophenyl.....	103-105/0.5 mm.	83-84	(19, 21)
Chloromethyl 2,4,6-trichlorophenyl.....	80-90/0.1 mm.	34-35	(19, 20, 21)
Chloromethyl pentachlorophenyl.....		93-94 (21)	(20, 21, 297)
		211-213 (297)	
Chloromethyl 2-nitrophenyl.....		About 0	(21)
Chloromethyl 4-chloro-2-nitrophenyl.....		45-47	(21)
Chloromethyl 5-chloro-2-nitrophenyl.....		74-80	(21)
Chloromethyl 4-chloro-3-nitrophenyl.....		42-44	(21)
Chloromethyl 4-nitrophenyl.....		36-37	(20, 21)
Chloromethyl 3-chloro-4,6-dinitrophenyl.....		82-84	(21)
Chloromethyl 2-methoxyphenyl.....	135-136/18 mm.		(20, 21)
Chloromethyl 4-chloro-2-methoxyphenyl.....		60.5-62.0	(21)
Chloromethyl 4-chloro-3-methoxyphenyl.....	141-150/18 mm.	27-28	(21)
Chloromethyl 4-methoxyphenyl.....	140-141/18 mm.		(19, 20, 21)
Chloromethyl 4-cyanophenyl.....	90/0.05 mm.	36-37	(19, 21)
Chloromethyl 3-carboxy-4-chlorophenyl.....		150-160	(21)
Chloromethyl 3-chlorocarbonyl-4-chlorophenyl.....	106-108/0.3 mm.		(21)
Chloromethyl 4-carboxyphenyl.....		150-151	(21)
Chloromethyl 4-(chlorocarbonyl)phenyl.....	100-102/0.1 mm.	32-34	(21)
Chloromethyl 4-carbethoxyphenyl.....	106-107/0.1 mm.		(21)
Chloromethyl 3,5-dicarboxy-4-chlorophenyl.....		168-169	(21)
Chloromethyl 3,5-bis(chlorocarbonyl)-4-chlorophenyl.....	121-122/0.3 mm.		(21)
Chloromethyl 4-chloro-2-methylphenyl.....		29-30	(20, 21)
Chloromethyl 4,6-dichloro-2-methylphenyl.....		27-28	(21)
Chloromethyl 4-chloro-2-(chloromethyl)phenyl.....			(21)
Chloromethyl 4-chloro-3-methylphenyl.....	128-132/18 mm.	18.5	(20, 21)
Chloromethyl 4-chloro-3-(chloromethyl)phenyl.....			(20)
Chloromethyl 4-methylphenyl.....	106-108/20 mm.	-16 to -15	(19, 20, 21)
Chloromethyl 2-chloro-4-methylphenyl.....		52.0-53.5	(21)
Chloromethyl 3-chloro-4-methylphenyl.....	121-122/22 mm.	3-4	(21)
Chloromethyl 4-chloro-3,5-dimethylphenyl.....		70.5-72.0	(20, 21)
Chloromethyl 4- <i>tert</i> -octylphenyl.....	106-110/0.4 mm.		(21)
Chloromethyl 1-naphthyl.....	164-165/18 mm.	37-38	(21)
Chloromethyl 2-naphthyl.....	90-110/0.15 mm.	39-41	(21)
Chloromethyl 1-chloro-2-naphthyl.....		74-75	(20, 21)
Bis(chloromethyl) <i>p</i> -phenylene.....		91.5-94.5	(19, 21)
Bis(chloromethyl) 4,6-dichloro-1,3-phenylene.....		95-98	(298)
Bromomethyl 2,4-dichlorophenyl.....		52-53	(19)
Iodomethyl 2,4-dichlorophenyl.....		59-62	(21)

methyl ether (371; see 44), dichloromethyl trichloromethyl ether (311), and bis(trichloromethyl) ether (314, 371).

Starting materials for chlorination may be acetals, alcohols, or alcohol-aldehyde mixtures, instead of the dialkyl ether. Dimethoxymethane gave various chloromethyl ethers (161), and 1,1-dimethoxyethane gave small amounts of

TABLE 11

 α -Haloalkyl aryl ethers hydrolyzable to an aldehyde (other than formaldehyde) and a phenolic compound

Ether	Boiling Point	n_D^{20}	References
	°C.		
1-Chloroethyl phenyl.....	97-98/24 mm.	1.5225	(184, 343, 348)
1,2,2,2-Tetrachloroethyl 4-chlorophenyl.....	169-171/16 mm.		(62, 405)
1,2,2,2-Tetrachloroethyl 2,4-dichlorophenyl.....	185-188/13 mm.		(62, 405)
1,2,2,2-Tetrachloroethyl 3,4-dichlorophenyl.....	180-183/12 mm.		(62, 405)
1,2,2,2-Tetrachloroethyl 2,4,5-trichlorophenyl.....	140-143/0.08 mm.		(62, 405)
1-Bromoethyl phenyl.....	87-89/7 mm.	1.5500	(340, 343, 347)
1,2-Dibromoethyl phenyl.....	140-145/18 mm.	1.5845	(264)
1,2-Dibromo-2-phenylethyl phenyl.....	91 (m. p.)		(380)

TABLE 12

 α,α -Dihaloalkyl aryl ethers hydrolyzable to a carboxylic acid and a phenolic compound

Ether	Boiling Point	n_D^{20}	References
	°C.		
Dichloromethyl phenyl.....	68.6-76/0.6 mm.		(20, 417)
Dichloromethyl 4-chlorophenyl.....			(20)
Dichloromethyl 2,4-dichlorophenyl.....			(20)
Dichloromethyl 2,4,6-trichlorophenyl.....			(20)
Dichloromethyl 4-chloro-2-methylphenyl.....			(20)
Dichloromethyl 4-chloro-3-methylphenyl.....			(20)
α,α -Dichlorobenzyl 4-chlorophenyl.....		1.5269 (25°C.)	(61)
α,α -Dichlorobenzyl 2,4-dichlorophenyl.....		1.5300 (25°C.)	(61)
1,1,2-Tribromoethyl phenyl (?).....	173-175/5 mm.	1.6012	(264)
Related compounds			
Chloromethylene ethyl 2,4-dichlorophenyl.....			(20)
Chloromethylene bis(2,4-dichlorophenyl).....			(20)

TABLE 13

Trihalomethyl aryl ethers hydrolyzable to a diaryl carbonate

Ether	References
Trichloromethyl 4-chlorophenyl.....	(20)
Trichloromethyl 2,4-dichlorophenyl.....	(20)
Trichloromethyl 2,4,6-trichlorophenyl.....	(20)
Trichloromethyl pentachlorophenyl.....	(20)
Trichloromethyl 4-chloro-2-methylphenyl.....	(20)
Trichloromethyl 4-chloro-2-(chloromethyl)phenyl.....	(20)
Trichloromethyl 4-chloro-3-methylphenyl.....	(20)
Trichloromethyl 2,4-bis(trifluoromethyl)phenyl.....	(262)

1,2-dichloroethyl methyl ether (315). Chlorination of methanol gave bis(chloromethyl) ether, among other products (49). 1-Propanol gave 1,2,2-trichloropropyl propyl ether (267), and 2-methyl-1-propanol produced 1,2-dichloro-2-methylpropyl 2-methylpropyl ether (49). A mixture of ethanol and acetaldehyde gave 1,2-dichloroethyl ethyl ether (16).

TABLE 14
α-Halovinyl alkyl or aryl ethers hydrolyzable to a carboxylate ester

Ether	Boiling Point °C.	n_D^{20}	References
1-Chlorovinyl ethyl.....	88-90	1.4208	(99, 123)
1-Chlorovinyl propyl.....	112-114	1.4230	(99)
1,2-Dichlorovinyl ethyl.....	122-126		(22, 75, 76, 125, 187, 188, 189, 190, 360)
1,2-Dichlorovinyl 4-chlorophenyl.....	124-126/13 mm.		(65)
Trichlorovinyl methyl.....			(154)
Trichlorovinyl ethyl.....	154.8/755 mm.	1.47551 (16°C.)	(52, 125, 127, 131, 293, 360)
1,2-Dichloro-2-bromovinyl ethyl.....	177/754 mm.	1.50427 (17.5°C.)	(360)
1-Chloro-2,2-diphenylvinyl phenyl.....	114-115 (m. p.)		(330)
1-Chloro-2,2-diphenylvinyl 2,4,6-trichloro-phenyl.....	91 (m. p.)		(330)
1-Bromovinyl phenyl (?).....	120-121/13 mm.	1.5700	(264)
1,2-Dibromovinyl phenyl.....	81.5-82/2 mm.		(31, 193, 194)
Tribromovinyl phenyl.....			(194)
1,2-Diodovinyl phenyl.....	77.5-78.5 (m. p.)		(193)
Triiodovinyl phenyl.....			(194)

TABLE 15
Bis(α-haloalkyl) ethers hydrolyzable to one aldehyde

Ether	Boiling Point °C.	Melting Point °C.	References
Bis(chloromethyl).....	102-103; $n_D^{20} = 1.44433$	-41.5	(2, 6, 8, 25, 29, 40, 45, 56, 63, 64, 66, 70, 71, 78, 83, 87, 108, 109, 110, 137, 138, 139, 140, 142, 170, 175, 177, 186, 199, 200, 207, 222, 227, 234, 241, 243, 245, 246, 248, 249, 261, 270, 271, 272, 284, 314, 315, 327, 331, 336, 361, 362, 363, 366, 367, 371, 379, 397, 403, 410)
Bis(1-chloroethyl).....	113-114; $n_D^{20} = 1.4183$		(55, 114, 119, 126, 128, 145, 215, 235, 238)
Bis(1,2-dichloroethyl).....			(48)
Bis(1,2,2-trichloroethyl).....			(266)
Bis(1,2,2,2-tetrachloroethyl).....	130-131/11 mm.	47	(111, 132)
Bis(α-chloro- <i>o</i> -nitrobenzyl).....		Solid	(211, 212)
Bis(α-chloro- <i>m</i> -nitrobenzyl).....		144	(212)
Bis(α-chloro- <i>p</i> -nitrobenzyl).....		ca. 170	(212)
Bis(bromomethyl).....	154-155	-35 to -40	(2, 3, 4, 7, 8, 25, 70, 71, 84, 158, 159, 241, 284, 295, 310, 315, 321, 379, 397, 398)
Bis(1-bromoethyl).....			(55)
Bis(1,2-dibromoethyl).....		Prisms: 65-66 Needles: 62-63	(48, 143, 167, 282, 323)
Bis(1,2-dibromo-2-methylpropyl) (?).....			(88)
Bis(α-bromo- <i>o</i> -nitrobenzyl).....		d. 137-147	(212)
Bis(α-bromo- <i>p</i> -nitrobenzyl).....		ca. 175	(212)
Bis(iodomethyl).....	219		(157, 397)
Related compounds			
Chloromethyl methoxymethyl.....			(78; see 161)
Bis(chloromethyl) methylene.....			(78; see 161)
Bis(chloromethoxy)methyl.....	Not isolated pure		(241, 245; see 140)

TABLE 16
 α -Haloalkyl α' -haloalkyl ethers hydrolyzable to two aldehydes

Ether	Boiling Point	n_D^{20}	References
	°C.		
Chloromethyl 1-chloroethyl.....	112-114		(244)
Chloromethyl 1,2-dichloroethyl.....	144-148		(244)
Chloromethyl 1,2,2-trichloroethyl.....	174-176		(244)
Chloromethyl 1,2-dibromopropyl.....	121/15 mm.	1.5372	(134)
Bromomethyl 1,2-dibromopropyl.....	140/16 mm.	1.5700	(134)

TABLE 17
Bis(α -haloalkyl) ethers hydrolyzable to one ketone

Ether		References
Bis(α -chloroisopropyl).....	Never prepared	(See 144, 218)

TABLE 18
 α -Haloalkyl α' , α' -dihaloalkyl ethers hydrolyzable to an aldehyde and a carboxylic acid

Ether	Boiling Point	Reference
	°C.	
Fluoromethyl fluorochloromethyl.....		(43)
Chloromethyl dichloromethyl.....	130-132	(371)

TABLE 19
Bis(α , α -dihaloalkyl) ethers hydrolyzable to one carboxylic acid

Ether	Melting Point	Reference
	°C.	
Bis(tetrachloroethyl) (?).....	40-42	(See 132)
Bis(pentachloroethyl).....	Below 69	(314)

TABLE 20
 α , α -Dihaloalkyl α' , α' -dihaloalkyl ethers hydrolyzable to two carboxylic acids

Ether	Boiling Point	n_D^{20}	Reference
	°C.		
1,1,2,2-Tetrafluoro-2-chloroethyl 1,1-dichloro-2,2,2-trifluoroethyl.....	89.6/746 mm.	1.3303	(151)

TABLE 21
 α , α -Dihaloalkyl trihalomethyl ethers

Ether		Reference
Dichloromethyl trichloromethyl.....	Liquid; $n_\alpha = 1.4772$	(311)

TABLE 22
Bis(trihalomethyl) ethers

Ether	Boiling Point	References
Bis(trichloromethyl).....	°C. 98	(314, 371)

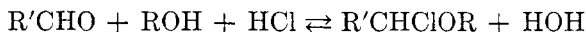
TABLE 23
Bis(α -halovinyl) ethers

Ether	Boiling Point	Reference
Bis(trichlorovinyl).....	°C. 210	(256)

Chlorination of methyl phenyl ether in the vapor phase gives chloromethyl phenyl ether (389, 417), plus other products. A more general procedure for chloromethyl, dichloromethyl, or trichloromethyl aryl ethers is the chlorination of methyl aryl ethers at 190–200°C. in the presence of phosphorus trichloride (20). For the monochloromethyl compounds, preparation from aryloxymethane-sulfonates is more convenient and more general (21) (see Section IV,B,4).

2. Action of hydrogen halide on an aldehyde or an aldehyde-alcohol mixture

The reaction

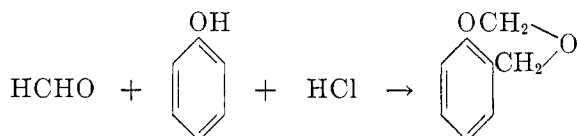


was first reported in 1858 by Wurtz and Frapolli (421), who obtained 1-chloroethyl ethyl ether in this way. This is the method most commonly used for the preparation of α -chloroalkyl alkyl ethers. The reaction is reversible, and the probable nature of the reaction process is discussed below (Section VI,A,3,(b)) in connection with the hydrolysis of α -haloalkyl ethers.

The preparations are carried out simply by passing hydrogen chloride gas into an equimolar mixture of the aldehyde and the alcohol. Formalin (157), paraformaldehyde (415), or trioxane (412) may be used for chloromethyl ethers; for 1-chloroethyl ethers paraldehyde may be employed (117). The product appears as a separable organic layer. Even α -haloalkyl ethers which are water-soluble do not dissolve in the concentrated aqueous hydrochloric acid. Cooling of the reaction mixture is desirable in order to minimize formation of the acetal which is the main by-product (see Section VI,A,3,(c)) and which often cannot be removed from the product by distillation. Cooling also helps to avoid thermal dehydrohalogenation (Section VI,C) and polymerization with the formation of dark tarry materials. It is desirable to pass the hydrogen chloride slowly, since much mixing of the two phases often leads to very dark products. Hurd and Wehrmeister (181) found that this darkening was prevented by the addition of sodium sulfate, and that the gas could then be passed very rapidly. These considerations are of lesser importance in the case of halomethyl ethers, which can-

not undergo dehydrohalogenation. The preparation of chloromethyl methyl ether (259), essentially according to the method of Henry (157) and Favre (101), is a good example of this type of reaction. Use of aqueous solutions, as in the Henry method (157), requires passage of sufficient hydrogen chloride to saturate the water. For this reason the Wedekind modification (415), in which para-formaldehyde is employed, is of some advantage for chloromethyl ethers. Addition of anhydrous calcium chloride (see 250) or zinc chloride may also improve the yields.

In the preparation of $R'CHClOR$ ethers by this process, R must be alkyl, and may be primary or secondary, but not tertiary. If phenols are treated with, for example, formaldehyde and hydrogen chloride, cyclization occurs,



and compounds such as 2,4,6-trichlorophenol do not react at all (21). Primary or secondary alcohols form α -haloalkyl ethers, but tertiary alcohols under these conditions give largely alkyl halide. No α -haloalkyl alkyl ether in which the R group is tertiary has been prepared. The group R' must be alkyl, arylalkyl, or hydrogen. α -Halobenzyl ethers are prepared otherwise (see Section IV,B,3). Unsaturation can be maintained in the group R , but this has not been possible with R' groups.

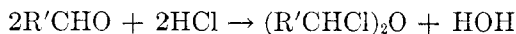


Otherwise the groups R or R' may be variously substituted, but may not contain substituents reactive toward hydrogen halide or α -haloalkyl ethers.

This method may be used for α -bromoalkyl (see 33, 250) or α -iodoalkyl (157) alkyl ethers.

Ketones have not been employed successfully in such reactions (see 140). Ethers such as $(\text{CH}_3)_2\text{CClOCH}_3$ (384) are very unstable substances.

The related reaction



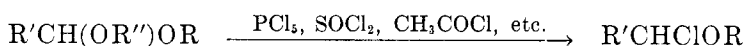
is used for the preparation of bis(α -chloroalkyl) ethers. The preparation of bis(1-chloroethyl) ether in this way was described by Lieben (235) in 1858, and was the subject of considerable research by Geuther and others (126, 128). Tishchenko (396; see 397) extended the reaction to the preparation of bis(chloromethyl), bis(bromomethyl), and bis(iodomethyl) ethers. The reactions are carried out as in the preparation of α -haloalkyl alkyl ethers, and the difficulties are due mainly to the unstable and reactive nature of the products. Aromatic aldehydes have not been converted into bis(α -haloalkyl) ethers in this fashion (see Section IV,B,3).

Acetaldehyde and liquid hydrogen chloride react to produce bis(1-chloroethyl) ether (119).

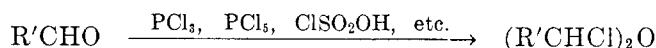
Preparations involving the use of acid halides (below) have been more widely employed for the synthesis of bis(α -haloalkyl) ethers.

3. Preparations using organic or inorganic acid halides

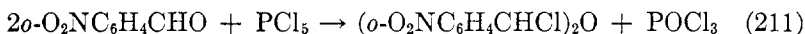
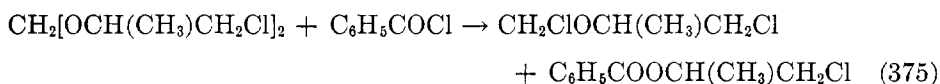
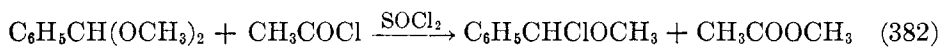
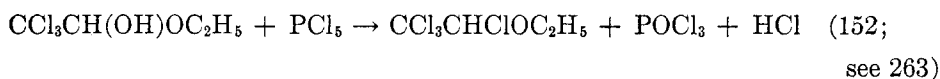
Reactions of the types



and



are perhaps the most general methods of preparation of α -haloalkyl ethers. Acid halides employed have included phosphorus pentachloride, phosphorus trichloride, chlorosulfonic acid, thionyl chloride, acetyl chloride, and benzoyl chloride. The group R is alkyl in all cases. The R' group may be alkyl, aryl, or hydrogen. α -Chlorobenzyl ethers, which have not been obtained from benzaldehyde with hydrogen chloride, can be made in this way. The very unstable α -chloroisopropyl methyl ether has been obtained from such a reaction (384). R'' may be alkyl or hydrogen.



α -Bromoalkyl ethers have been prepared similarly, using phosphorus tri- or pentabromide (212, 398).

4. Reaction of aryloxymethanesulfonates with inorganic acid halides

Barber, Fuller, Green, and Zwartouw (19, 21) found the reaction of aryloxymethanesulfonates with phosphorus pentachloride to be a general method for the preparation of chloromethyl aryl ethers.



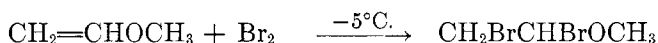
Phosphorus pentabromide gave the bromomethyl ethers. Phosphoryl trichloride was also effective. Thionyl chloride did not attack these salts, but did react with the free aryloxymethanesulfonic acids. The reactions with phosphorus pentachloride took place at room temperature, on simply grinding together the dry

reagents. The isolation processes were simple, and yields were good (80 or 90 per cent or better in many cases).

This ready elimination of sulfur dioxide is, the authors point out, an extreme development of a tendency common to sulfonyl chlorides, and other examples are cited. It has been reported (36) that (1-methylpropyloxy)acetic acid and thionyl chloride gave an 18 per cent yield of chloromethyl 1-methylpropyl ether, along with 58 per cent of the acid chloride, and other products. Thus a carbon-carbon bond can also undergo this type of reaction.

5. Addition of hydrogen halide or halogen to vinyl ethers

Addition of chlorine or bromine to vinyl ethyl ether was described by Wislicenus (420) in 1878. With lower alkyl vinyl ethers reaction is vigorous, and cooling is necessary. Addition of bromine to alkyl vinyl ethers has been studied particularly by Shostakovskiĭ and coworkers (100, 337, 338), who usually employed temperatures near 0°C., with carbon tetrachloride or chloroform as solvent. A typical example is the preparation of 1,2-dibromoethyl methyl ether from vinyl methyl ether (355).



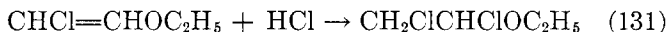
For chlorination Shostakovskiĭ (349) employed chlorine gas at low temperatures, in the presence of peroxides to prevent polymerization. Some 1,2,2-trichloroethyl ethyl ether might also be produced (see Section VI,D). The reaction is exemplified by the preparation of 1,2-dichloroethyl ethyl ether (351). Vinyl aryl ethers react readily in such preparations as these.

This method is satisfactory and general, and its practical utility depends mostly on the availability of the appropriate vinyl ether.

Divinyl ether reacts with bromine to produce bis(1,2-dibromoethyl) ether (167, 323).

Iodine causes polymerization of vinyl alkyl ethers (58, 328, 420) to a solid iodine-containing product. 1,2-Diiodoethyl ethers have not been prepared. With pure divinyl ether a similar polymerization does not occur (328).

Addition of hydrogen halides to vinyl ethers gives 1-haloethyl ethers (131, 184, 277).



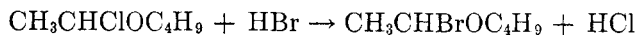
Operation at low temperatures is necessary, in order to avoid polymerization of the vinyl ether and thermal decomposition of the product. An example of the technique is the preparation of 1-chloroethyl butyl ether according to Shostakovskiĭ and Bogdanova (346).

Alkoxyacetylenes react with hydrogen chloride to give 1-chlorovinyl alkyl ethers (99).

6. Displacement reactions involving other α -haloalkyl ethers

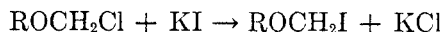
Hamonet (146) in 1904 observed that chloromethyl methyl ether reacted with hydrogen bromide to produce bromomethyl methyl ether. Other α -chloroalkyl

ethers react similarly. For instance, Shostakovskii and Bogdanova (341) obtained 1-bromoethyl butyl ether in 98 per cent yield by passing hydrogen bromide through 1-chloroethyl butyl ether at 15–20°C.



Since reactions of this type are properties of α -haloalkyl ethers, they are discussed below (Section VI,A,3,(a)).

Displacements involving halide ions (see Section VI,A,2,(b)) offer perhaps the most convenient method of preparation of α -iodoalkyl ethers (for examples, see 223).

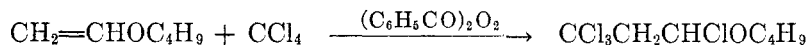


Iodomethyl aryl ethers have been made only in this way, from sodium iodide in acetone. However, chloromethyl aryl ethers did not react thus with sodium bromide in ethanol (21).

7. Other methods

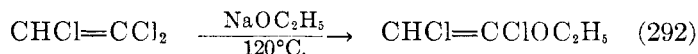
Other reactions which produce α -haloalkyl ethers have been mentioned. 1,2,2-Trichloroethene and chlorine monoxide (132) gave a product which was possibly bis(1,2,2,2-tetrachloroethyl) ether. Chloroacetic acid, heated in a red-hot tube, produced some bis(chloromethyl) ether (139). *p*-Methoxybenzenesulfonyl chloride and thionyl chloride at 250°C. gave a product believed to contain chloromethyl pentachlorophenyl ether (297). These reactions are of no use for synthesis.

Other reactions have been described which, although perhaps limited in scope, are of preparative usefulness for certain α -haloalkyl ethers. An example is the reaction of an α -haloalkyl ether with an aldehyde (382, 384) (see Section VI,A,3,(e)). Radical addition of tetrahalomethanes to vinyl ethers gives good yields of the α -haloalkyl ether (130, 232, 233).

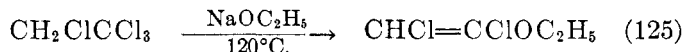


8. Preparation of α -halovinyl ethers

α -Halovinyl ethers may be prepared by a displacement reaction of the Williamson type, starting with an appropriate polyhaloalkene.



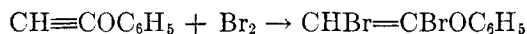
The polyhaloalkene may be obtained by the dehydrohalogenation of a polyhaloalkane in the same mixture.



These reactions, first described by Geuther (123, 125) and by Paternò (292, 293), have been employed for both alkyl (75, 76, 187, 188, 189, 190, 360) and aryl (65) ethers.

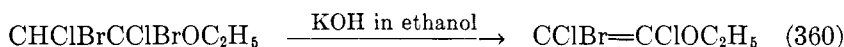
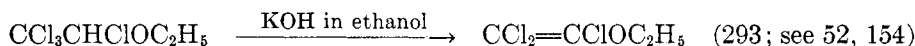
Reaction of alkoxy- or aryloxyacetylenes with hydrogen chloride gave 1-chlo-

rovinyl ethers (99), and of phenoxyacetylene with bromine or iodine gave the corresponding 1,2-dihalovinyl ethers (193).

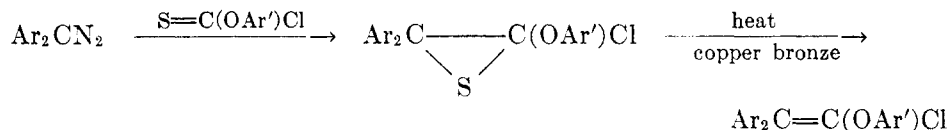


Phenoxyethynylmagnesium bromide reacted with iodine to give triiodovinyl phenyl ether as the only detectable product (194).

Dehydrohalogenation or dehalogenation of α -haloalkyl ethers involves ordinarily halogen on the α -carbon atom (see Section VI,B). Such reactions will be expected to yield α -halovinyl ethers, therefore, only in special cases.



The series of reactions



(where Ar and Ar' are aryl groups) has been used to prepare a few substituted α -halovinyl ethers (330).

V. PHYSICAL PROPERTIES

The general physical properties of α -haloalkyl ethers are normal, and none of the available physical data seem to indicate that the structure of these substances is other than that which is commonly written. Data on the physical and other properties of haloalkyl ethers, especially on refractometry, are listed by Karvonen (205, 206). The lower members of the series are mobile liquids, soluble in organic solvents. Boiling points or melting points are given in the tables.

Bis(chloromethyl) ether forms azeotropes with acetone (87 per cent acetone, b.p. 56.1°C.) and with carbon disulfide (75 per cent carbon disulfide, b.p. 43.1°C.), but not with 1-chloropropane (226, 227).

The Raman spectra of chloromethyl methyl ether (207, 214) and of bis(chloromethyl) ether (207) have been determined, and the ultraviolet spectrum of bis(chloromethyl) ether is on record (403).

Dipole moment measurements give values of 1.82 D (313) or 1.78 D (271) for chloromethyl methyl ether, and 0.70 D (271) for bis(chloromethyl) ether.

VI. CHEMICAL PROPERTIES

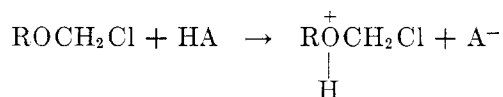
A. DISPLACEMENT REACTIONS

1. General discussion

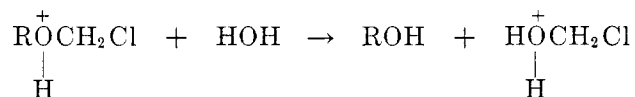
Two different electronegative atoms, oxygen and halogen, are bonded to the same carbon atom in the α -monohaloalkyl ethers. Such a structure should facil-

itate nucleophilic displacements on this carbon atom. Reactions which appear to be of this nature are in fact typical of the α -haloalkyl ethers. When such processes occur under basic conditions, the atom displaced from carbon is invariably the halogen atom. Displacement is subject to catalysis also by electrophilic reagents, which would be expected, since coordination with an acid should facilitate displacement of electronegative atoms. Oxygen and (for example) chlorine differ considerably in the ease with which they can coordinate with electrophilic reagents. Protonic acids should affect almost exclusively oxygen, since it is usually believed that chlorine in an organic structure is nearly incapable of being protonated. Other acid catalysts (for example, zinc chloride or aluminum chloride) might be capable of attacking in the initial step either oxygen or chlorine.

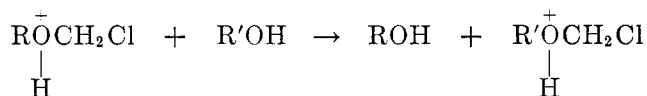
Catalysis by protonic acids occurs in such reactions of α -haloalkyl ethers as hydrolysis, alcoholysis, or α -haloalkylation. The reaction with alcohols was studied by Leimu (228, 229), and the hydrolysis reaction by Böhme (40) (Sections VI,A,3,(b) and (c)). If the initial step in such processes is protonation of the oxygen atom,



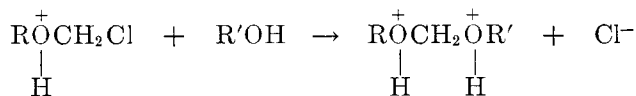
then it might be expected that displacement of oxygen from carbon, to form the alcohol ROH, would follow. Böhme (40) suggested essentially such a reaction as the rate-determining step in hydrolysis.



The ion $\text{H}_2\overset{+}{\text{O}}\text{CH}_2\text{Cl}$, the protonated form of the unknown chloromethanol, is then pictured as yielding finally formaldehyde and hydrogen chloride. If reaction of chloromethyl ethers with alcohols is an analogous process, the step



would represent essentially an equilibration between two chloromethyl ethers. Instead, the typical product is an acetal. For direct formation of such a product, the equation

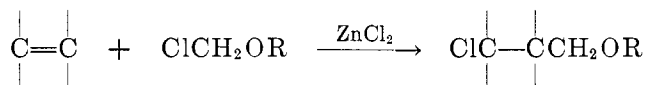


can be written. An analogous step during hydrolysis would give formaldehyde through the protonated diol $\text{CH}_2(\overset{+}{\text{O}}\text{H}_2)_2$. Such a step would require the develop-

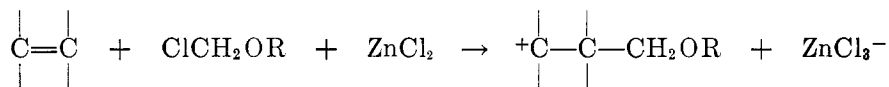
ment and separation of a new pair of charges. These reactions do proceed much faster in polar media, such as alcohols or water, than in the relatively non-polar dioxane (40, 229). Also, in the reaction with alcohols the rate of the forward reaction is proportional to the first power, but the rate of the reverse reaction to the second power, of the hydrogen chloride concentration (229). For such reactions, experimental data which could establish unequivocally whether it is oxygen or halogen which is initially displaced from carbon would be of interest.

Some other less-studied reactions of α -haloalkyl ethers, as for instance with carboxylic acids (Section VI,A,3,(c)) or with carbonyl compounds (Section VI, A,3,(e)), may be of the same general nature as the reactions with alcohols or with water.

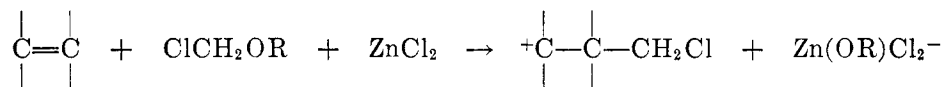
While protonic acids can presumably protonate only the oxygen atom in α -haloalkyl ethers, such catalysts as anhydrous metal halides should be capable of coördination with either halogen or oxygen. Chloromethyl ethers add to olefins in the presence of such catalysts (Section VI,A,3,(f)). In all reported cases the addition is as $-\text{Cl}$ and CH_3OCH_2- .



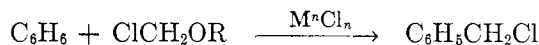
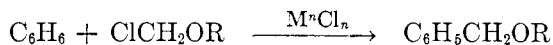
If this reaction is formulated in the usual fashion, as involving an initial displacement to give a carbonium ion,



then the reported reaction products do not indicate any occurrence of the alternative reaction



Electrophilic aromatic substitution is believed to proceed in general through a type of intermediate ion similar to that involved in addition to olefins. However, reaction of α -haloalkyl ethers with aromatic compounds in the presence of metal halides (see Section VI,A,3,(g)) leads to both types of products.



There is no predominance of the ether product (first reaction above), and the yields of this product are in fact usually low, so that the reaction does not find use for the preparation of substituted benzyl ethers. In many cases, if a catalyst of moderate activity (such as zinc chloride) is used, the chloromethylation predominates to the extent that little or no ether product can be detected. In this reaction, again, it is difficult to devise experiments which will answer the ques-

tion of the nature of the initial displacement. No existing experimental data serve this purpose. α -Haloalkylation is discussed further below (Section VI,A,3, (g)).

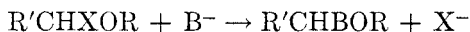
A halogen atom in the α -position in a haloalkyl ether is quite reactive, much more so than is halogen attached to some other carbon atom. Selective reactions can therefore usually be accomplished, to produce an ether still containing a reactive functional group, especially a halogen atom.



2. Displacements involving basic reagents

(a) General

The reactions of α -haloalkyl ethers with a great variety of basic reagents are among their most useful synthetic applications. Such reactions always involve displacement of halogen.



When the base is strong enough, dehydrohalogenation may occur simultaneously, but in general simple displacement is much favored (see Section VI,B).

(b) Displacements by inorganic anions

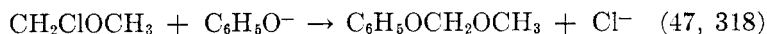
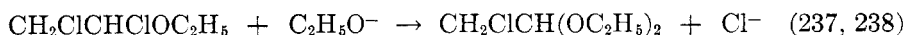
Reaction with hydroxyl ion involves the use of aqueous solutions, and the products are the same as those obtained on hydrolysis with water, except when the aldehyde is acted upon further by the base. Simple α -haloalkyl ethers can be titrated as acids with aqueous sodium hydroxide (339, 341). This is not the case with less reactive or less soluble ethers, such as chloromethyl phenyl ether (389).

α -Monohaloalkyl ethers react, probably reversibly, with halide ions. The reactions of chloromethyl ethyl ether or of 1-chlorobutyl ethyl ether with potassium iodide were too fast to follow kinetically (274). Iodomethyl ethers may be prepared from chloromethyl ethers in this way (see Section IV,B,6). The analogous reaction with hydrogen bromide (Section VI,A,3,(a)) is more usually employed for α -bromoalkyl ethers.

Chloromethyl butyl ether and sodium sulfide gave bis(butoxymethyl) sulfide (345). Inorganic disulfides and bis(chloromethyl) ether gave resins (199). Alkylthiosulfonic acids may be prepared from α -haloalkyl ethers and salts of thiosulfonic acid, $H_2S_2O_3$ (79).

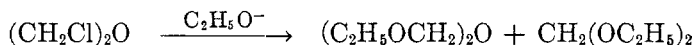
(c) Displacements by alkoxide or phenoxide ions

The reactions of α -monohaloalkyl ethers with alkoxide or phenoxide ions lead to acetals.



Numerous examples of the use of such reactions may be found in the literature. Yields are good, although dehydrohalogenation is a possible concurrent reaction

(except in the case of halomethyl ethers). Further reaction of the initially formed acetal with the base may take place. Thus, 1-chloroethyl phenyl ether and sodium allyloxide gave a 30 per cent yield of allyl phenyl acetal, a 26 per cent yield of diallyl acetal, and a 23 per cent yield of diphenyl acetal (350); and bis(chloromethyl) ether reacted with potassium ethoxide as follows (245):



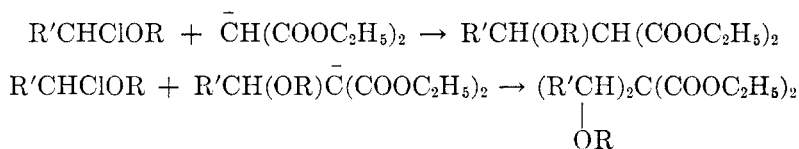
α -Monohaloalkyl aryl ethers react readily with either alkoxide or phenoxide ions (21, 343, 350), although they are less reactive than the alkyl compounds (343, 389). Dichloromethyl or trichloromethyl aryl ethers and sodium alkoxides gave only the parent phenol of the haloalkyl ether, but sodium aryloxides in acetone produced the triaryloxy- or tetraaryloxymethane, respectively (20).

1,2-Dichlorovinyl ethyl ether and excess sodium ethoxide gave sodium ethoxyacetate. With trichlorovinyl ethyl ether, ethyl dichloroacetate and sodium diethoxyacetate were produced (125).

Potassium 2,4-dinitrothiophenoxide can be employed for the characterization of bis(chloromethyl) ether (45).

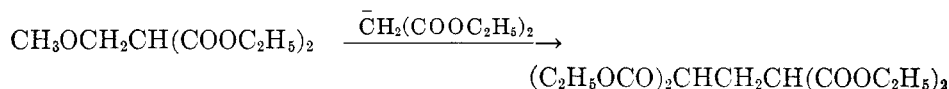
(d) Reactions with enolate ions

α -Monohaloalkyl alkyl ethers react as expected with sodium or magnesium diethyl malonate.

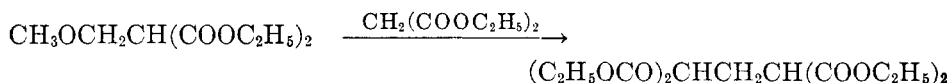


The mono(alkoxyalkyl)malonic esters can be produced in good yields. The di(alkoxyalkyl) product (210) usually contains much of the mono compound (168).

Chloromethyl alkyl ethers produce, in addition to the products above, tetraethyl 1,1,3,3-propanetetracarboxylate. Kleber (210) attributed this to cleavage of the primary product by the enolate anion,

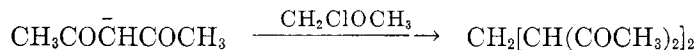


but Renard (316) concluded that the cleavage took place under acid conditions, and that the necessary acid was furnished by the chloromethyl ether, which usually contains hydrogen chloride.



(This reaction was easily realized separately.) This step was slow, when sodium diethyl malonate was the starting material, so that the amount of the propanetetracarboxylate produced was a function of the rate of distillation. Copper diethyl malonate, however, gave essentially complete conversion to the pro-

panetetrcarboxylate. β -Diketones react similarly with chloromethyl ethers (316).

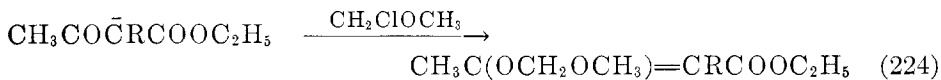
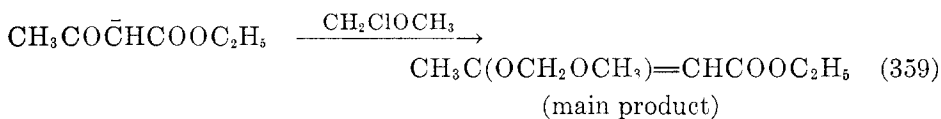


Chloromethyl aryl ethers with sodium diethyl malonate or sodium ethyl acetoacetate gave only the propanetetrcarboxylate, plus phenol and bis(aryloxy)-methane (21).

Bis(bromomethyl) ether and magnesium diethyl malonate gave the expected product, $(\text{C}_2\text{H}_5\text{OCO})_2\text{CHCH}_2\text{OCH}_2\text{CH}(\text{COOC}_2\text{H}_5)_2$ (7). From the sodium salt and bis(chloromethyl) ether, however, tetraethyl 1,1,3,3-propanetetrcarboxylate resulted (83).

The reactions of malonic esters and related substances with α -monohaloalkyl ethers have been used for synthetic purposes by a number of workers (168, 210, 312, 316, 317, 356, 357, 358).

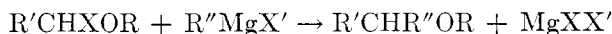
In all the cases above, *C*-alkylation is the rule, but chloromethyl methyl ether causes *O*-alkylation of the sodium enolates from ethyl acetoacetate or ethyl alkylacetoacetates. Simonsen and Storey (359) obtained ethyl β -(methoxymethoxy)crotonate, plus a little diethyl 1,3-diacetyl-1,3-propanedicarboxylate (see above), from ethyl acetoacetate.



R was CH_3 or $\text{C}_6\text{H}_5\text{CH}_2$.

(e) Reactions with organometallic compounds

The reaction of Grignard reagents with α -monohaloalkyl ethers,



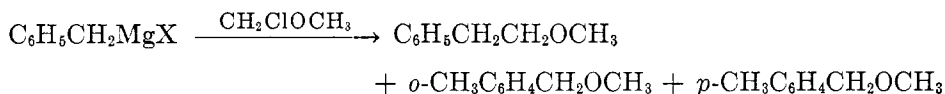
first described by Hamonet (146), is broadly applicable for the synthesis of ethers. It takes place with α -chloro, α -bromo, or α -iodo ethers. The groups R, R', or R'' may be variously alkyl or aryl, and may contain substituents, as long as these are less reactive toward the Grignard reagent than is the α -halogen atom. Many examples of this type of reaction occur in the literature (37, 42, 46, 86, 111, 117, 133, 146, 180, 204, 208, 216, 222, 223, 230, 231, 257, 283, 295, 309, 319, 372, 385, 388, 389, 414, 423). Organolithium (390) and organozinc (163, 237, 239) derivatives cause analogous reactions, as do organosodium compounds (30, 272), although in the latter case the yields reported are low. Reduction of 1,2-dichloroethyl ethyl ether by lithium aluminum hydride gave 2-chloroethyl ethylether (400).

Of particular synthetic interest in this reaction is the fact that R' may con-

tain halogen, since halogen in the R' group is always less reactive than is halogen on the α -carbon atom. However, halogen will react in the β - or other positions if an excess of organometallic reagent is used, or such an excess may also react by cleavage of the ether linkage. These succeeding reactions may be employed for synthetic purposes. If their occurrence is not desired, the amount of organometallic reagent should be limited to one equivalent, and it should be added to the solution of the α -haloalkyl ether. With phenyllithium, chlorine or bromine in the β -position reacts mainly by dehydrohalogenation, while iodine gives halogen-metal interconversion (390). Halogen in the γ -position reacts mainly by displacement, in a fashion more typical of an alkyl halide.

The reaction of 1-chloroethyl ethyl ether with phenylmagnesium bromide in the presence of optically active substances did not lead to an optically active product (42).

The α -haloalkyl ethers are among the many reactants which may give rearrangement with benzylmagnesium halides (46) or with other allylic Grignard reagents (423).



The α -haloalkyl ethers would appear to be of special interest for the study of this rearrangement, since in these saturated structures (particularly in halo-methyl ethers) the electronic influences may be largely inductive effects. With ethers of the type R'CHXOR and benzylmagnesium chloride, the percentage of rearrangement (ortho and para combined) decreased gradually as R was changed from CH₃ to C₂H₅ to *n*-C₃H₇ (257). When R' was changed from H to CH₃ or *n*-C₃H₇, rearrangement decreased sharply. Thus electron release toward the reaction center appeared to facilitate the normal reaction, more distinctly when operating on the α -carbon atom than when exerted through oxygen. On this basis correct empirical predictions as to the probability of rearrangement can be made (388). In the past, in some cases, investigators have overlooked the possibility of this rearrangement in assigning structures. For instance, the product described in the literature as 1-benzyl-2-chloroethyl ethyl ether (176) contains in fact perhaps 15 or 20 per cent of rearranged material (388). On the other hand, rearrangement does not proceed to the exclusion of the "normal" reaction, and the product initially believed to be *o*-tolylmethyl methyl ether is not a pure substance (46). Chloromethyl methyl ether and benzylmagnesium chloride, under one set of conditions, gave rearranged material corresponding to 12 per cent of the total ether product (257). Chloromethyl phenyl ether gave 38-50 per cent of rearrangement (388). Butenylmagnesium bromide and chloromethyl butyl ether gave a 70 per cent yield of "rearranged" product, and not more than 10 per cent (if any) of the "normal" product (423).

Recently, Lapkin and Lapkina (222, 223) have found that, while mono-ortho-substituted arylmagnesium halides (for instance, *o*-tolylmagnesium bromide) react normally with α -haloalkyl ethers, di-ortho-substituted Grignard reagents

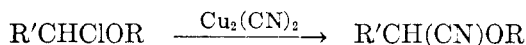
give a certain amount of the substituted benzyl chloride when reacting with chloromethyl ethers.



Mainly the normal ether products were obtained from bromomethyl or iodomethyl ethers, or from α -chloroethyl ethers. Chloromethyl methyl ether added to mesitylmagnesium bromide gave 9 per cent of dimesitylethane, plus the normal product. Addition of the Grignard reagent to the ether gave 42 per cent of the normal product and 58 per cent of 2,4,6-trimethylbenzyl chloride. Durylmagnesium bromide gave 79 per cent of the benzyl chloride, and pentamethylphenylmagnesium bromide 74 per cent.

(f) Reactions with metal cyanides

α -Monohaloalkyl ethers react with inorganic cyanides to form α -alkoxyalkyl cyanides. In some respects this reaction appears to differ from a simple displacement reaction, since alkali cyanides are reported to react only slowly or not at all with various α -haloalkyl alkyl ethers (52, 67, 117). The common reagent for the purpose is instead cuprous or mercuric cyanide (117, 369).



This reaction is a convenient preparative process, and yields are good in general (67, 117, 165, 240, 300, 326, 369, 373). Silver cyanide is said to produce unstable carbylamines (369), but in some cases at least it gives the nitrile (164).

In contrast to the unreactivity of α -haloalkyl alkyl ethers toward potassium cyanide, chloromethyl 2,4-dichlorophenyl ether reacted in aqueous acetone to give a 70–80 per cent yield of the nitrile (21).

(g) Reactions with other organic anions

Other organic anions react with α -monohaloalkyl ethers in the expected fashion. Carboxylate salts give α -alkoxyalkyl (68, 97, 115, 404) or α -aryloxyalkyl (21) esters (as do also carboxylic acids; see Section VI,A,3,(c)). Potassium thiocyanate produces organic thiocyanates (21, 198). Potassium phthalimide reacted with chloromethyl aryl ethers to form the *N*-aryloxymethyl phthalimide, and sodium phthalimidomalonate and chloromethyl methyl ether gave methoxymethyl phthalimidomalonate (253).

Chloromethyl aryl ethers decomposed on heating with sodium sulfite, alone or in ethanol (21). Dichloromethyl phenyl ethers did not react metathetically with carboxylate salts, sodium sulfite, or potassium thiocyanate (20).

(h) Reactions with amines or amides

Reaction of halomethyl alkyl or aryl ethers with tertiary amines gives well-defined quaternary salts.



These salts form stable chloroplatinate or chloroaurate complexes, and the reaction has been used extensively for characterization of these ethers (see, for instance, 205, 241, 245, 246). Amines employed have included trimethylamine, pyridine, strychnine, quinoline, and others.

Dichloromethyl aryl ethers gave little reaction with tertiary amines (20).

When the α -haloalkyl ether has hydrogen atoms on the β -carbon atom, the quaternary salts are less stable and dehydrohalogenation products are readily obtained (341) (see Section VI,B). α -Bromoethyl alkyl ethers react further, to give acetals with, for instance, *N,N*-diethylaniline (342).

Primary and secondary amines react vigorously with α -monohaloalkyl ethers, but complete aminolysis of the α -haloalkyl ether usually occurs, with formation of the corresponding alcohol and secondary products, plus the amine hydrochloride. This result is reported for α -monohaloalkyl alkyl (246) and aryl (21) ethers. Undoubtedly the primary reaction in these cases proceeds as expected, but the instability of the product leads to further decomposition. In some cases intermediate compounds have been isolated—for instance, $(\text{CH}_3\text{OCH}_2)_2\overset{+}{\text{N}}(\text{CH}_3)_2\text{Cl}^-$, as the gold chloride complex, from chloromethyl methyl ether and dimethylamine (246). 2-Phenylethylamine and bis(chloromethyl) ether reacted, in anhydrous ether in the presence of zinc chloride, to give a 59 per cent yield of tetrahydroisoquinoline and a 10 per cent yield of bis(2-phenylethylamino)-methane (336). Ammonium hydroxide with chloromethyl ethers gives hexamethylenetetramine (49, 106).

Chloromethylation of 6-methyluracil in position 5, without reaction on nitrogen, has been accomplished (96). However, theobromine is said to react with chloromethyl ethers to give the 1-alkoxymethyl derivatives (185).

Dichloromethyl aryl ethers and aniline gave the phenol, aniline hydrochloride, and diphenylformamidine, $\text{C}_6\text{H}_5\text{NHCH}=\text{NC}_6\text{H}_5$. Trichloromethyl aryl ethers gave triphenylguanidine, $(\text{C}_6\text{H}_5\text{NH})_2\text{C}=\text{NC}_6\text{H}_5$ (20).

1,2-Dichlorovinyl ethyl ether and aniline gave the ethyl ester and the anilide of phenylglycine (189).

The reaction of various amides with chloromethyl ethers, to produce products of undetermined chemical composition, is mentioned in numerous patents (60, 63, 64, 66, 137, 138, 361, 362, 363, 364, 365, 366, 367).

Among the well-known applications of α -haloalkyl ethers in organic synthesis is the preparation of substituted thiazoles from thiourea (or thiocarboxylic amides) by the use of 1,2-dihaloalkyl alkyl ethers (48, 147, 181, 275, 299, 399) (see Section VIII). This reaction is almost always carried out in aqueous solution, occasionally in alcohol. The active agent is undoubtedly the α -haloaldehyde. This was the opinion of Traumann (147, 399), the discoverer of the method. Another such case is the use of 1,2-dichloroethyl ethers in the Benary synthesis of pyrrole or furan derivatives from ethyl β -aminocrotonate, the latter often formed *in situ* from ethyl acetoacetate and aqueous ammonia (26, 27, 28; see also 112, 197). Here again, under the conditions of the process, α -chloroacetaldehyde must be the actual reactant.

Hydrolysis of chloromethyl ethyl ether, in dioxane, was studied by Böhme (40). The reaction was catalyzed by acids, and was therefore autocatalytic, and exhibited an induction period when free acid was not present initially. The reaction was apparently first order, even in the presence of only one mole of water per mole of chloro ether. Chloromethyl ethyl ether was hydrolyzed about 1500 times as fast as chloromethyl ethyl sulfide. The probable nature of the reaction of hydrolysis of α -haloalkyl ethers has been discussed above (Section VI,A,1).

The α -monohaloalkyl ethers of lower molecular weight are water-soluble and are hydrolyzed rather rapidly. They must be stored with careful exclusion of atmospheric moisture, although extreme precautions are necessary only for special reasons. The α -haloalkyl ether should in any case be distilled through a column immediately before use. Böhme (40) found that the rate constant for hydrolysis of acetyl chloride was approximately twenty times that for hydrolysis of 1-chloroethyl ethyl ether, although a strict comparison was not possible because of the differing nature of the reaction processes. The reaction of water with chloromethyl methyl ether is much less violent than with acetyl chloride.

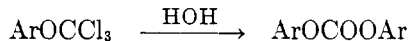
The effect of changes in the structure of the α -haloalkyl ether has been studied less for hydrolysis than for the reaction with alcohols. α -Monohaloalkyl ethers which are less soluble in water react much more slowly. Wedekind (415) reported hydrolysis to be more rapid the smaller the R group in $R'CHClOR$, but this would be the reverse of the known effect of alkyl groups on the velocity of reaction with alcohols (229). If R in such a structure is aryl, hydrolysis is very slow (21, 343, 389). Chloromethyl phenyl ether may be washed with water (or even with aqueous sodium bicarbonate) during preparation (389). This result, again, is undoubtedly attributable in part to the very low solubility of these compounds in water. Barber, Fuller, Green, and Zwartouw (21) found that in dioxane containing 10 per cent water the chloromethyl aryl ethers were hydrolyzed at a reasonable rate, to give the aldehyde and the phenol. Nevertheless, the half-lives reported indicate a considerably slower reaction than would be expected for similar ethers in which R was alkyl.

α -Monobromoalkyl ethers are reportedly more reactive than are the chlorine compounds (342). The half-life of iodomethyl 2,4-dichlorophenyl ether in aqueous alcohol (10 per cent water; the reaction process involved both hydrolysis and alcoholysis) was 2.8 min., as compared with 396 min. for the corresponding chloromethyl ether (21).

The hydroxyl compound which is produced on hydrolysis of α -monohaloalkyl ethers can react with the latter to give an acetal. Acetals are therefore often present in the hydrolysis product, and under some conditions may become the chief component. For example, chloromethyl butyl ether gave 70–80 per cent of dibutoxymethane (305; see 260). Alkyl halides may also occur among the hydrolysis products, particularly when hydrobromic or hydriodic acid is produced. Hydrolysis of 1,2-dibromoethyl butyl ether by water at room temperature gave bromoacetaldehyde and 1-bromobutane (338).

The α -polyhaloalkyl alkyl ethers have been little investigated. Better data are available for the aryl ethers, from the work of Barber, Fuller, and Green (20). Hydrolysis of dichloromethyl aryl ethers in dioxane gave almost the theo-

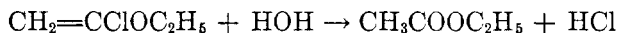
retical amounts of hydrogen chloride, formic acid, and the phenolic compound. Hydrolysis of trichloromethyl aryl ethers with aqueous alcohol led to the phenolic compound and the diaryl carbonate, rather than carbon dioxide. The diaryl carbonate was also the chief product of hydrolysis by aqueous acids.



1,2-Dichloro-1,2,2-tribromoethyl ethyl ether was converted by moist air to oxalic acid (360). Dichloromethyl trichloromethyl ether was insoluble in cold water; heated with water, it hydrolyzed slowly to carbon monoxide, carbon dioxide, hydrogen chloride, hexachloroethane, and other products (311).

1-Chloroethyl ethyl ether and hydrogen sulfide gave trithioacetaldehyde (218).

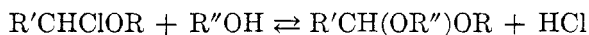
Hydrolysis of α -halovinyl alkyl ethers produces a carboxylate ester. Thus 1-chlorovinyl ethyl ether gives ethyl acetate, in a violent reaction (99).



Imbert (187, 190) and Crompton and others (75, 76, 360) described the preparation of chloroacetate or dichloroacetate esters from 1,2-dichlorovinyl or trichlorovinyl ethers, respectively.

(c) Reactions with alcohols, phenols, thiols, or carboxylic acids

α -Monohaloalkyl ethers react with alcohols to give acetals (157), either symmetrical or unsymmetrical.



The reaction is catalyzed by protonic acids, and can be formulated as a displacement of halide ion from the oxonium ion (see Section VI,A,1). From the researches of Leimu (228, 229) and others, more exact experimental data are available for this than for any other reaction of the α -haloalkyl ethers. In pure alcohols the reaction was rapid and appeared as first order. In dioxane (229), at low alcohol concentrations, it was slower and was reversible. Leimu believed that the results suggested a bimolecular process in dioxane. For ethers of the structure CH_2ClOR , the rate of reaction as R was varied increased in the order $\text{CH}_3 < \text{C}_2\text{H}_5 < n\text{-C}_3\text{H}_7 < \text{iso-C}_3\text{H}_7$ (229), an order which has been confirmed for the first-order reaction in methanol (274). For different R'' groups in the alcohol, the rate decreased in the order $\text{CH}_3 > \text{C}_2\text{H}_5 > \text{ClCH}_2\text{CH}_2$. The rate of the forward reaction was approximately proportional to the concentration of hydrogen chloride, and the rate of the reverse reaction was proportional to the square of this concentration.

Solubility effects do not enter into this reaction as they do into hydrolysis (see above), since the α -monohaloalkyl ethers are soluble in alcohols.

Because of this reaction, α -monohaloalkyl ethers prepared by the common process involving an aldehyde, an alcohol, and hydrogen halide often contain the corresponding acetal as impurity (see Section IV,B,2).

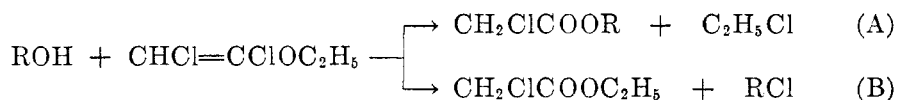
Bis(α -haloalkyl) ethers react in the same way. Bis(bromomethyl) ether and ethanol produce bis(ethoxymethyl) ether (8).

Little information is available on the reactions of α -polyhaloalkyl alkyl ethers with alcohols. Dichloromethyl aryl ethers in dry ethanol gave the theoretical amount of the parent phenol (20).

Phenols react with α -monohaloalkyl ethers in the same manner as do alcohols, but with more difficulty. Since alkali aryloxides react readily, they are more usually employed for preparative purposes than are the phenols themselves (Section VI,A,2,(c)). 1,2,2,3-Tetrachlorobutyl ethyl ether, refluxed under reduced pressure for 5 hr. with phenol, gave 1-ethoxy-1-phenoxy-2,2,3-trichlorobutane, and many substituted phenols reacted similarly (149). In the case of chloromethyl ethers (whose relationship is to formaldehyde), reaction with phenol gives a polymer (246).

α -Monohaloalkyl ethers react with carboxylic acids as with other hydroxyl compounds (341; see 387). 1-Chloroethyl butyl ether and acetic acid gave an 85 per cent yield of butoxyethyl acetate (341). For preparative purposes, carboxylate salts are more usually employed (Section VI,A,2,(g)).

α -Halovinyl alkyl ethers react with hydroxyl compounds on heating, without added catalyst, as shown by Imbert (188) and by Crompton and others (75, 76, 360). The reaction may proceed in two ways.



Alcohols give products of both types of reactions, but reaction A predominates, except when the alcohol is methanol (76). Carboxylic acids react mainly in accordance with reaction B, to give acyl chlorides. 1,2-Dichlorovinyl ethyl ether, heated with acetic, chloroacetic, phenylacetic, benzoic, *p*-methoxybenzoic, or α -naphthoic acid, gave ethyl chloroacetate (76). 1-Chloro-2,2-diphenylvinyl phenyl ether and a mixture of acetic and sulfuric acid gave diphenylacetic acid (330). Phenols give only the aryl chloroacetate (reaction A) in good yield.

The action of chloromethyl ethers on wool may involve reaction with thiol groups (92).

The reaction of thiourea with α -haloalkyl ethers is mentioned above (Section VI,A,2,(h)).

(d) Reactions with inorganic halides or oxides

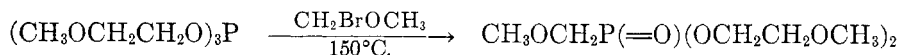
Simple α -monohaloalkyl ethers are fairly stable toward anhydrous acidic inorganic halides. Chloromethyl methyl ether may be refluxed with zinc chloride with little change (102, 386). Chloromethyl phenyl ether was not decomposed by heating with zinc chloride (389). Bis(bromomethyl) ether did not decompose in the presence of aluminum bromide at room temperature, although dibromomethane was produced at 100° or 180°C. (398). Warming phosphorus pentachloride with 1,2-dichloroethyl ethyl ether caused no reaction, but at 140°C. in a sealed tube the products were phosphorus trichloride and chlorination and

decomposition products from the ether (238). Data for the system chloromethyl ether-arsenic trichloride indicate compound formation (394), as do experiments with aluminum chloride and chloromethyl butyl ether in carbon disulfide (260). Quite stable complexes are formed with mercuric chloride and some α -haloalkyl ethers (382). In general, the equilibrium in complex formation may be largely in favor of the separate components. When, however, a nucleophilic reagent (for instance, a benzenoid ring) is present, acidic inorganic halides can catalyze displacement reactions of α -haloalkyl ethers.

Antimony trifluoride and a trichlorinated methyl ether (which was probably $\text{CH}_2\text{ClOCHCl}_2$) gave a mixture of difluorinated and trifluorinated products (44).

Chloromethyl methyl ether and sulfur trioxide gave chloromethyl methyl sulfate, $\text{CH}_2\text{ClOSO}_2\text{OCH}_3$ (175). The reaction of bis(chloromethyl) ether with sulfur trioxide is not clean-cut (142, 175) but produces bis(chloromethyl) sulfate (142).

Abramov and others (2, 3, 4, 5) have studied the reactions of halomethyl ethers with alkyl phosphites.



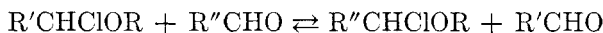
(e) Reactions with active methylene groups

Such reactions with active methylene groups as have been carried out "without catalyst" or in the presence of an intentionally added acidic catalyst are discussed here. For reactions under basic conditions, see Section VI,A,2,(d).

Straus and Heinze (382) reported the reaction of α -monohaloalkyl ethers with acetone or acetophenone, to give unsaturated ketones.

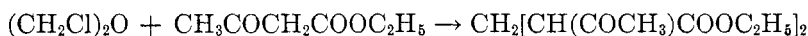


Aldehydes did not react in this way, but instead (382, 384) entered into an equilibrium of the type



α -Chlorobenzyl methyl ether and cinnamaldehyde gave α -chlorocinnamyl methyl ether and benzaldehyde, in an equilibrium which could be reached from either side. With aldehydes containing an α -methylene group (for example, butyraldehyde), equilibrium was disturbed by side reactions. This equilibration occurred on simple mixing of the components, although in many cases the experiments were carried out in the presence of mercuric chloride, in order to favor the precipitation of one desired component as a complex. α -Chlorobenzyl methyl ether and acetaldehyde gave only paraldehyde, but in saturated mercuric chloride solution the mercuric chloride complex of α -chlorocinnamyl methyl ether was produced.

Bis(chloromethyl) ether reacted with ethyl acetoacetate in the presence of boron trifluoride (234) (see Section VI,A,2,(d)).

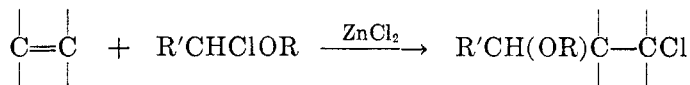


The reaction of impure chloromethyl methyl ether with ethyl phenyl ketone reportedly leads to a chlorine-containing product, $C_6H_5COCH(CH_3)CH_2Cl$ (395). The nature of this reaction is not clear, since pure chloromethyl methyl ether is said to be unreactive.

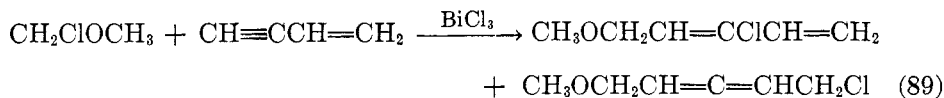
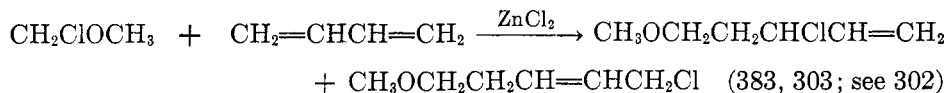
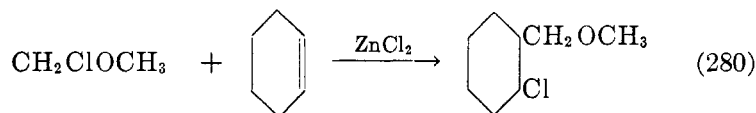
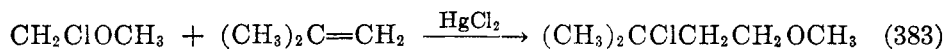
(f) Addition of α -haloalkyl ethers to alkenes

α -Monohaloalkyl ethers add to alkenes in the presence of acidic inorganic halides (87, 89, 383). Catalysts which have been used include zinc chloride (87, 383), bismuth trichloride (87, 89), mercuric chloride (383), and others. Zinc chloride has been most commonly employed. The reaction, which was first reported by Scott (331) and by Straus and Thiel (383), has been studied at some length by Pudovik and others (301, 302, 303, 304, 305). It proceeds at low temperatures, usually over a period of several hours, and may be carried out either without a solvent or in solution in carbon disulfide. In the absence of a catalyst, butadiene and chloromethyl methyl ether do not react, even after a year (303).

In all cases, addition proceeds with displacement of halogen (rather than oxygen) from the α -carbon atom in the α -haloalkyl ether.



Reported examples include addition to alkenes, cycloalkenes, conjugated alkenes, vinylacetylene, and ketenes.



Different α -haloalkyl ethers have also been employed with most of these reagents. Yields are generally good with α -haloalkyl alkyl ethers. Chloromethyl phenyl ether probably did not add to ethylene or isobutylene in the presence of zinc chloride (389), although some polymeric material was obtained.

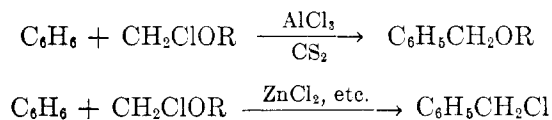
Addition of α -monohaloalkyl alkyl ethers to an olefinic bond is thus a useful, general, and usually uncomplicated synthetic process. In the case of conjugated dienes or vinylacetylene, both 1,2- and 1,4-addition products are produced.

Since these unsaturated halides are capable of isomerization under the influence of the same catalysts used for the addition itself, a decision as to the mode of the initial addition in such cases is difficult. Pudovik (302) concludes, from his results (301, 302, 303, 304, 305) and those of others, that 1,2-addition predominates, to the extent of perhaps 75 per cent in the initial product.

(g) Reactions of α -haloalkyl ethers with benzenoid nuclei

Almost all the displacement reactions of α -monohaloalkyl ethers, whether under acidic or basic conditions, lead to products in which halogen (rather than oxygen) has been displaced from the α -carbon atom. This was pointed out in Section VI,A,1 and is exemplified in the reactions discussed in Sections VI,A,2 and VI,A,3. The reaction with aromatic compounds is of special interest, because it is the only well-known case in which the typical product results from displacement of oxygen. This is in spite of the fact that the reaction with alkenes proceeds uniformly in the more usual way (see above).

In fact, the reaction of α -monohaloalkyl ethers with aromatic compounds, in the presence of acidic catalysts, produces both types of product (370).



Chloromethylation (or, in general, α -haloalkylation) is, however, the predominant reaction. The yields of substituted benzyl ethers are always low, and sometimes this product is not detectable. The reaction mixture is complex, especially with the less reactive aromatics such as benzene, because the products may react with themselves or with the initial aromatic compound to produce various products, including polymers. For example, the actual products reported from chloromethyl ethyl ether and benzene (aluminum chloride catalyst) include diphenylmethane (182, 408) and anthracene (182), as well as benzyl chloride (370) and benzyl ethyl ether (408).

Chloromethylation with chloromethyl alkyl ethers was described by Sommelet (370), who employed aluminum chloride or stannic chloride as catalyst. The reaction was investigated at some length by Stephen, Short, and Gladding (388). Aluminum chloride is too active to be a satisfactory catalyst and usually causes extensive further reaction. Sommelet preferred stannic chloride, used in carbon disulfide or carbon tetrachloride, at low temperatures. In the hands of other investigators (247, 386) this method has given almost no yields of chloromethylated product. The best procedure for the chloromethylation of benzene with chloromethyl methyl ether is that of Lock (247), which employs zinc chloride as catalyst and excess benzene as solvent. This procedure may be modified by omitting the use of hydrogen chloride; the same yields are obtained if it is not used (386).

All the processes mentioned above are heterogeneous, since the reactants and catalyst form the "red oil" which is typical of Friedel-Crafts processes (51)

and which is insoluble in the organic phase. Homogeneous chloromethylation with chloromethyl ethers may be carried out in acetic acid solution, with "no catalyst," as first described by Vavon, Bolle, and Calin (406, 407). The catalyst in this case is undoubtedly hydrogen chloride produced by the reaction of acetic acid with the chloromethyl ether (see 341, 387). The reaction proceeds more slowly than does the heterogeneous process using inorganic halides. Sulfuric acid may also be used as a chloromethylation catalyst (25, 70, 71).

Chloromethylation (or α -chloroalkylation) is usually carried out, not with a chloromethyl ether, but with formaldehyde (or other aldehyde) and hydrogen chloride (in which case the agent may be a bis(α -chloroalkyl) ether formed in the reaction mixture). Chloromethylation in general has been reviewed (113), and is discussed here only insofar as it is a phase of the chemistry of the α -haloalkyl ethers.

The relative reactivities of a number of aromatic compounds with chloromethyl methyl ether were studied by Vavon, Bolle, and Calin (407; see 118, 387). Neither these nor any other existing data, however, serve for an analysis of the nature of the reaction on the basis of chemical kinetics. It seems probable that satisfactory kinetic studies will have to involve analysis of the reaction mixture for some other component than hydrogen chloride, because so many of the simultaneous or succeeding reactions also produce hydrogen chloride. The chloromethylation reaction might conceivably involve initial displacement of halogen with formation of the benzyl ether, followed by splitting of the latter by hydrogen chloride or by the chloromethyl ether (408). The initial reaction process would then be in line with other reactions of α -chloroalkyl ethers, such as addition to alkenes. Benzyl methyl ether, for instance, is converted readily to benzyl chloride by hydrogen chloride or by chloromethyl methyl ether, in the presence of zinc chloride, under the Lock chloromethylation conditions described above (386). However, it is difficult to devise experiments to show unequivocally whether this is the course of the reaction.

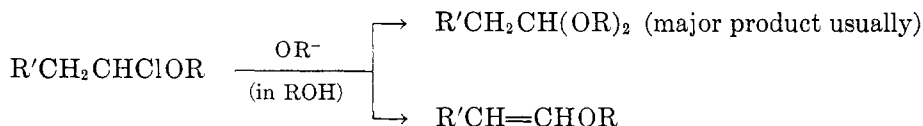
For the scope of the reaction, and for examples of the use of α -haloalkyl ethers in α -haloalkylation, the review by Fuson and McKeever (113) should be consulted. Certain recent researches (50) on orientation in chloromethylation (with paraformaldehyde) are also of importance.

Chloromethyl phenyl ether did not react with benzene under the usual conditions (389). Dichloromethyl ethyl ether has been used for formylation (103). Bromomethyl methyl ether reacted about ten times as fast with aromatic compounds as did chloromethyl methyl ether (407).

Alkoxyalkylation with α -monohaloalkyl alkyl ethers was investigated by Mason and Gist (260). With chloromethyl butyl ether and benzene, yields from traces up to 37 per cent of benzyl butyl ether were obtained. The method of Sommelet (370) (aluminum chloride in carbon disulfide), although poor, was the best technique for production of the benzyl ether. A temperature of -40° to -30°C. and a reaction time of 17 hr. gave the best yield. The reaction is not useful, in general, for the synthesis of ethers. These can be prepared satisfactorily by the Grignard reaction (Section VI,A,2,(e)).

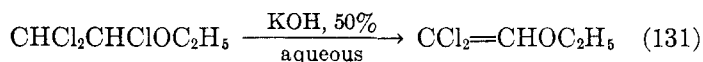
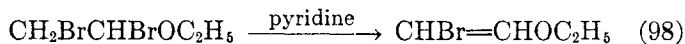
B. ELIMINATION REACTIONS

Dehydrochlorination in the presence of basic reagents is possible with α -chloroalkyl ethers in which a hydrogen atom is attached to the β -carbon atom. Heating with acids does not lead to elimination reactions (Section VI,A,3,(a)). With basic reagents, such as alkoxides, which can by displacement form stable products, displacement usually predominates over elimination.



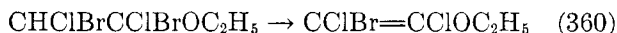
The best reagents for dehydrochlorination are tertiary amines. These reagents also may give rise to acetals, as well as to vinyl ethers.

1-Chloroethyl ethyl ether and pyridine (179) or 1-chloroethyl phenyl ether and *N,N*-diethylaniline (343) gave the respective vinyl ethers. With solid potassium or sodium hydroxide or with dibutylamine or *N,N*-dimethylaniline, this did not result. In this type of reaction, as in displacement, halogen on the α -carbon atom is more reactive than halogen elsewhere and is preferentially removed. 1,2-Dihaloalkyl alkyl ethers and tertiary amines give 2-halo-1-alkenyl alkyl ethers (98, 334, 354). 1,2,2-Trichloroethyl ethyl ether reacted similarly with 50 per cent potassium hydroxide (131).

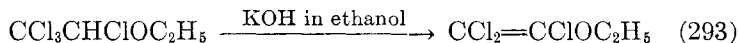


(In a reaction of 1,2-dibromoethyl phenyl ether with sodium phenoxide (264), the dehydrohalogenation product was assumed without proof to be 1-bromo-vinyl phenyl ether, but this appears improbable.) In spite of the greater facility of elimination of α - over β -halogen, vinyl ethers are better prepared from β -haloalkyl ethers, because the displacement side reaction is then almost absent.

Bromine apparently reacts more readily than chlorine.



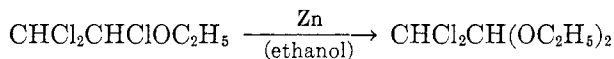
Dehydrohalogenation may be accomplished in other positions in the molecule of a polyhaloalkyl ether, if it is impossible for the α -halogen atom to be involved.



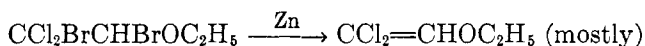
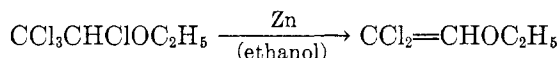
With α -bromoethyl ethers, treatment with tertiary amines led to such extensive reaction that no vinyl ethers were isolated (342), but the 1,2-dibromoalkyl ethers reacted satisfactorily (98) to give 2-bromovinyl alkyl ethers. 1,2-Dibromoethyl methyl ether did not give methoxyacetylene (307).

Dehalogenation of halogenated alkyl ethers with zinc was studied by Neher

(277, 279; see 263). In every case in which dehydrohalogenation could involve the halogen on the α -carbon atom, dehydrohalogenation predominated to such an extent that none of the dehalogenation product resulted. The actual products of the reaction with zinc in such cases were tarry polymers, or acetals if alcohol was present.

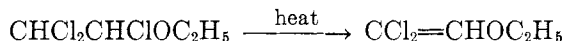


Ethers with no hydrogen on the β -carbon atom reacted by dehalogenation. Bromine was more reactive than chlorine.

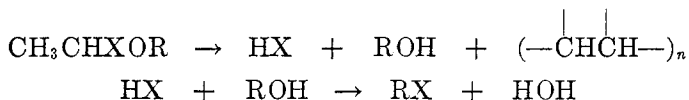


C. THERMAL DECOMPOSITION

α -Haloalkyl ethers which are capable of undergoing dehydrohalogenation involving the halogen on the α -carbon atom are unstable and decompose with evolution of hydrogen halide. This thermal instability has long been recognized, but the recent investigations of Shostakovskii and Bogdanova (342, 347, 348) represent the only connected studies on the nature of the reactions. The initial reaction step may be dehydrohalogenation, catalyzed by the ether itself. Simple dilution of the substances with about 15 per cent of benzene, dioxane, or diethyl ether is reported to increase their storage stability enormously (347). Long boiling (215 hr.) of 1,2,2-trichloroethyl ethyl ether gave 2,2-dichlorovinyl ethyl ether (290), the same product as was obtained by dehydrochlorination with potassium hydroxide (131).



Thermal decomposition usually gives more complicated results and leads to tarry products, alkyl halides, and water (347), besides hydrogen halide.



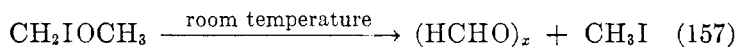
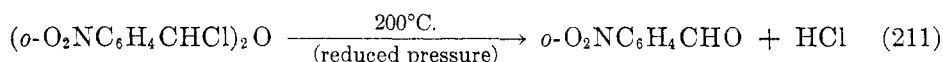
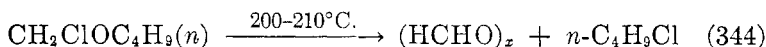
In addition, α -haloalkyl aryl ethers can produce reddish resinous products which are similar to phenol-aldehyde polymers (21, 348, 389, 417). α -Haloalkyl ethers in which the α -carbon atom is secondary are very unstable. α -Chloroisopropyl methyl ether (384) is an example of such a compound.

Thermal decomposition is accelerated notably by traces of moisture, which may in fact be required for the initiation of the process (347). Once decomposition has begun, secondary reactions (such as formation of the alkyl halide from the alcohol and hydrogen halide) will continue to produce water.

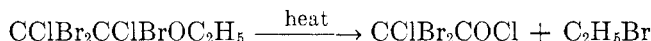
1,3,3,3-Tetrachloropropyl butyl ether at 130–135°C. gives 1,3,3-trichloro-

allyl butyl ether (233). This is the only recorded exception to the rule that dehydrohalogenation will involve the halogen on the α -carbon atom if possible (Section VI,B).

Halomethyl ethers cannot decompose in the fashion described above. Chloromethyl ethers are relatively stable compounds if moisture is strictly excluded. Chloromethyl butyl ether can be stored indefinitely (344). Stability of the simple chloromethyl alkyl ethers probably increases with increase in length of the alkyl group (33). The greater stability of the chloromethyl ethers is only relative, however, and all such compounds decompose on heating, to give the aldehyde and the alkyl halide. The bromomethyl ethers are less stable (33), and the iodomethyl ethers even less so (157).



The reaction (360; see 75)

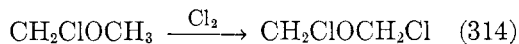


appears to be of this same type. It also involves a compound which cannot decompose by dehydrohalogenation.

Chloromethyl phenyl ether is unstable on storage, but chloromethyl 2,4-dichlorophenyl ether could be stored for a year with little change (21).

D. REACTIONS WITH HALOGENS

Chlorination of dialkyl or of alkyl aryl ethers is undoubtedly a radical process in the initial step and is usually carried out photochemically. The initial chlorination is on the α -carbon atom, so that in the succeeding steps the reactant is an α -haloalkyl ether. In ethers which cannot undergo dehydrohalogenation, chlorination continues to affect α -positions (the other α -carbon atom, if possible).



With bis(chloromethyl) ether, chlorination continues only slowly, but bis(trichloromethyl) ether can finally be produced (314, 371).

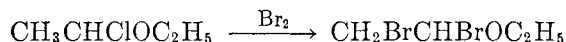
α -Chloroalkyl ethers which can undergo dehydrohalogenation are chlorinated, in succeeding steps, in the β -position. Diethyl ether gives successively 1-chloroethyl, 1,2-dichloroethyl, 1,2,2-trichloroethyl, and 1,2,2,2-tetrachloroethyl ethyl ethers. The results of the early work of investigators such as d'Arcet, Malaguti, Regnault, and Lieben (1, 15, 235, 236, 238, 255, 256, 314) on this chlorination were summarized by Jacobsen (195). The reaction probably involves thermal dehydrohalogenation of the α -chloroalkyl ether, followed by addition of chlorine.



Since the α -halogen atom will always be the one involved in the elimination reaction (see Section VI,B), halogenation will be in the β -position. Following this line of thought, Hall and Ubertini (145) were able to prepare bis(1-chloroethyl) ether in satisfactory yield by chlorination of either diethyl ether or 1-chloroethyl ether, simply by operating at -30° to -20°C ., a temperature low enough to avoid thermal decomposition. At this low temperature, continued passage of chlorine through the bis(1-chloroethyl) ether produced no further reaction.

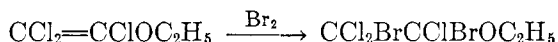
Products reported from the chlorination of di-*n*-propyl ether include the expected 1,2-dichloropropyl (49, 288) and 1,2,2-trichloropropyl (267) propyl ethers, but also 1,2-dichloropropyl 2-chloropropyl ether (288).

Reaction of α -monochloroalkyl ethers with bromine should, on the basis indicated above, give α,β -dibromoalkyl ethers. Swallen and Boord (391) showed that this reaction takes place readily on simple addition of bromine to the α -chloroalkyl ether at ice-bath temperature.



The α,β -dibromoalkyl ethers are thus easily obtained and are valuable synthetic reagents (see Section VIII).

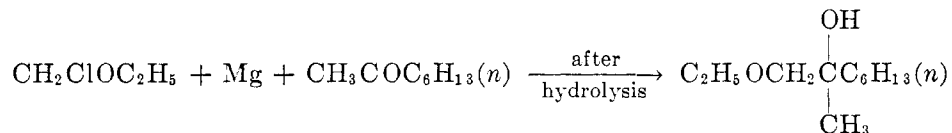
Unsaturated α -haloalkyl ethers add halogen readily (52, 99).



The above vinyl ether is reported not to add hydrogen chloride (52), but 2,2-dichlorovinyl ethyl ether gives 1,2,2-trichloroethyl ethyl ether (277). Acrolein, methyl alcohol, and hydrogen chloride react to produce 1,3-dichloropropyl methyl ether (417), and α -haloallyl ethers have not been made. However, α -chloroalkyl allyl ethers are obtained from aldehydes, allyl alcohol, and hydrogen chloride.

E. REACTIONS WITH METALS

Halomethyl ethers are not in general very active toward metals, although chloromethyl methyl ether is reported (102) to react violently with zinc to give a mixture of products. Bis(iodomethyl) ether did not react with sodium, or chloromethyl methyl ether with magnesium (319). Chloromethyl aryl ethers did not react with magnesium in ether, but iodomethyl aryl ethers gave the bis(aryloxy)-ethane (21). α -Haloalkyl ethers do not form Grignard reagents, but chloromethyl ethyl ether, magnesium, and ketones reacted in the presence of mercuric chloride to give ethyl ethers of 1,2-diols (369).



Aldehydes did not react thus. Esters gave the tertiary alcohols.

Reactions of the Wurtz type do not proceed satisfactorily with α -haloalkyl ethers, although copper powder or iron is said to cause dimerization of chloro-

methyl ethers (393). Bromobenzene, chloromethyl methyl ether, and sodium powder produced a limited yield of benzyl methyl ether, but in other cases the reaction did not work (196).

VII. PHYSIOLOGICAL PROPERTIES

α -Haloalkyl ethers are toxic substances, and precautions must be taken against inhalation of the vapors or contact of the material with the skin or mucous membranes. The degree of toxicity may not be extremely high. Bis(chloromethyl) ether is slightly irritant to the eyes, but it is not classed as a lachrymator, and it is not a vesicant (261). It is irritating to bronchial and pulmonary passages, and causes death from pulmonary edema in dogs or cats. In addition, there is a specific action. The toxic action of bromomethyl methyl ether and other halides may be due to combination with thiol groups in proteins, particularly enzymes (171). 1,2-Dichloroethyl ethyl ether caused bronchial asthma and bronchitis in three workers who were exposed, but bis(1-chloroethyl) ether has only a general toxic effect (201, 202). The 1,2-dibromoalkyl ethers are powerful lachrymators (322).

Bis(chloromethyl) ether and bis(bromomethyl) ether were manufactured in Germany during World War I for employment in gas warfare (56, 284), but they seem to have found little use. Apparently they are not now considered as chemical warfare agents.

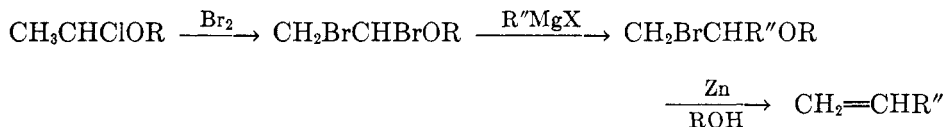
The ready hydrolysis of the α -haloalkyl ethers to give hydrogen halide and (in many cases) an aldehyde makes them unpleasant to handle, but they are less active in this respect than are the lower-molecular-weight acyl halides. In general, they are no more to be avoided in organic chemical work than are these latter compounds, but due precautions are to be taken.

VIII. USES

A. AS INTERMEDIATES IN ORGANIC SYNTHESIS

α -Haloalkyl ethers find quite occasional use as synthetic intermediates in the laboratory. Their reactivity with a variety of reagents makes possible the preparation of a number of types of organic compounds. The main limitation on their usefulness is that the same products can often be obtained directly from the corresponding aldehyde (for instance, acetals or chloromethyl derivatives of aromatic hydrocarbons). Since the α -haloalkyl ether is in many cases prepared from the aldehyde, its isolation then represents an unnecessary step in the synthesis. If the product in question is not obtainable from the aldehyde or the vinyl ether, or if the α -haloalkyl ether is readily prepared from some other starting material, the latter reagent is then of interest as a possible intermediate. For example, unsymmetrical acetals are conveniently prepared from the α -haloalkyl ethers, and unsymmetrical bis(aryloxy)methanes can be prepared only in this way (21). The description above (Section VI) of the chemical properties of the α -haloalkyl ethers indicates the variety of possible products which can be obtained from them. Below, only a few types of reactions which have found fairly wide synthetic application will be discussed.

The Hamonet synthesis of ethers from α -haloalkyl ethers and an organomagnesium halide is a very general reaction, and is the only useful method for direct production of ethers from a Grignard reagent. This synthesis (see Section VI,A,2,(e)) has probably been the most common application of α -haloalkyl ethers (37, 86, 111, 117, 133, 146, 176, 180, 204, 208, 216, 230, 231, 283, 294, 295, 309, 372, 414). The reactions are smooth, and fairly good yields are usually obtained. The occurrence of rearrangement with allylic Grignard reagents (46, 423) (see above) makes impossible the preparation of pure allyl or benzyl ethers in this way. The Boord synthesis of alkenes (90) involves as one step the reaction of an α,β -dibromoalkyl ether with a Grignard reagent (391).



This method, in various modifications, has been very useful for olefin synthesis (93, 225, 322, 329, 332, 335, 368, 418).

The addition of α -monohaloalkyl alkyl ethers to alkenes (87, 331, 383) (Section VI,A,3,(f)) in the presence of inorganic halides is another reaction which is quite general, and which gives products not as readily obtained otherwise. Numerous examples are given in the literature (13, 39, 72, 89, 94, 258, 280, 301, 302, 303, 304, 305, 378). This reaction failed with chloromethyl phenyl ether (389).

For α -haloalkylation of aromatic compounds, chloromethyl or other α -haloalkyl ethers have been employed frequently (113) (Section VI,A,3,(g)) and were the reagents first used (370). Chloromethylation can in most cases be as conveniently accomplished by the use of formaldehyde and hydrogen chloride (see 247, 333) rather than the isolated α -haloalkyl ether. For the chloromethylation of mesitylene, the use of chloromethyl methyl ether in glacial acetic acid (406) avoids the formation of much bis(chloromethyl)mesitylene. For less active hydrocarbons, this method is much too slow for preparative purposes (333).

The reactions of α -haloalkyl ethers with salts of diethyl malonate or ethyl acetoacetate (7, 83, 168, 210, 224, 312, 316, 317, 356, 357, 358, 359, 376) (Section VI,A,2,(d)) and the reactions of these compounds with cyanides (67, 117, 164, 165, 240, 300, 326, 369, 373) (Section VI,A,2,(f)) have also found fairly frequent use.

1,2-Dichloroethyl ethyl ether, available from the chlorination of diethyl ether, is employed in aqueous solution as chloroacetaldehyde and is used for the synthesis of derivatives of furan, pyrrole, pyridine, or thiazole (26, 27, 28, 48, 112, 147, 181, 197, 275, 299, 399). The preparation of 2-aminothiazole from thiourea (147, 399) is a well-known example. Substituted 1,2-dihaloalkyl ethers (181), or thiocarboxylic amides in place of the thiourea, give variously substituted thiazoles. The cyclic nitrogen and oxygen compounds are produced by the use of ethyl β -aminocrotonate (26, 27) or related compounds.

B. OTHER APPLICATIONS

The Velan process for treatment of textiles to increase water repellency is based on the use of quaternary ammonium salts derived from cyclic or aliphatic tertiary amines and a halomethyl ether (273, 320). The quaternary salts are not necessarily prepared from previously isolated halomethyl ethers, although they may be (220, 221). Bis(chloromethyl) polymethylene ethers, when used for the treatment of wool, increase water repellency and wash resistance, while lowering the tensile strength (91, 92, 209). Sulfur-containing groups in the wool are affected, since the cysteine groups are fewer than before treatment (92). The cystine content is largely unchanged. New cross-links not containing sulfur are also apparently formed (209).

Since 1940, thirty or forty patents have appeared which describe the preparation of various textile aids from a chloromethyl ether and amides, amines, alcohols, and other reagents (6, 60, 63, 64, 66, 79, 137, 138, 361, 362, 363, 364, 365, 366, 367). The products are said to contribute wash resistance, water repellency, or slip resistance to the fabric, or to be useful as softening agents or detergents for textiles.

α -Haloalkyl ethers of the type $\text{CCl}_3\text{CHClOR}$ (where R is aromatic) have been suggested for use as insecticides, as have a few other α -haloalkyl ethers (32, 61, 62, 120, 121, 148, 405). Such compounds may be active contact insecticides, stomach poisons, or fumigants (62). α -Haloalkyl ethers and hexamethylenetetramine are said to give products more powerfully antiseptic *in vitro* than hexamethylenetetramine itself (245).

Other suggested applications of α -haloalkyl ethers include their use in the preparation of resins from alkaline earth disulfides (199), or their employment as scavengers for leaded fuels (55).

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