

THE DEGRADATION OF CARBOXYLIC ACID SALTS BY MEANS OF HALOGEN

THE HUNSDIECKER REACTION

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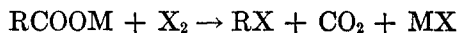
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I. INTRODUCTION

The degradation of a carboxylic acid salt in anhydrous medium by means of halogen to a halide of one less carbon atom than the original acid can be expressed by the equation:



Largely because of the extensive contributions of the Hunsdieckers (96, 97, 98, 99, 100, 101, 102) to our knowledge of this reaction, many chemists refer to the reaction under discussion as the "Hunsdiecker reaction." Others designate the reaction by the names "silver salt reaction" or "silver salt-halogen reaction." It has been proposed (95) that the name "Borodine reaction" be used, in recognition of the discovery of the reaction by Borodine (33). The authors of a recent book (179) incorrectly name this reaction as the Simonini reaction.

The reviewers favor the use of "Hunsdiecker reaction," if a name is to be given to this reaction, because of the many instances of the use of this terminology already in the literature and because of the large amount of developmental work carried out by the Hunsdieckers. The often-used descriptive names are contraindicated by the fact that the reaction is successful with salts other than silver salts, halogens other than bromine can be used, and the reaction of salts

with halogen can yield a variety of organic products depending on experimental conditions.

Kleinberg (110) has previously considered the Hunsdiecker reaction in his general review of the reactions of silver salts of carboxylic acids with halogens. However, his discussion is not comprehensive with respect to the Hunsdiecker reaction.

A brief discussion of the reaction has also appeared in a somewhat inaccessible publication of limited distribution (185a).

More recently a review appeared in a Czech journal (174). While fairly thorough in coverage of the literature, the review is uncritical and located in a relatively obscure journal.

Chemical Abstracts through the issue of July 25, 1955 has been consulted for pertinent references. In addition, current issues of the more important domestic and foreign chemical journals have been checked in the original, and likely looking references in *Current Chemical Papers* have been investigated.¹

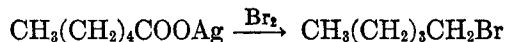
The reviewers have attempted to follow the *Chemical Abstracts* system of nomenclature throughout this review. Occasionally, departures from this style were made for convenience.

II. SYNTHETIC APPLICATIONS

A. Aliphatic halides (table 1)

The greatest utility of the Hunsdiecker reaction lies in the preparation of aliphatic halides, and most of the investigations of the reaction have been in the aliphatic series. The discovery of the reaction in 1861 by Borodine (33) involved the preparation of methyl bromide from silver acetate. It was not until the mid 1930's, however, that the reaction was shown (96, 99, 100, 102) to be generally applicable in the aliphatic series.

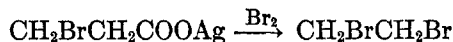
With the silver salts of unsubstituted aliphatic monocarboxylic acids and of most substituted aliphatic acids, good yields of the corresponding alkyl halides can be obtained. For example, silver caproate gives a 92 per cent yield of 1-bromopentane (142),



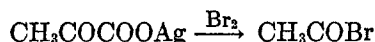
silver stearate gives 1-bromoheptadecane in 70–90 per cent yield (132, 135, 142),



1,2-dibromoethane (69 per cent) is obtained from silver 3-bromopropionate (50),

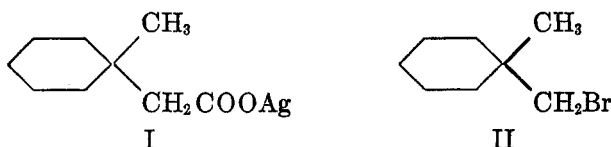


acetyl bromide is prepared from silver pyruvate (96, 99, 100, 102),

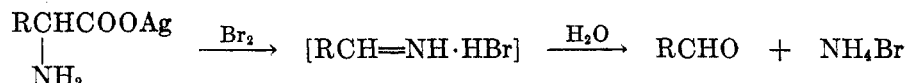
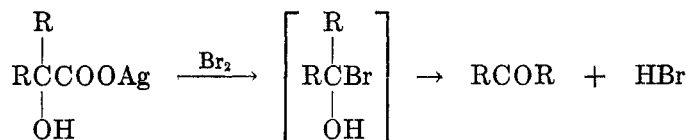
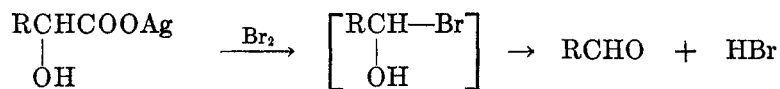


¹ Subsequent to the initiation of work on this review, the authors learned that a chapter dealing with the reactions of silver salts of carboxylic acids with halogens will appear in a forthcoming volume of *Organic Reactions*.

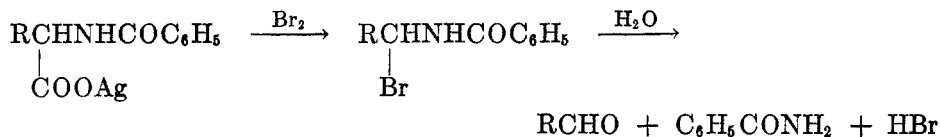
and silver 1-methylcyclohexyl acetate (I) gives a 94 per cent yield of 1-bromo-1-methylcyclohexane (II) (145).



The silver salts of α -hydroxy and α -amino acids yield aldehydes and ketones rather than the anticipated halides; this behavior can be explained by the following equations:



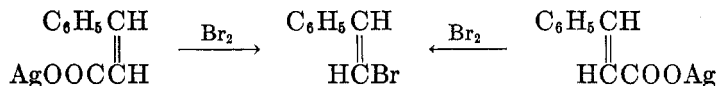
Protection of the amino group makes possible the isolation of the Hunsdiecker products from *N*-acylamino acids. Thus it was possible to obtain normal products from the silver salts of *N*-benzoylalanine and *N*-benzoylnorleucine (90, 91). The bromides, however, were found to undergo easy hydrolysis to an aldehyde, benzamide, and hydrogen bromide:



The Hunsdiecker reaction has been used widely in the aliphatic series for the preparation of compounds containing an odd number of carbon atoms from the readily available acids of an even number of carbon atoms. The yields of halides obtained vary in the order: primary > secondary > tertiary. The reaction appears to be equally applicable to the preparation of both long-chain and short-chain alkyl halides.

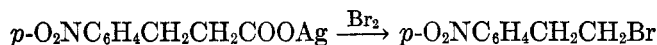
In most of the aliphatic applications of the Hunsdiecker reaction bromine has been the halogen employed. When iodine is used, there is a greater tendency toward ester formation (see Section V) and with chlorine, the yields of alkyl halides are usually lower. A comparison of the reaction of the different halogens with silver palmitate has been made (133). When a solution of bromine was added to silver palmitate in boiling carbon tetrachloride, nearly two equivalents (a molar ratio of 1:1) were absorbed before the color of bromine persisted, while with iodine the color became evident after a little more than one equivalent

(75). It is of interest that the silver salt of either *cis*-cinnamic or *trans*-cinnamic acid yields *trans*- β -bromostyrene (156).

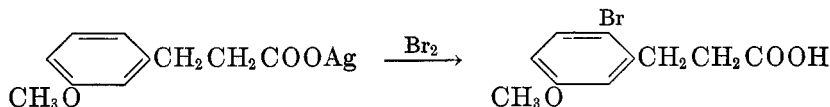


With the monoesters of aliphatic dicarboxylic acids, good yields of ω -haloesters are obtained (4, 15, 21, 96, 97, 99, 100, 101, 102, 104, 120, 176). Although silver succinate gives only 32–37 per cent yields of 1,2-dibromoethane (50), the silver salt of the monoethyl ester of succinic acid gives a 65 per cent yield of ethyl ω -bromopropionate (15).

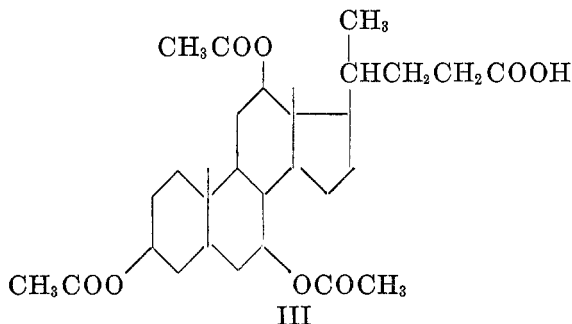
The reaction has been utilized with a number of aryl-substituted acids (2, 12, 18, 22, 36, 86, 125, 129, 142, 144, 156, 184). As will be pointed out with the salts of aromatic acids, best yields are obtained if the aromatic grouping possesses electron-attracting, or deactivating, groups. For example, silver 3-phenylpropionate gives only a 5 per cent yield of 2-phenylethyl bromide, while silver 3-(*p*-nitrophenyl)propionate yields 80 per cent of 2-(*p*-nitrophenyl)ethyl bromide under similar conditions (18).

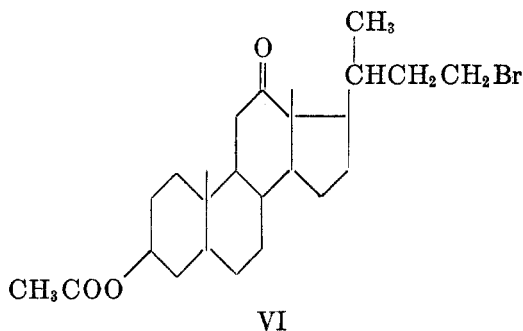
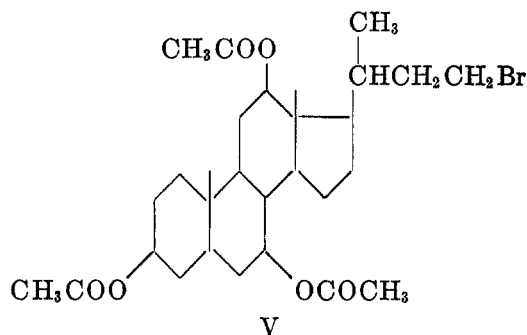
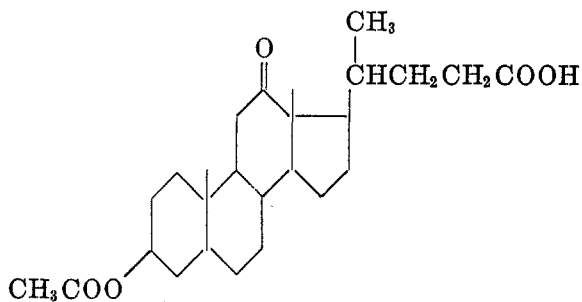


A high percentage of the parent acid is often obtained (26, 86), and halogenation of the aromatic nucleus may also occur (86). With an activated aromatic grouping, ring substitution may become dominant with little or none of the aliphatic halide resulting; thus, silver 3-(*m*-anisyl)propionate reacts with bromine to give an 88 per cent yield of 3-(2-bromo-5-methoxyphenyl)propionic acid (144).



The Hunsdiecker reaction has been successfully employed in the steroid field. For example, 3 α ,7 α ,12 α -triacetoxycholanic acid (III) and 3 α -acetoxy-12-ketocholanic acid (IV) have been converted to 3 α ,7 α ,12 α -triacetoxy-23-bromonorcholane (V) and 3 α -acetoxy-12-keto-23-bromonorcholane (VI), respectively (25, 36). 23-Bromonorcholane was obtained in 96 per cent (crude) yield from silver cholanate (25). Although 3 β -acetoxyandrostanol bromide has been prepared from



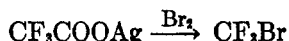


silver 3 β -acetoxyetioallocholanate (115, 163), poor yields are usually obtained when the carboxyl group is attached to the steroid ring (see Section II, B). It is probable that the reaction will prove useful in the future to other workers in the steroid field.

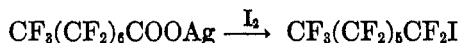
A number of unsuccessful attempted reactions of the Hunsdiecker type have been reported. Conly (50) was unable to obtain a dibromide from the reaction of silver succinate with bromine in tetrachloroethane; however, the reaction was successful with carbon tetrachloride as a solvent (50). Müller and Kindlmann (136) failed to obtain 1,8-dibromoöctane by reacting silver sebacate with bromine in carbon tetrachloride, although other workers (96, 99, 100, 102, 127, 142) have reported 62–81 per cent yields of the dibromide. The reaction has not been successful with short-chain unsaturated acids such as methacrylic acid (50), maleic acid (30, 184), and fumaric acid (30, 184).

Considerable attention has been focused during recent years on the application of the Hunsdiecker reaction to salts of fluorinated acids. The large amount of research concerning these compounds warrants a separate listing of the aliphatic fluoro acids in table 1. Usually the silver salt of the fluoro acid and the halogen are reacted without a solvent and yields of 70–98 per cent are common. Higher temperatures and sealed containers are also generally employed (65, 74, 171), although satisfactory yields have been reported with temperatures of 25–50°C. (73, 74, 82, 118) and at atmospheric pressure (53).

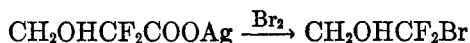
Examples illustrating the utilization of the reaction with salts of fluoro acids include: bromotrifluoromethane (88–98 per cent) from trifluoroacetic acid (73, 82),



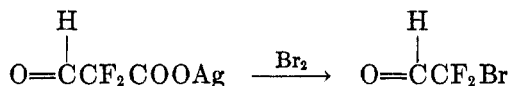
1-iodopentadecafluoroheptane (85 per cent) from pentadecafluorocaprylic acid (74),



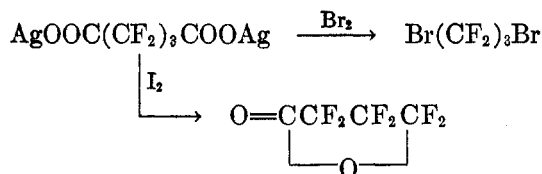
2-bromo-2,2-difluoroethanol from 2,2-difluoroacrylic acid (51),



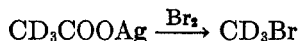
and 2-bromo-2,2-difluoroacetaldehyde from 2,2-difluoromalonaldehydic acid (51).



It is noteworthy that while only a very small amount of 1,3-dibromopropane is obtained from silver glutarate (142), an 80 per cent yield of 1,3-dibromohexafluoropropane is obtained with silver hexafluoroglutarate (83); however, if iodine is employed rather than bromine, considerable lactone is formed (84).



An interesting recent employment of the Hunsdiecker reaction involves the preparation of deuterium-substituted alkyl halides from the corresponding deuterated acids (7, 138, 139, 140). Methyl- d_3 bromide has been obtained in 82 per cent yield from acetic-2- d_3 acid (140).



Earlier workers (117) reported that the treatment of the silver salt of acetic-2- d_1 acid with bromine resulted in hydrogen-deuterium exchange; the product of the

TABLE 1
Aliphatic halides prepared by the Hunsdiecker reaction

Silver Salt of Acid	Halogen	Products and Yields	Conditions	References
<i>Aliphatic monobasic acids:</i>				
Acetic acid.....	Br	Bromomethane (69%)	CCl ₄	(32)
	Br	Bromomethane (> 50%)	CCl ₄	(139)
	Br	Bromomethane (80%)	No solvent	(96, 99, 100, 102)
	Br	Bromomethane	—	(33)
Butyric acid.....	Br	1-Bromopropane (61%), propyl butyrate	C ₆ H ₅ NO ₂	(32)
	Br	1-Bromopropane (30%), propyl butyrate (9%)	CS ₂	(86)
2-Butenoic acid.....	I	—	No solvent	(184)
2-Methylpropionic acid.....	Br	2-Bromopropane (14%), isopropyl 2-methylpropionate, parent acid (15%)	CS ₂	(86)
	Br	A hypobromite	CCl ₄	(158)
Methacrylic acid.....	Br	A polymer	CCl ₄ , reflux	(50)
Valeric acid.....	Br	1-Bromobutane (31.2%), butyl valerate (7%), parent acid (5%)	CS ₂	(86)
	Br	A bromolactone	CCl ₄ , reflux	(50)
	Br	2-Bromobutane (14%), <i>sec</i> -butyl 2-methylbutyrate	CS ₂	(86)
2-Methylbutyric acid.....	Br	<i>dl</i> -2-Bromobutane (30-60%), parent acid (15-30%)	CCl ₄ or Freon 113, -20° to -40°C.	(26)
(+)-2-Methylbutyric acid.....	Cl	<i>dl</i> -2-Chlorobutane (74%)	C ₆ H ₅ NO ₂	(86)
	Br	1-Bromo-2-methylpropane (10%), parent acid (17%)	CS ₂	(86)
3-Methylbutyric acid.....	Br	1-Bromo-2-methylpropane (not pure), 6-bromo-4,4-dimethyl-2-methylpropane (7-8%), parent acid (not isolated)	CCl ₄ , 25°C.	(26)
	Br	1-Bromo-2-methylpropane (9-10% crude), 6-bromo-4,4-dimethyl-2-methylpropane, parent acid (50%)	CCl ₄ , 0°C., then reflux	(26)
	Br	1-Bromo-2-methylpropane (8%), 6-bromo-4,4-dimethyl-2-methylpropane (12%), parent acid (32%)	CCl ₄ , hot	(26)
2, 2-Dimethylpropionic acid.....	Br	An unidentified compound with a camphorlike odor and an unidentified ester	CS ₂	(86)
	Br	1-Bromopentane (92%), amyl caproate (2.4%), parent acid (5.5%)	CCl ₄ , heat	(142)
Caproic acid.....	Br	1-Bromopentane (67%), some parent acid	CCl ₄ , cold	(26)
	Br	2-Bromopentane (55-65%)	CCl ₄ , 0°C., then reflux	(45)
<i>dl</i> -2-Methylvaleric acid.....	Br	2-Bromopentane, some bromodichloromethane	CH ₂ Cl ₂ , reflux	(45)
4-Methylvaleric acid.....	Br	4-Bromo-2-methylbutane (42%), 3-methylbutyl 4-methylvalerate (trace), parent acid (20%)	CS ₂	(86)
3, 3-Dimethylbutyric acid.....	Br	1-Bromo-2, 2-dimethylpropane (62%), parent acid (18%)	CaH ₂ NO ₂ , 0°C., then heat	(172)

3, 3-Dimethylbutyric acid.....	Br	1-Bromo-2, 2-dimethylpropane (82.9%), 2, 2-dimethylpropyl 3, 3-dimethylbutyrate (3.9%), parent acid (13.2%)	CCl ₄ , heat	(142)
4, 2-Ethylbutyric acid.....	Br	1-Bromo-2, 2-dimethylpropane (53%)	CCl ₄ , cold	(26)
Caprylic acid.....	Br	3-Bromopentane (76%)	CCl ₄ , 0°C., then reflux	(45)
2-Ethylcaproic acid.....	Br	1-Bromoheptane (79%), caprylic acid, dibromoheptane	CCl ₄ , reflux	(44)
(+)-2-Ethylcaproic acid.....	Br	3-Bromoheptane (21%) (inactive)	CCl ₄ , reflux	(22)
(-)-2-Ethylcaproic acid.....	Br	3-Bromoheptane (35%) (inactive)	CCl ₄ , reflux	(13)
(-)-2-Ethylcaproic acid.....	Br	(+)-3-Bromoheptane (35%)	CCl ₄ , -10°C., then reflux	(2)
(+)-3, 7-Dimethylcaprylic acid.....	Br	3-Bromoheptane (29.3%) (inactive)	CCl ₄ , reflux	(13)
Lauric acid.....	Br	4, 2-Bromoheptane (40-60%), parent acid (15-25%)	CCl ₄ , cold	(26)
	Br	(-)-3-Bromoheptane (47%)	CCl ₄ , 0-10°C.	(2)
	Br	(-)-1-Bromo-2, 6-dimethylheptane (55%)	CCl ₄ , reflux	(105)
	Br	1-Bromoundecane (75-80%)	CCl ₄	(96, 99, 100, 102)
	Br	1-Bromoundecane (67%), parent acid (18%)	CCl ₄ , reflux	(127)
	Br	1-Bromoundecane (59-73%)	CCl ₄ , reflux	(132)
	Br	1-Bromoundecane (75-80%)	CHCl ₃	(96, 99, 100, 102)
	Br	1-Bromoundecane (75-80%)	(C ₂ H ₅) ₂ O	(96, 99, 100, 102)
	Br	1-Bromoundecane	CCl ₄	(103)
	Br	1-Bromoundecane	CCl ₄	(128)
	Br	1-Bromoundecane	CCl ₄ , 35-40°C., then 65-70°C.	(14)
	I	1-Iodoundecane (72.5-87.7%)	C ₂ H ₅ , reflux	(143)
	I	1-Iodoundecane (70.2-78%)	CCl ₄ , reflux	(143)
	I	1-Iodoundecane (51.7-65.7%)	Petroleum ether, reflux	(143)
	I	1-Iodoundecane (76% crude), undecyl laurate, parent acid	CCl ₄ , reflux	(133)
2-Dodecanoic acid.....	Br	1-Bromo-1-undecene	CCl ₄	(129)
2-Isoamyl-5-methylcaproic acid.....	Br	5-Bromo-2, 8-dimethylnonane (66%), 2, 8-dimethyl-5-nonyl 2-isomyl-5-methylcaproate (4.1%), parent acid (13.2%)	CCl ₄ , heat	(142)
Myristic acid.....	Br	1-Bromotridecane (65-77%)	CCl ₄ , reflux	(132)
	Br	1-Bromotridecane	CCl ₄ , reflux, N ₂ atmosphere	(8)
	Br	1-Bromotridecane (70% crude)	CCl ₄ , 0°C., then reflux	(48)
	I	1-Iodotridecane (51.5%), tridecyl myristate (27%)	CCl ₄ , reflux	(133)
Pentadecanoic acid.....	Br	1-Bromotetradecane	CCl ₄ , reflux, N ₂ atmosphere	(8)
Palmitic acid.....	Br	1-Bromopentadecane (69-83%)	CCl ₄ , reflux	(132)
	Br	1-Bromopentadecane (68%), pentadecyl palmitate (trace)	CCl ₄ , reflux	(133)
	Br	1-Bromopentadecane (75-80%)	No solvent, 30-50°C.	(96, 99, 100, 102)
	Br	1-Bromopentadecane (93%)	CCl ₄ , reflux, N ₂ atmosphere	(8)
	Br	1-Bromopentadecane (73.5-77.4%)	CCl ₄	(3)
	Br	1-Bromopentadecane (58-60%)	(C ₂ H ₅) ₂ O	(3)

TABLE 1—Continued

Silver Salt of Acid	Halogen	Products and Yields	Conditions	References
<i>Aliphatic monobasic acids (Continued):</i>				
Palmitic acid (Continued)	Br	1-Bromopentadecane (55-63%)	CH ₃ COOC ₂ H ₅	(3)
	Br	1-Bromopentadecane (43-45%)	C ₂ H ₅ Cl	(3)
	Br	1-Bromopentadecane (41-43%)	C ₂ H ₅ CH ₃	(3)
	Br	1-Bromopentadecane (39-42%)	Petroleum naphtha	(3)
	Br	1-Bromopentadecane (37-38%)	CHCl ₃	(3)
	Br	1-Bromopentadecane (3-45%)	C ₂ H ₅ Br	(3)
	Br	1-Bromopentadecane (21-22%)	C ₂ H ₅ Br	(3)
	Br	1-Bromopentadecane (11-13%)	Ligroin	(3)
	Br	1-Bromopentadecane (3.5%)	C ₂ H ₅ Cl	(3)
	Br	1-Bromopentadecane (72.8%)	CCl ₄ , mixture of silver salt and free acid, reflux	(164)
	Br	1-Bromopentadecane (44% crude)	C ₂ H ₅ Br, CH ₃ COOAg, CH ₃ COOH, (CH ₃ CO) ₂ O, HBr, reflux	(164)
	Br	1-Bromopentadecane (89.4%)	CCl ₄ , heat	(142)
	Cl	1-Chloropentadecane (12-18%)	CHCl ₃ , reflux	(133)
	Cl	1-Chloropentadecane (25-31%)	CCl ₄ , room temperature	(133)
	Cl	1-Chloropentadecane (49-55%)	CCl ₄ , reflux	(133)
	Cl	1-Chloropentadecane (25-31%)	CH ₂ ClCH ₂ Cl, reflux	(133)
	Cl	1-Chloropentadecane (24-28%)	—	(3)
	I	1-Iodopentadecane (13-48%), pentadecyl palmitate (24-36%)	CCl ₄ , reflux	(133)
Palmitic acid-1-C ¹⁴	Br	1-Bromopentadecane	CCl ₄ , reflux, N ₂ atmosphere	(126)
Stearic acid	Br	1-Bromoheptadecane (89.4%)	CCl ₄ , reflux	(142)
	Br	1-Bromoheptadecane (61.7%)	CCl ₄ , 0°C., then heat	(17)
	Br	1-Bromoheptadecane (73-86%)	CCl ₄ , reflux	(132)
	Br	1-Bromoheptadecane (84%)	CCl ₄ , reflux	(135)
	Br	1-Bromoheptadecane (64.8%)	C ₂ H ₅ Br, CF ₃ COOH, 0°C., then reflux	(164)
	Br	1-Bromoheptadecane (38.8%)	C ₂ H ₅ Br, CH ₃ COOAg, 0°C., then reflux	(164)
	Cl	1-Chloroheptadecane	No solvent, 100°C.	(95, 99, 100, 102)
	I	1-Iodoheptadecane (60.5%), heptadecyl stearate (23%)	CCl ₄ , reflux	(133)
	I	1-Iodoheptadecane (64.4%)	C ₂ H ₅ Br, reflux	(143)
Stearic acid-1-C ¹⁴	Br	1-Bromoheptadecane	CCl ₄ , reflux, N ₂ atmosphere	(126)
Oleic acid	Br	1-Bromo-8-heptadecene, 1, 8, 9-tribromoheptadecane	CCl ₄	(129)
Behenic acid	Br	1-Bromoheneicosane (65%)	CCl ₄	(173)
3-Methyltetracosanoic acid	Br	1-Bromo-2-methyltricosane (46.7%)	CCl ₄	(43)
3-Methyltetracosanoic acid	Br	<i>dl</i> -1-Bromo-2-methyltricosane	CCl ₄ , reflux	(173)
<i>n</i> (+)-3-Methylheptacosanoic acid	Br	<i>n</i> (+)-1-Bromo-2-methylhexacosane (55%)	CCl ₄ , reflux	(173)

<i>Aliphatic dibasic acids:</i>				
Oxalic acid.....	Br	Carbon dioxide	No solvent	(30, 39)
	I	Carbon dioxide	Quartz	(30, 184)
Malonic acid.....	Br	Carbon dioxide	No solvent	(30)
Maleic acid.....	I	Maleic anhydride	No solvent	(184)
	I	Fumaric acid, maleic anhydride	No solvent, 50-55°C.	(30)
Fumaric acid.....	I	Carbon monoxide, carbon dioxide	No solvent	(184)
	I	Parent acid only	No solvent, 125°C.	(50)
Ethylmalonic acid.....	Br	1,1-Dibromopropane (28%), 1,1,1-tribromopropane (24%)	CCl ₄ , 0°C.	(50)
		1,2-Dibromoethane (37%)	CCl ₄ , 15°C.	(50)
Succinic acid.....	Br	1,2-Dibromoethane (32%)	CCl ₄ , 76°C.	(39)
	Br (also Cl and I)	1,2-Dibromoethane (odor of)	—	
	Br	No dibromide isolated	C ₂ H ₅ Cl ₄ , 135°C.	(50)
	Br	No dibromide isolated, 3-bromopropionic acid (19.6%)	CCl ₄ , heat	(142)
	Br	Succinic anhydride, parent acid	—	(30, 108)
	I	Maleic acid	No solvent, heat	(184)
Methylsuccinic acid.....	Br	1,2-Dibromopropane (12.6%), a monobromo acid (5.1%)	CCl ₄ , heat	(142)
Isoamylsuccinic acid.....	Br	5,6-Dibromo-2-methylhexane (25%)	CCl ₄ , heat	(142)
Glutaric acid.....	Br	1,3-Dibromopropane (3%), butyrolactone (69.4%), parent acid (1.6%)	CCl ₄ , heat	(142)
	I	Butyrolactone (30%)	—	(185b)
2-Methylglutaric acid.....	Br	1,3-Dibromobutane (6.6%), α-methyl-γ-butyrolactone (87%), 4-bromo-2-methylbutyric acid (5.1%)	CCl ₄ , heat	(142)
3,3-Dimethylglutaric acid.....	Br	1,3-Dibromo-2,2-dimethylpropane (9.8%), β,β-dimethyl-γ-butyrolactone (50.6%)	CCl ₄ , heat	(142)
2-Ethylglutaric acid.....	I	γ-Caprolactone	No solvent, heat	(185b)
2,4-Diethylglutaric acid.....	I	α-Ethyl-γ-caprolactone	No solvent, heat	(185b)
2-Isoamylglutaric acid.....	Br	5,7-Dibromo-2-methylheptane (15.8%), α-isoamyl-γ-butyrolactone (60.5%), 4-bromo-2-isoamylbutyric acid (18.6%), parent acid (2.8%)	CCl ₄ , heat	(142)
Adipic acid.....	Br	1,4-Dibromobutane (11%), polymeric δ-valerolactone	CCl ₄	(32)
	Br	1,4-Dibromobutane (21%)	CCl ₄	(127)
	Br	1,4-Dibromobutane (58%)	CCl ₄ , 50°C., then reflux	(167)
	Br	1,4-Dibromobutane (28.7%), ω-bromovaleric acid (4.4%), δ-valerolactone (46.1%)	CCl ₄ , heat	(142)
	I	δ-Valerolactone	Quartz, 90-150°C.	(184)
2-Isoamyladipic acid.....	Br	5,8-Dibromo-2-methyloctane (33.1%), α-isoamyl-δ-valerolactone (30.5%), 5-bromo-2-isoamylvaleric acid (28.6%), parent acid (1.7%)	CCl ₄ , heat	(142)
Pimelic acid.....	Br	1,5-Dibromopentane (44.1%), ω-bromocaproic acid (20.2%), parent acid (1.9%)	CCl ₄ , heat	(142)

TABLE 1—Continued

Silver Salt of Acid	Halogen	Products and Yields	Conditions	References
<i>Aliphatic dibasic acids (Continued):</i>				
Azeleic acid.....	Br	1, 7-Dibromooheptane (82.5%), ω -bromocaprylic acid (6.7%)	CCl ₄ , heat	(142)
Sebacic acid.....	Br	1, 8-Dibromooctane (81.3%), ω -bromopelargonic acid (7.3%)	CCl ₄ , heat	(142)
	Br	1, 8-Dibromooctane (69%)	CCl ₄	(96, 99, 100, 102)
	Br	1, 8-Dibromooctane (66%)	CCl ₄ , heat	(127)
	Br	No dibromide isolated	CCl ₄	(136)
Dodecanedioic acid.....	Br	1, 10-Dibromodecane (60%)	CCl ₄	(96, 99, 100, 102)
Thapsic acid.....	Br	1, 14-Dibromotetradecane (44%)	CCl ₄	(127)
2-Carboxycyclohexanecarboxylic acid.....	I	Hexahydrophthalide (26%)	No solvent	(44, 186)
1, 1-Cyclohexanedi-acetic acid.....	I	Lactone of 1-(hydroxymethyl)cyclohexanecarboxylic acid	No solvent	(186)
4-Methyl-1, 1-cyclohexanedi-acetic acid.....	I	Lactone of 4-methyl-1-(hydroxymethyl)cyclohexanecarboxylic acid	No solvent	(86a)
<i>Aliphatic tribasic acids*:</i>				
1, 2, 4-Butanetricarboxylic acid.....	Br	1, 2, 4-Tribromobutane (4-6%)	CCl ₄ , 76°C.	(50)
<i>Aryl-substituted aliphatic acids:</i>				
Phenylacetic acid.....	Br	Benzyl bromide (53.7%), benzyl phenylacetate (21%), parent acid (14%)	CCl ₄ , heat	(142)
	Br	Benzyl bromide (30%), parent and brominated acids (20-30%), a small amount of an impure ester	CCl ₄ , cold	(86)
<i>p</i> -Nitrophenylacetic acid.....	Br	Benzyl bromide (37.3%), parent and brominated acids	CCl ₄ , reflux	(86)
	Br	<i>p</i> -Nitrobenzyl bromide (85%)	CCl ₄ , reflux	(18)
Mandelic acid.....	Br	Benzaldehyde hydrobromide	(C ₆ H ₅) ₂ O	(88, 96, 99, 100, 102)
	Br	Benzaldehyde (49.1%), α -bromophenylacetic acid (30.5%), parent acid (14.4%)	CCl ₄ , reflux	(141)
	I	Benzaldehyde (60% crude)	C ₆ H ₆ , heat	(184)
<i>dl</i> -2-Phenylpropionic acid.....	Br	<i>dl</i> -1-Phenylethyl bromide, 1-phenylethyl 2-phenylpropionate	CCl ₄ , reflux	(2)
	Br	(+)-1-Phenylethyl bromide	CCl ₄ , reflux	(12)
(+)-2-Phenylpropionic acid.....	Br	1-Phenylethyl 2-phenylpropionate (20-40%), styrene dibromide (small amount), parent acid (30-50%)	CCl ₄ or Freon 113, 48°C.	(25)
2-Phenylpropionic acid.....	Br	1-Phenylethyl 2-phenylpropionate (not isolated), styrene dibromide (20-30%), parent acid (20-50%)	CCl ₄ , reflux	(26)
	Br	2-Phenylethyl bromide (5%)	CCl ₄ , reflux	(18)
3-Phenylpropionic acid.....	Br	2-Phenylethyl bromide (15%), parent and brominated acids (50%)	CCl ₄ , reflux	(86)

* Silver 1, 2, 3, 4-butanetetracarboxylate has been treated with bromine in refluxing carbon tetrachloride, but no detectable amount of tetrabromide was produced (50).

Cinnamic acid.....	Br	β -Bromostyrene	CCl ₄	(129)
cis-Cinnamic acid.....	I	An unsaturated resin, parent acid (36%)	No solvent	(184)
trans-Cinnamic acid.....	Br	trans- β -Bromostyrene (10%), tribromostyrene (28.6%), parent acid (11.7%), a neutral tar	CCl ₄ , room temperature, then reflux	(156)
trans-Cinnamic acid.....	Br	trans- β -Bromostyrene (17.5%), tribromostyrene (35.8%), parent acid (16.2%), a neutral tar	CCl ₄ , room temperature, then reflux	(156)
Phenylpropionic acid.....	I	1-Iodo-2-phenylacetylene (94%), some triiodostyrene	C ₆ H ₆ , reflux	(184)
3-(<i>p</i> -Nitrophenyl)propionic acid.....	Br	2-(<i>p</i> -Nitrophenyl)ethyl bromide (80%)	CCl ₄ , reflux	(18)
Benzylmalonic acid.....	Br	No pure product isolated	CCl ₄ , heat	(142)
(+)-2-Benzylbutyric acid.....	Br	(-)-2-Bromo-1-phenylbutane	CCl ₄ , reflux	(22)
(-)-2-Benzylbutyric acid.....	Br	2-Bromo-1-phenylbutane (inactive)	CCl ₄ , reflux	(22)
3-Methyl-4-phenyl-2-propylbutyric acid.....	Br	3-Bromo-2-methyl-1-phenylhexane (18%) (?)	CCl ₄ or petroleum ether, both at high and low temperatures	(125)
N-Benzoylalanine.....	Br	Acetaldehyde	CCl ₄	(90)
N-Benzoylvaline.....	Br	Benzoyl(1-bromoethyl)amine (40%)	CH ₃ COOH, 45°C., Al ₂ O ₃	(91)
N-Benzoylphenylalanine.....	Br	Valeraldehyde	CCl ₄	(90)
Diphenylacetic acid.....	Br	Benzoyl(1-bromoamyl)amine (28%)	CCl ₄	(91)
Benzilic acid.....	Br	Diphenylmethyl bromide (8%)	CCl ₄ , 25°C.	(86)
Phenylacetic acid.....	I	Benzophenone	(C ₆ H ₅) ₂ O	(88a)
2,3-Diphenylsuccinic acid, (+) and (-).....	I	Benzophenone	C ₆ H ₆ , heat	(184)
Triphenylacetic acid.....	Br	meso-Stilbene dibromide, <i>dl</i> -stilbene dibromide	CCl ₄ , reflux	(22)
Aliphatic acid esters:	Br	Triphenylcarbinol (8%), parent acid (42%)	CCl ₄ , O ₂ atmosphere	(86)
Malonic acid, monoethyl ester.....	Br	Ethyl bromoacetate	CCl ₄	(97)
Succinic acid, monoethyl ester.....	Br	Ethyl ω -bromopropionate (65%)	CCl ₄	(16)
Ethylmalonic acid, monomethyl ester.....	Br	Methyl 2-bromobutyrate	CCl ₄	(97)
Adipic acid, monomethyl ester.....	Br	Methyl ω -bromovalerate (88.5%)	CCl ₄	(97)
	Br	Methyl ω -bromovalerate (88.5%)	CCl ₄ , room temperature	(101)
	Br	Methyl ω -bromovalerate (68-68%)	CCl ₄ , reflux	(4)
	Br	Ethyl ω -bromovalerate (55%)	CCl ₄	(15)
	Br	Ethyl ω -bromovalerate (80%)	CCl ₄ , reflux	(104)
	Br	Ethyl ω -bromovalerate	CCl ₄	(122)
Pimelic acid, monoethyl ester.....	Br	Ethyl ω -bromocaproate	CCl ₄	(122)
Suberic acid, monomethyl ester.....	Br	Methyl ω -bromocanthate (60.8%)	CCl ₄ , room temperature	(101)
Suberic acid, monoethyl ester.....	Br	Ethyl ω -bromocanthate	CCl ₄ , room temperature	(101)
Azelaic acid, monomethyl ester.....	Br	Methyl ω -bromocaprylate (69.7%)	CCl ₄ , room temperature	(21)
Azelaic acid, monoethyl ester.....	Br	Ethyl ω -bromocaprylate (69%)	CCl ₄ , reflux	(120)
Sebacic acid, monomethyl ester.....	Br	Ethyl ω -bromocaprylate (55%)	CCl ₄	(96, 98, 100, 102)
Sebacic acid, monoethyl ester.....	Br	Methyl ω -bromopelargonate (75%)	CCl ₄ , room temperature	(101)
Heptadecanedioic acid, monomethyl ester.....	Br	Ethyl ω -bromopelargonate (50%)	CCl ₄	(15)
	Br	Methyl ω -bromocaprate (71%)	CCl ₄ , room temperature	(101)

TABLE 1—Continued

Silver Salt of Acid	Halogen	Products and Yields	Conditions	References
<i>Aliphatic acid esters (Continued):</i>				
Heptadecanedioic acid, monomethyl ester...	Br	Methyl ω -bromocaproate	CCl ₄	(97)
Di- <i>n</i> -butylmalonic acid, monomethyl ester...	Br	Ethyl 2-bromo-2- <i>n</i> -butylacrylate	CCl ₄ , room temperature	(44)
Brassylic acid, monomethyl ester.....	Br	Methyl ω -bromolaurate (78.4%)	CCl ₄ , room temperature	(101)
	Br	Methyl ω -bromolaurate	CCl ₄	(97)
Tetradecanedioic acid, monomethyl ester..	Br	Methyl ω -bromotridecanoate (71%)	CCl ₄ , room temperature	(101)
Pentadecanedioic acid, monomethyl ester..	Br	Methyl ω -bromomyristate (73.2%)	CCl ₄	(101)
	Br	Methyl ω -bromomyristate	CCl ₄	(97)
Thapsic acid, monomethyl ester.....	Br	Methyl ω -bromopentadecanoate (70.5%)	CCl ₄ , room temperature	(101)
	Br	Methyl ω -bromopentadecanoate (65-75%), parent acid (18-25%)	CCl ₄	(176)
	Br	Methyl ω -bromopentadecanoate (75-85%), parent acid (18-25%)	CCl ₄ =CHCl	(176)
Heptadecanedioic acid, monomethyl ester..	Br	Methyl ω -bromopentadecanoate (85.5%)	CCl ₄	(97)
	Br	Methyl ω -bromopalmitate (70.1%)	CCl ₄	(101)
	Br	Methyl ω -bromopalmitate	CCl ₄	(97)
Octadecanedioic acid, monomethyl ester....	Br	Methyl ω -bromomargarate (75.2%)	CCl ₄	(101)
	Br	Methyl ω -bromomargarate	CCl ₄	(97)
<i>Substituted aliphatic acids:</i>				
Glycolic acid.....	I	Formaldehyde	C ₂ H ₅ OH	(88a)
	I	Formaldehyde	C ₆ H ₆	(184)
3-Bromopropionic acid.....	Br	1,2-Dibromoethane (69%)	CCl ₄ , 0°C.	(50)
	Br	1,2-Dibromoethane (<4%)	CCl ₄ , reflux	(50)
Lactic acid.....	I	Acetaldehyde	C ₂ H ₅ OH	(88a)
	I	Acetaldehyde	C ₆ H ₆	(184)
Glyceric acid.....	I	Formaldehyde	(C ₂ H ₅) ₂ O	(88a)
2-Bromovaleric acid.....	Br	1,1-Dibromobutane (52%)	CCl ₄ , 0°C.	(50)
Malic acid.....	I	Carbon monoxide, carbon dioxide	—	(31)
Tartaric acid.....	I	Carbon monoxide, carbon dioxide	—	(31)
	I	Carbon dioxide	Quartz, 165-170°C.	(184)
2-Hydroxy-2-methylpropionic acid.....	I	Acetone	(C ₂ H ₅) ₂ O	(88a)
2-Hydroxypalmitic acid.....	Br	Pentadecanal hydrobromide	No solvent, 30-50°C.	(96, 99, 100)
2-Bromostearic acid.....	Br	1,1-Dibromohexadecane (71-77%)	CCl ₄ , low temperature	(96, 99, 100, 102)
9,10-Dichlorostearic acid.....	Br	1-Bromo-8,9-dichloro-heptadecane (77%)	CCl ₄	(96, 99, 100, 102)
9,10-Dibromostearic acid.....	Br	1-Bromo-8-heptadecene	CCl ₄ , below 0°C.	(129)
9,10,12,13-Tetrabromostearic acid.....	Br	1,8,9,11,12-Pentabromohexadecane (71.3%), parent acid (20.2%), 8,9,11,12-tetrabromohexadecyl 9,10,12,13-tetrabromostearate	CCl ₄ , reflux	(94, 95)
	Br	1,8,9,11,12-Pentabromohexadecane (88%)	C ₂ H ₅ Br, CH ₃ COOAg	(24)

<i>erythro</i> -9, 10-Diacetoxystearic acid.....	Br	1-Bromo-8, 9-diacetoxystearic acid	CCl ₄ , CH ₂ Cl ₂ , CH ₃ COOAg, reflux	(23)
Pyruvic acid.....	Br	Acetyl bromide	CCl ₄ , cold	(96, 99, 100, 102)
ω -Propionylphenanthic acid.....	Br	9-Bromo-3-nonanone, a monobrominated acid, parent acid	CCl ₄ , heat	(142)
ω -Acetylbelargonic acid.....	Br	10-Bromo-2-decanone (39.8%), a monobromo acid (4.8%), parent acid (50.7%)	CCl ₄ , heat	(142)
Cyclopentanecarboxylic acid.....	Br	Cyclopentylbromomethane (67-93%)	CCl ₄	(98)
1-Methylcyclohexanecarboxylic acid.....	Br	1-Bromomethyl-1-methylcyclohexane (94%)	C ₂ H ₅ Br, CH ₃ COOAg, reflux	(145)
1-Carbomethoxycyclohexanecarboxylic acid.....	Br	1-Bromomethyl-1-carbomethoxycyclohexane (60%)	C ₂ H ₅ Br, CH ₃ COOAg, reflux	(145)
Cholanic acid.....	Br	23-Bromonorcholane (96.5% crude)	CH ₃ COOAg, C ₂ H ₅ Br, reflux	(25)
3 α -Acetoxycholanic acid.....	Br	3 α -Acetoxy-23-bromonorcholane	CH ₃ COOAg, C ₂ H ₅ Br, reflux	(25)
3 α , 7 α -Diacetoxycholanic acid.....	Br	3 α , 7 α -Diacetoxy-23-bromonorcholane	CH ₃ COOAg, C ₂ H ₅ Br, reflux	(25)
3 α , 12 α -Diacetoxycholanic acid.....	Br	3 α , 12 α -Diacetoxy-23-bromonorcholane	CH ₃ COOAg, C ₂ H ₅ Br, reflux	(25)
3 α , 12 β -Diacetoxycholanic acid.....	Br	3 α , 12 β -Diacetoxy-23-bromonorcholane (28%)	CCl ₄ , reflux	(36)
3 α , 7 α , 12 α -Triacetoxycholanic acid.....	Br	3 α , 7 α , 12 α -Triacetoxy-23-bromonorcholane	CH ₃ COOAg, C ₂ H ₅ Br, reflux	(25)
Nordesoxycholic acid diacetate.....	Br	unidentified compounds	C ₂ H ₅ Br, CH ₃ COOAg	(163)
Bisnordesoxycholic acid diacetate.....	Br	3 α , 12 β -Diacetoxy-22-bromobisnorcholane (40%)	CCl ₄ , reflux	(36)
3 α -Acetoxy-12-ketocholanic acid.....	Br	3 α , 12 β -Diacetoxy-20 α -bromopregnane, 3 α , 12 β -diacetoxy-20 β -bromopregnane	CCl ₄ , reflux	(36)
Aliphatic fluoro acids:				
Fluoroacetic acid.....	Br	3 α -Acetoxy-12-keto-23-bromonorcholane (60%)	CCl ₄ , reflux	(36)
Bromofluoroacetic acid.....	Br	Bromofluoromethane	No solvent, heat	(92)
Chlorofluoroacetic acid.....	Br	Bromofluoromethane (62%)	No solvent, sealed tube, 50-120°C.	(74)
	Br	Bromofluoromethane	No solvent, or with CCl ₄ or CS ₂	(51)
	Cl	Chlorofluoromethane (52%)	No solvent, sealed tube, 50-120°C.	(74)
	I	Fluoriodomethane (55%)	No solvent, sealed tube, 50-120°C.	(74)
	Br	Dibromofluoromethane (64%)	No solvent, sealed tube, 100°C.	(74)
	Cl	Chlorobromofluoromethane (67%)	No solvent, sealed tube, 40°C.	(74)
	I	Bromofluoriodomethane (19%)	No solvent, heated at 1 mm.	(74)
	Br	Bromochlorofluoromethane (67%)	No solvent, sealed tube, 50-120°C.	(74)
	Cl	Dichlorofluoromethane (73%)	No solvent, sealed tube, 50-120°C.	(74)
	I	Chlorofluoriodomethane (35%)	No solvent, 150-260°C.	(74)
	I	Fluorodichloromethane (18%)	No solvent, heated at 1 mm.	(74)
	Br	Bromodifluoromethane (88%)	No solvent, 50-100°C.	(74)
	Br	Bromodifluoromethane (93%)	No solvent, heated in autoclave	(74)
	Br	Bromodifluoromethane	No solvent, or with CCl ₄ or CS ₂	(51)
	Cl	Chlorodifluoromethane (91%)	No solvent, sealed tube, 50°C.	(74)
	Cl	Chlorodifluoromethane (87%)	No solvent, heated at atmospheric pressure	(74)
	I	Difluoriodomethane (93%)	No solvent, heated at 150°C.	(74)

TABLE 1—Continued

Silver Salt of Acid	Halogen	Products and Yields	Conditions	References
<i>Aliphatic fluoro acids (Continued):</i>				
Bromo-chlorofluoroacetic acid.....	Br Cl	Dibromo-chlorofluoromethane (71%) Bromo-dichlorofluoromethane (83%)	No solvent No solvent	(74) (74)
Dibromo-fluoroacetic acid.....	Br	Tribromo-fluoromethane	No solvent, or with CCl ₄ or CS ₂	(51)
Dichloro-fluoroacetic acid.....	Br Cl	Bromo-dichlorofluoromethane (58%) Trichloro-fluoromethane (63%)	No solvent No solvent	(74) (74)
	I	Dichloro-fluoroiodomethane (10%)	No solvent	(74)
Bromo-difluoroacetic acid.....	Br	Dibromo-difluoromethane (81%)	No solvent	(74)
	I	Bromo-difluoroiodomethane (15%) (not definitely identified)	No solvent, or with CCl ₄ or CS ₂	(61)
	I		No solvent	(74)
Chloro-difluoroacetic acid.....	Br	Bromo-chlorodifluoromethane (91%)	No solvent, sealed bomb, 50°C.	(74)
	Br	Bromo-chlorodifluoromethane	No solvent, or with CCl ₄ or CS ₂	(51)
	Cl	Dichloro-difluoromethane (88%)	No solvent, sealed bomb, 50°C.	(74)
	I	Chloro-difluoroiodomethane (78%)	No solvent, heated at 10 min.	(74)
Trifluoroacetic acid.....	Br	Bromo-trifluoromethane (88%)	No solvent, sealed tube, room temperature and then 50°C.	(73)
	Br	Bromo-trifluoromethane (98%)	No solvent, 65–58°C.	(82)
	Br	Bromo-trifluoromethane (21–39%)	No solvent, sealed tube, heat	(65)
	Br	Bromo-trifluoromethane	No solvent, or with CCl ₄ or CS ₂	(51)
	Cl	Chloro-trifluoromethane (90%)	No solvent, sealed tube, room temperature	(73)
	Cl	Chloro-trifluoromethane (88%)	No solvent, room temperature	(82)
	I	Trifluoroiodomethane (89–94%)	No solvent, heat	(73)
	I	Trifluoroiodomethane (95%)	No solvent, 120°C.	(80)
	I	Trifluoroiodomethane	No solvent, 120°C.	(55)
	I	Trifluoroiodomethane (80–87%)	No solvent, 100°C.	(87)
	I	Trifluoroiodomethane	No solvent, sand, 110–150°C.	(171)
	I	Trifluoroiodomethane	No solvent	(79)
	I	Trifluoroiodomethane (71–78%)	No solvent, 140–160°C., 400–500 mm.	(53)
	I	Trifluoroiodomethane (74–90%)	No solvent, 150–160°C., atmospheric pressure	(53)
	I	<i>p</i> -Chloroiodobenzene, parent acid	C ₆ H ₅ Cl, reflux	(80)
	I	Iodobenzene	C ₆ H ₅	(168)
	Br	1-Bromopentadecane (94% crude)	CCl ₄ , palmitic acid, reflux	(164)
2,2-Difluoropropionic acid.....	Br	1-Bromo-1,1-difluoroethane	No solvent, or with CCl ₄ or CS ₂	(51)
3,3-Trifluoropropionic acid.....	Br	1-Bromo-2,2,2-trifluoroethane	No solvent, or with CCl ₄ or CS ₂	(51)
Pentafluoropropionic acid.....	Br	Bromopentafluoroethane (98.9%)	No solvent, 63–70°C.	(82)
	Br	Bromopentafluoroethane (98%)	No solvent	(74)

Pentafluoropropionic acid	Br	Bromopentafluoroethane	No solvent, or with CCl ₄ or CS ₂	(51)
	Cl	Chloropentafluoroethane (35%)	No solvent, sealed tube, room temperature	(82)
	Cl	Chloropentafluoroethane (94%)	No solvent	(74)
	I	Pentafluoroiodoethane (85.8%)	No solvent, 100°C.	(80)
	I	Pentafluoroiodoethane (94%)	No solvent	(74)
	I	Pentafluoroiodoethane	No solvent, heat	(77)
	I	Pentafluoroiodoethane		(171)
2,2,3,4,4,4-Hexafluorobutyric acid	Br	1-Bromo-1,1,2,3,3,3-hexafluoropropane (29%)	No solvent, room temperature	(118)
Heptafluorobutyric acid	Br	1-Bromoheptafluoropropane (95.8%)	No solvent, 50-75°C.	(82)
	Br	1-Bromoheptafluoropropane (97%)	No solvent	(74)
	Br	1-Bromoheptafluoropropane	No solvent, or with CCl ₄ or CS ₂	(51)
	Br	1-Bromoheptafluoropropane	No solvent, 130-150°C., atmospheric pressure	(53)
	Cl	1-Chloroheptafluoropropane (71%)	No solvent, heat	(82)
	Cl	1-Chloroheptafluoropropane (79%)	No solvent, 100°C.	(79)
	Cl	1-Chloroheptafluoropropane (91%)	No solvent	(74)
	I	Heptafluoro-1-iodopropane (86.7-93%)	No solvent, 100°C.	(80)
	I	Heptafluoro-1-iodopropane (90%)	No solvent	(74)
	I	Heptafluoro-1-iodopropane	No solvent, sand, 110-180°C.	(171)
	I	Heptafluoro-1-iodopropane (87-93%)	No solvent, 140-160°C., 400-500 mm.	(53)
	I	Heptafluoro-1-iodopropane (94-95%)	No solvent, 130-160°C., atmospheric pressure	(53)
Heptafluoro-4-pentenoic acid	I	Heptafluoro-4-iodo-1-butene	No solvent, 300 mm., heat	(75)
Heptafluoro-2-pentenoic acid	Cl	1,2,4-Trichloroheptafluorobutane (68%)	No solvent, sealed tube, 100°C.	(75)
	I	Heptafluoro-4-iodo-1-butene (72%)	No solvent	(75)
Nonafluorovaleric acid	Br	1-Bromononafluorobutane (95%)	No solvent	(74)
	Br	1-Bromononafluorobutane	No solvent, or with CCl ₄ or CS ₂	(51)
	Cl	1-Chlorononafluorobutane (89%)	No solvent	(74)
	I	Nonafluoro-1-iodobutane (89%)	No solvent	(74)
Hendecafluorocaproic acid	Br	1-Bromohendecafluoropentane (82.5%)	No solvent, 90°C.	(81)
	Br	1-Bromohendecafluoropentane (91%)	No solvent	(74)
	Br	1-Bromohendecafluoropentane	No solvent, or with CCl ₄ or CS ₂	(51)
	Cl	1-Chlorohendecafluoropentane (71.2%)	No solvent, 100°C.	(81)
	Cl	1-Chlorohendecafluoropentane (85%)	No solvent	(74)
	I	Hendecafluoro-1-iodopentane (73.9%)	No solvent, 100°C.	(81)
	I	Hendecafluoro-1-iodopentane (89%)	No solvent	(74)
	I	Hendecafluoro-1-iodopentane	No solvent	(171)
Tridecafluorooctanoic acid	Br	1-Bromotridecafluorohexane (90%)	No solvent	(74)
	Cl	1-Chlorotridecafluorohexane (83%)	No solvent, or with CCl ₄ or CS ₂	(51)
	I	Tridecafluoro-1-iodohexane (90%)	No solvent	(74)

TABLE 1—Continued

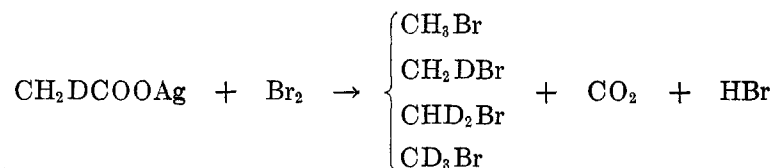
Silver Salt of Acid	Halogen	Products and Yields	Conditions	References
<i>Aliphatic fluoro acids (Continued):</i>				
Pentadecafluorocaprylic acid	Br	1-Bromopentadecafluoroheptane (86%)	No solvent	(74)
	Br	1-Bromopentadecafluoroheptane	No solvent, or with CCl ₄ or CS ₂	(51)
	Cl	1-Chloropentadecafluoroheptane (80%)	No solvent	(74)
	I	Pentadecafluoro-1-iodoheptane (85%)	No solvent	(74)
	I	Pentadecafluoro-1-iodoheptane		(171)
Heptafluoropropylargonic acid	Br	1-Bromohexadecafluorooctane	No solvent, or with CCl ₄ or CS ₂	(51)
Nonadecafluorocapric acid	Br	1-Bromononadecafluorononane	No solvent, or with CCl ₄ or CS ₂	(51)
Henicosadecahydrodecanoic acid	Br	1-Bromohenticosadecanodecane	No solvent, or with CCl ₄ or CS ₂	(51)
Tetrafluorosuccinic acid	Br	1,2-Dibromotetrafluoroethane	No solvent, or with CCl ₄ or CS ₂	(51)
Hexafluoroglutaric acid	Br	1,3-Dibromohexafluoropropane (80.3%)	No solvent, 80–90°C.	(83)
	Br	1,3-Dibromohexafluoropropane	No solvent, or with CCl ₄ or CS ₂	(51)
	Cl	1,3-Dichlorohexafluoropropane (64.5%)	No solvent, 100°C.	(83)
	I	Hexafluoro-1,3-diiodopropane (18.2%), perfluoro-γ-butyrolactone (53%)	No solvent, 120°C.	(80)
	I	Hexafluoro-1,3-diiodopropane (10–18.2%), perfluoro-γ-butyrolactone (44–56%)		(84)
Octafluoroadipic acid	Br	1,4-Dibromooctafluorobutane	No solvent, or with CCl ₄ or CS ₂	(51)
	I	Octafluoro-1,4-diiodobutane (64.2%)	No solvent, 120°C.	(84)
2,2-Difluoroacetoacetic acid	Br	1-Bromo-1,1-difluoroacetone	No solvent, or with CCl ₄ or CS ₂	(51)
4,4,4-Trifluoroacetoacetic acid	Br	1-Bromo-3,3,3-trifluoroacetone	No solvent, or with CCl ₄ or CS ₂	(51)
Tetrafluorosuccinic acid, monomethyl ester	Br	Methyl 3-bromotetrafluoropropionate	No solvent, or with CCl ₄ or CS ₂	(51)
Octafluoroadipic acid, monoethyl ester	Br	Ethyl 5-bromooctafluorovalerate	No solvent, or with CCl ₄ or CS ₂	(51)
2,2-Difluorohydracrylic acid	Br	2-Bromo-2,2-difluoroethanol	No solvent, or with CCl ₄ or CS ₂	(51)
3-Amino-2,2-difluoropropionic acid	Br	2-Bromo-2,2-difluoroethylamine	No solvent, or with CCl ₄ or CS ₂	(51)
3-Methoxy-2,2-difluoropropionic acid	Br	Methyl 2-bromo-2,2-difluoroethyl ether	No solvent, or with CCl ₄ or CS ₂	(51)
2,2-Difluoromalonaldelydic acid	Br	2-Bromo-2,2-difluoroacetaldehyde	No solvent, or with CCl ₄ or CS ₂	(51)
3-Nitro-2,2-difluoropropionic acid	Br	1-Bromo-1,1-difluoro-2-nitroethane	No solvent, or with CCl ₄ or CS ₂	(51)
<i>Deuterium-substituted aliphatic acids:</i>				
Acetic-2-d ₁ acid	Br	Methyl-d ₁ bromide, 5% of product indicated as methyl bromide	CCl ₄	(7)
	Br	Methyl bromide, methyl-d ₁ bromide, methyl-d ₂ bromide, methyl-d ₃ bromide	CCl ₄ , reflux	(117)
Acetic-2-d ₂ acid	Br	Methyl-d ₂ bromide	No solvent, sealed tube	(138)
	Br	Methyl-d ₃ bromide (81.7%)	No solvent, sealed tube	(140)
Propionic-2-d ₂ acid	Br	Methyl-d ₃ bromide (25%)	CCl ₄	(139)
Propionic-3-d ₂ acid	Br	Ethyl-1-d ₂ bromide	No solvent, sealed tube	(138)
	Br	Ethyl-2-d ₃ bromide	No solvent, sealed tube	(138)

Salt of Acid	Cation	Halogen	Products and Yields	Conditions	Reference
<i>Salts of aliphatic acids other than silver salts:</i>					
Acetic acid.....	K	Br	Bromomethane	No solvent, sealed tube, heat	(49)
Glycine.....	Hg(II)	Br	Formaldehyde (60-80%)	CS ₂	(96, 99, 100, 102)
Enanthic acid.....	Tl(I)	Br	1-Bromohexane (100%)	CCl ₄	(96, 99, 100, 102)
Caprylic acid.....	Tl(I)	Cl	1-Chlorohexane (100%)	CCl ₄	(96, 99, 100, 102)
	K	Br	1-Bromoheptane (44.5%), n-heptyl caprylate (11%), parent acid (18%)	CCl ₄ , room temperature	(101)
	Hg(I)	Br	1-Bromoheptane (54-61%)	CCl ₄ , 60-80°C.	(96, 99, 100, 102)
	Hg(II)	Br	1-Bromoheptane (75.5%), caprylic acid (10%)	CS ₂ , reflux	(101)
	Hg(II)	Br	1-Bromoheptane (75.5%)	CS ₂	(96, 99, 100, 102)
Lauric acid.....	K	Br	1-Bromohendecane	CCl ₄	(103)
	K	Br	1-Bromohendecane	CCl ₄ CCl ₄	(103)
	Hg(I)	Br	1-Bromohendecane	CCl ₄	(103)
	Hg(II)	Br	1-Bromohendecane	CCl ₄	(103)
	Zn	Br	1-Bromohendecane	CCl ₄	(128)
	Cd	Br	1-Bromohendecane	CCl ₄	(128)
	Pb(II)	Br	1-Bromohendecane	CCl ₄	(103)
Palmitic acid.....	Ca	Br	1-Bromopentadecane (6-7%)	CCl ₄	(3)
	Hg(II)	Br	1-Bromopentadecane (60-70%)	CCl ₄	(96, 99, 100, 102)
	Hg(II)	Br	1-Bromopentadecane (84%), parent acid	CCl ₄ , reflux	(133)
	Hg(II)	I	1-Iodopentadecane (12-35%), pentadecyl palmitate (15-35%), parent acid	CCl ₄ , reflux	(133)
	Pb(II)	Br	1-Bromopentadecane (83%), parent acid	CCl ₄ , reflux	(133)
Malonic acid, monoethyl ester.....	K	Br	Ethyl 2-bromoacetate (23%), ethyl dibromoacetate (20%)	CCl ₄ , 0°C.	(59)
Succinic acid, monoethyl ester.....	K	Br	Ethyl α-bromopropionate	CCl ₄	(15)
	Cu(II)	Br	Ethyl α-bromopropionate	CCl ₄	(15)
	Hg(II)	Br	Ethyl α-bromopropionate	CCl ₄	(15)
	Pb(II)	Br	Ethyl α-bromopropionate	CCl ₄	(15)
Adipic acid, monoethyl ester.....	K	Br	Ethyl α-bromovalerate	CCl ₄	(15)
	Cu(II)	Br	Ethyl α-bromovalerate	CCl ₄	(15)
	Hg(II)	Br	Ethyl α-bromovalerate	CCl ₄	(15)
	Pb(II)	Br	Ethyl α-bromovalerate	CCl ₄	(15)
Sebacic acid, monoethyl ester.....	K	Br	Ethyl α-bromopelargonate	CCl ₄	(15)
	Cu(II)	Br	Ethyl α-bromopelargonate	CCl ₄	(15)
	Hg(II)	Br	Ethyl α-bromopelargonate	CCl ₄	(15)
	Pb(II)	Br	Ethyl α-bromopelargonate	CCl ₄	(15)
Ethylmalonic acid, monoethyl ester.....	K	Br	Ethyl 2-bromobutyrate (36%)	CCl ₄ , 0°C.	(59)
	K	Cl	Ethyl 2-chlorobutyrate (41%)	CCl ₄ , 0°C., then reflux	(42)
	K	I	Ethyl 2-iodobutyrate	CaH ₂ , reflux	(42)

TABLE 1—*Concluded*

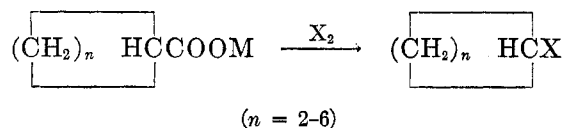
Salt of Acid	Cation	Halogen	Products and Yields	Conditions	Reference
<i>Salts of aliphatic acids other than silver salts (Continued):</i>					
Isopropylmalonic acid, monoethyl ester.....	K	Br	Ethyl 2-bromoisovalerate (30%)	CCl ₄ , 0°C.	(50)
Butylmalonic acid, monoethyl ester.....	K	Br	Ethyl 2-bromocaproate (67%)	CCl ₄ , 0°C.	(50)
	K	Br	Ethyl 2-bromocaproate (67%)	CCl ₄ , 0°C., then reflux	(42)
	K	Cl	Ethyl 2-chlorocaproate (52%)	CCl ₄ , 0°C., then reflux	(42)
	K	I	Ethyl 2-iodocaproate (30%)	C ₆ H ₆ , reflux	(42)
	K	Cl	Ethyl 2-chlorocaprylate (54%)	CCl ₄ , 0°C., then reflux	(42)
Hexylmalonic acid, monoethyl ester.....	K	Br	Ethyl 2-bromo-2-cyclohexylacetate (45%)	CCl ₄ , 0°C.	(50)
Cyclohexylmalonic acid, monoethyl ester.....	K	Br	Ethyl 2-bromo-3-phenylpropionate (80%)	CCl ₄ , 0°C.	(50)
Benzylmalonic acid, monoethyl ester.....	K	Cl	Ethyl 2-chlorocaproate (20%)	CCl ₄ , 0°C., then reflux	(42)
Octylmalonic acid, monoethyl ester.....	K	Br	Ethyl 2-bromolaurate (11%)	CCl ₄	(42)
Decylmalonic acid, monoethyl ester.....	K	Cl	Ethyl 2-chlorolaurate (10%)	CCl ₄ , 0°C., then reflux	(42)
	Na	I	Trifluoroiodomethane (61%)	No solvent, steel autoclave, 280°C.	(73)
	Na	I	Trifluoroiodomethane	No solvent	(71)
	Na	I	Trifluoroiodomethane (58%)	No solvent, sealed tube, heat	(73)
	K	I	Trifluoroiodomethane (40%)	No solvent, heated at atmospheric pressure	(73)
	K	I	Trifluoroiodomethane	No solvent	(71)
	K	I	Trifluoroiodomethane (55%)	No solvent, steel autoclave, 280°C.	(73)
	Hg(II)	I	Trifluoroiodomethane (35%)	No solvent, steel autoclave, 280°C.	(73)
	Hg(II)	I	Trifluoroiodomethane (74% crude)	No solvent, sealed tube, heat	(65)
	Pb(II)	I	Trifluoroiodomethane (26%)	No solvent, steel autoclave, 250°C.	(73)
	Pb(II)	I	Trifluoroiodomethane	No solvent	(71)
Pentafluoropropionic acid.....	Na	Br	1-Bromopentafluoroethane (8%), 1,2-dibromotetrafluoroethane (43%)	No solvent, autoclave, 260°C.	(74)
	Na	I	Pentafluoro-1-iodoethane (7%), tetrafluoro-1,2-diiodoethane (35%), perfluorocyclobutane (13%)	No solvent, autoclave, 260°C.	(74)
Heptafluorobutyric acid.....	Na	Br	1-Bromheptafluoropropane (18%), 1,2-dibromohexafluoropropane (27%)	No solvent	(74)
	Na	Br	1-Bromheptafluoropropane (32%), 1,2-dibromohexafluoropropane (34%)	No solvent, autoclave, 260°C.	(74)
	Na	I	Heptafluoro-1-iodopropane (9%), hexafluoropropylene (41%)	No solvent	(74)
	Na	I	Heptafluoro-1-iodopropane (5%), hexafluoropropylene (37%)	No solvent, autoclave, 250°C.	(74)

reaction was a mixture of methyl bromide, methyl- d_1 bromide, methyl- d_2 bromide, and methyl- d_3 bromide.



B. Alicyclic halides (table 2)

Salts of the cycloalkanecarboxylic acids from cyclopropanecarboxylic acid through cycloheptanecarboxylic acid have been degraded by the Hunsdiecker reaction.



Roberts and Chambers (159) found that in dichlorodifluoromethane, silver cyclopropanecarboxylate could be converted to bromocyclopropane in better than 50 per cent yield. The use of *sym*-tetrachloroethane as solvent resulted in a marked decrease in yield.

A number of studies have been made of the preparation of bromocyclobutane by the Hunsdiecker reaction.

Initially this compound was prepared (98) from the mercuric salt of cyclobutanecarboxylic acid with carbon disulfide as the solvent.

Subsequently three reports appeared in each of which the silver salt was indicated as the starting material (37, 47, 160). While either dichlorodifluoromethane or carbon tetrachloride proved satisfactory as a solvent, a low reaction temperature (-25°C . to -30°C .) appeared necessary regardless. A higher temperature favored ring substitution and cleavage and formation of the so-called "Simonini ester" (see Section V).

The bromination of the silver salts of cyclopentanecarboxylic acid (98), cyclohexanecarboxylic acid (98, 142), and cycloheptanecarboxylic acid (98) has given good yields of bromocycloalkane in each case.

What appears to be the sole reported instance of the chlorination of a salt of a cycloalkanecarboxylic acid is the preparation of chlorocyclohexane in 70 per cent yield (98).

Silver undecafluorocyclohexanecarboxylate has been converted to the monoiodo and monobromo cyclic fluorocarbons in good yield (35, 171). Details of the preparation of the corresponding chloro compound (72) have not been published. For these Hunsdiecker reactions in the fluorocarbon series the recommended solvent is heptacosafuorotributylamine.

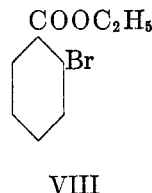
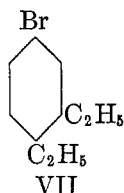
Substituted cyclohexanecarboxylic acids have also been degraded to the corresponding bromocyclohexanes.

Prelog and Zalan (148) prepared 1-bromo-*cis*-3,4-diethylcyclohexane (VII),

TABLE 2
Alicyclic halides prepared by the Hunsdiecker reaction

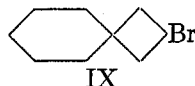
Carboxylic Acid Salt	Halogen	Products and Yields	Conditions	References
Silver cyclopropanecarboxylate.....	Br	Bromocyclopropane (15-20% crude)	<i>sym</i> -C ₆ H ₅ Cl ₄ , -20 to -25°C.	(158)
Mercuric cyclobutanecarboxylate.....	Br	Bromocyclopropane (52-62%)	CF ₃ Cl, -30°C.	(159)
Silver cyclobutanecarboxylate.....	Br	Bromocyclobutane (45.8%)	CS ₂ , room temperature	(98)
	Br	Bromocyclobutane (57%)	CF ₃ Cl	(160)
	Br	Bromocyclobutane (44%), 1,2,4-tribromobutane (10%), cyclobutyl cyclobutanecarboxylate (6%)	CCl ₄ , 10-12°C.	(37)
	Br	Bromocyclobutane (83%), cyclobutyl cyclobutanecarboxylate (16%), tribromobutane (5.7%), cyclobutyl 1-bromocyclobutanecarboxylate (?)	CCl ₄ , -25°C.	(47)
Silver cyclopentanecarboxylate.....	Br	Bromocyclopentane (73-80%)	CHCl ₃	(98)
Silver cyclohexanecarboxylate.....	Br	Bromocyclohexane (73-80%)	CCl ₄ , room temperature	(98)
	Br	Bromocyclohexane (57.5%), cyclohexyl cyclohexanecarboxylate (6.4%), cyclohexanecarboxylic acid (13.2%)	CCl ₄ , reflux	(142)
	Cl	Chlorocyclohexane (70%)	CCl ₄	(98)
Silver cycloheptanecarboxylate.....	Br	Bromocycloheptane (80%)	CCl ₄	(98)
Silver undecafluorocyclohexanecarboxylate.....	Br	Bromoundecafluorocyclohexane (54%)	(C ₂ F ₅) ₂ N, 60-70°C.	(35)
	I	Iodoundecafluorocyclohexane (63%)	(C ₂ F ₅) ₂ N, up to 170°C.	(35)
Silver <i>cis</i> -3,4-diethylcyclohexane-1-carboxylate.....	Br	1-Bromo- <i>cis</i> -3,4-diethylcyclohexane (37.8%)	CCl ₄ , reflux	(148)
Silver ethyl cyclohexane-1,2-dicarboxylate.....	Br	Ethyl 2-bromocyclohexane-1-carboxylate (68.1-72.3%)	CCl ₄ , room temperature	(98)
Silver 2,3-dimethyl-2,3-dicarboethoxycyclohexane-1,4-dicarboxylate.....	Br	1-Hydroxy-2,3-dimethyl-2-carboethoxy-4-bromocyclohexane-3-carboxylic acid- γ -lactone, 2,3-dimethyl-2,3-dicarboethoxy-4-bromocyclohexane-1-carboxylic acid, 2,3-dimethyl-2(?)-carboethoxy-1-hydroxycyclohexane-3,4-dicarboxylic acid- γ -lactone	CCl ₄ , reflux	(189, 190)
Silver spiro[3.5]nonane-2-carboxylate.....	Br	2-Bromospiro[3.5]nonane (80%)	CCl ₄ , 0°C., then reflux	(38)
Silver apocamphane-1-carboxylate.....	Br	1-Bromosapocamphane (50%)	Petroleum ether (b.p. 30-60°C.), -10°C., then reflux	(185)
Silver camphane-4-carboxylate.....	Br	4-Bromocamphane (54%), camphane-4-carboxylic acid	CCl ₄ , reflux	(124)
Silver norcamphane-1-carboxylate.....	Br	1-Bromonorcamphane (57%)	CCl ₄ , room temperature, then reflux	(182)
Silver norcamphane-2-carboxylate.....	Br	2-Bromonorcamphane (55%)	CCl ₄ , 0°C.	(131)
Silver bicyclo[2.2.2]octane-1-carboxylate.....	Br	1-Bromobicyclo[2.2.2]octane (66%)	CCl ₄ , room temperature, then reflux in dark	(166)
Silver bicyclo[2.2.2]octane-2-carboxylate.....	Br	2-Bromobicyclo[1.2.3]octane	CCl ₄	(60)
	Br	2-Bromobicyclo[2.2.2]octane	CCl ₄ , -10°C.	(131)
		2-Bromobicyclo[1.2.3]octane (78% of mixture of the two)	CF ₃ Cl	(161)
Silver ethyl bicyclo[2.2.2]octane-1,4-dicarboxylate.....	Br	Ethyl 4-bromobicyclo[2.2.2]octane-1-carboxylate (55%)	CCl ₄ , room temperature, then 50°C.	(52)
Silver bicyclo[3.3.1]nonane-1-carboxylate.....	Br	1-Bromobicyclo[3.3.1]nonane (74%)	CCl ₄ , reflux	(147)
Silver adamantane-1,3-dicarboxylate.....	Br	1,3-Dibromoadamantane (28%)	CCl ₄ , heat	(115)
Silver 3- β -acetoxyethylcholestanate.....	Br	3- β -Acetoxyandrostan-1 bromide, 3- β -acetoxyethylcholestanic acid		
	Br	3- β -Acetoxyandrostan-1 bromide, more highly brominated compounds	C ₂ H ₅ Br, CH ₃ COOAg, reflux	(163)

and a patent of Hunsdiecker, Hunsdiecker, and Vogt (98) reported the preparation of ethyl 2-bromocyclohexane-1-carboxylate (VIII).

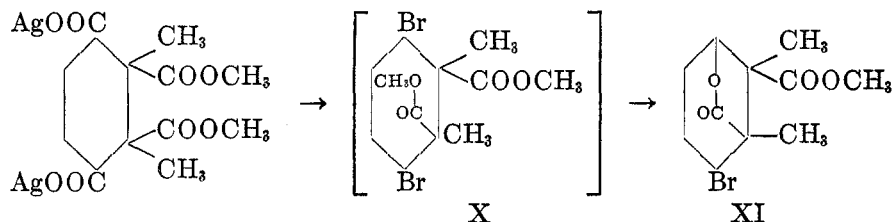


Two fractions of technical naphthenic acids have been converted to the silver salts and then subjected to the action of bromine in carbon tetrachloride (98). In each case the bromides obtained included polysubstituted compounds in addition to the normal Hunsdiecker product.

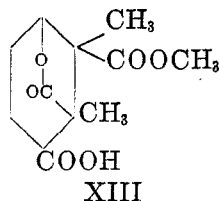
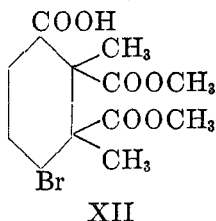
There is one example of a Hunsdiecker reaction in the spirane series. En route to spiro[3.5]nonane, 2-bromospiro[3.5]nonane (IX) was prepared (38) from silver spiro[3.5]nonane-2-carboxylate.



The earliest use of the Hunsdiecker reaction in the preparation of halogenated alicyclic compounds was in the synthesis (189, 190) of an intermediate in the cantharidin-seeking series of reactions. The anticipated dibromide (X) was not



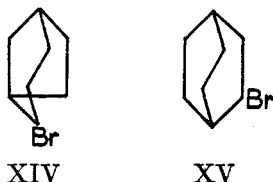
isolated, but instead a monobromolactone (XI) was found. Presumably the dibromide was formed initially, and then underwent lactonization through displacement of bromine.



The two other products (XII and XIII) obtained from this reaction are those to be expected from Hunsdiecker reactions at the other possible sites.

It is in the replacement of a bridgehead carboxyl group by halogen that the Hunsdiecker reaction has proven to be most valuable in the alicyclic series. A recent review (9) has mentioned the early work (52, 124, 147, 161, 166, 182, 185) in the preparation of bridgehead bromides by this means.

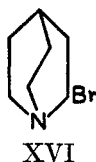
Of theoretical interest is the report (60) that the silver salt of bicyclo[2.2.2]octane-2-carboxylic acid yielded 2-bromobicyclo[1.2.3]octane (XIV). Since silver bromide or a mixture of silver acetate and bromine can convert the anticipated product, 2-bromobicyclo[2.2.2]octane (XV), into 2-bromobicyclo[1.2.3]octane, it is not clear whether the rearrangement occurred as part of the brominative decarboxylation² process or subsequent to it.



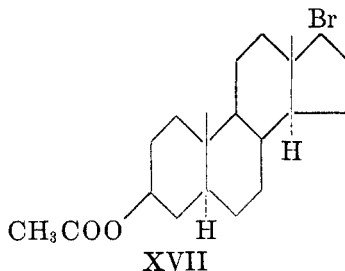
Martin (131), however, found that a mixture of the two bromides was formed. This mixture could be completely converted to the rearranged bromide by the action of silver bromide in carbon tetrachloride. The somewhat different results obtained by Martin were attributed by him to the low reaction temperature ($-10^{\circ}\text{C}.$).

When silver norcamphane-2-carboxylate was treated with bromine at $0^{\circ}\text{C}.$, only 2-bromonorcamphane (131) was found.

Recently, the silver salt of 2-quinuclidinecarboxylic acid was converted (165) to 2-bromoquinuclidine (XVI) by means of the Hunsdiecker reaction. Although these molecules are heterocyclic, inclusion of this information is made here because of the similarity of XVI to XV. Unfortunately experimental details are lacking in the Russian paper (165); therefore no comparison of yields can be made.



Two attempts (115, 163) have been made to introduce bromine into a "steroid-type" nucleus by means of the reaction of this halogen with the proper silver salt. In neither case were significant amounts of the anticipated bromide (XVII) obtained.



² In line with the suggestions of Bunnett (40), names of the type "bromodecarboxylation" can be used to describe the overall effect of Hunsdiecker reactions.

C. Aromatic halides (table 3)

The first attempts to investigate the reaction between halogens and salts of aromatic carboxylic acids seem to have been those of Peligot (146), Kekulé (108), and Bunge (39). In no case was bromobenzene obtained as a result of the action of bromine on silver benzoate. The product of Peligot and Bunge was a monobromobenzoic acid; apparently Kekulé's experiment was completely unsuccessful.

In 1941, Lüttringhaus and Schade (127) reported that the Hunsdiecker reaction could not be applied successfully to the preparation of aryl halides. This conclusion seems to have been based solely on their failure to obtain a good yield of bromobenzene from silver benzoate. Six years previously however, an 80 per cent conversion had been reported for this reaction (32).

In 1950 three papers appeared which dealt with the Hunsdiecker degradation of aromatic carboxylic acid salts (18, 57, 142). The bulk of the present-day knowledge in this area is derived from these reports.

It should be noted that different workers have obtained widely divergent results in the bromination of silver benzoate. Where at all successful in the production of bromobenzene, reported yields range from 14 to 80 per cent. The low yields reported for some Hunsdiecker reactions in the aromatic series may be lower than the maxima which could be obtained. Differences in yield may be attributed to variations in experimental procedures and/or in the purity of the reagents used.

The silver salts of substituted benzoic acids give varying yields of halide, the best results being obtained when the substituent is electron-withdrawing, e.g., chloro or nitro. Thus, the three isomeric nitrobenzoic acids (as silver salts) were converted to the corresponding bromides in excellent yields (ortho, 95 per cent; meta, 89 per cent; para, 79 per cent). The yields from the chlorobenzoic acids were less satisfactory, but sufficiently high to indicate the efficacy of the chloro group (18, 57).

The strongly electron-withdrawing groups fluoro and trifluoromethyl have been present in a number of substituted benzoic acids subjected to Hunsdiecker degradation (51). It might be expected that the yields in these preparations would be high, but this suspicion cannot be verified since no yield data are given in the patent.

Electron-donating groups, e.g., methyl or methoxyl, activate the ring to direct substitution and at best only fair yields of the expected halide can be secured. Silver *p*-toluate (18) gave only 17 per cent of *p*-bromotoluene (plus other products), and silver *m*-methoxybenzoate (57) failed to yield *m*-bromoanisole but gave 50 per cent of 2-bromo-5-methoxybenzoic acid.

Insufficient evidence is at hand to permit the evaluation of the overall effect of two groups, one electron-withdrawing and the other electron-donating, in the same molecule.

The "non-Hunsdiecker" halogenation which may occur can be attributed to the halogenating ability of the initially formed acyl hypohalite or to "halonium" ions generated from the halogen. It is well recognized that silver salts assist in

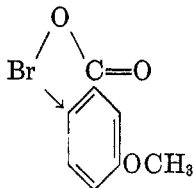
TABLE 3
Aromatic halides prepared by the Hunsdiecker reaction

Carboxylic Acid Salt	Halogen	Products and Yields	Conditions	Reference
Silver benzoate.....	Br	Bromobenzene (80%)	CCl ₄ , reflux	(32)
	Br	Bromobenzene, benzoic acid, <i>m</i> -bromobenzoic acid	CCl ₄ , dark, 0°C.	(32)
	Br	Bromobenzene (14%), benzoic acid, higher boiling acids	CCl ₄	(127)
	Br	Bromobenzene	CCl ₄	(128)
	Br	Bromobenzene (53%), chlorobenzene (5.3%), bromotrichloromethane (6.7%)	CCl ₄ , reflux	(57)
	Br	Bromobenzene (18%)		
	Br	Bromobenzene (45.8%), phenyl benzoate (43.9%), benzoic acid (10.8%)	CCl ₄ , addition in the cold, then reflux	(18)
	Br	Bromobenzoic acid, benzoic acid	CCl ₄ , reflux	(142)
	Br	Bromobenzoic acid, benzoic acid	Room temperature	(146)
	I	Iodobenzene (14%)		(39)
Silver <i>o</i> -chlorobenzoate.....	Br	<i>o</i> -Bromochlorobenzene (48%)	CCl ₄ , addition in the cold, then reflux	(18)
	Br	<i>o</i> -Bromochlorobenzene (38%)	CCl ₄ , reflux	(57)
Silver <i>m</i> -chlorobenzoate.....	Br	<i>m</i> -Bromochlorobenzene (44%)	CCl ₄ , addition in the cold, then reflux	(18)
Silver <i>p</i> -chlorobenzoate.....	Br	<i>p</i> -Bromochlorobenzene (55%)	CCl ₄ , addition in the cold, then reflux	(18)
Silver <i>o</i> -fluorobenzoate.....	Br	<i>o</i> -Bromofluorobenzene		(51)
Silver <i>m</i> -fluorobenzoate.....	Br	<i>m</i> -Bromofluorobenzene		(51)
Silver <i>p</i> -fluorobenzoate.....	Br	<i>p</i> -Bromofluorobenzene		(51)
Silver <i>m</i> -methoxybenzoate.....	Br	2-Bromo-5-methoxybenzoic acid (50.5%), 2,4-dibromo-5-methoxybenzoic acid (7.7%), <i>m</i> -methoxybenzoic acid (6.7%)	CCl ₄ , reflux	(57)
Silver <i>p</i> -methoxybenzoate.....	Br	2,4-Dibromoisole (19-23%)		
Silver <i>o</i> -nitrobenzoate.....	Br	<i>o</i> -Bromonitrobenzene (95%)	CCl ₄ , addition in the cold, reflux	(18)
	Br	<i>o</i> -Bromonitrobenzene (71.2%), <i>o</i> -Nitrophenyl <i>o</i> -nitrobenzoate (30.4%), <i>o</i> -nitrobenzoic acid (10.7%)	CCl ₄ , addition in the cold, reflux	(18)
Silver <i>m</i> -nitrobenzoate.....	Br	<i>m</i> -Bromonitrobenzene (80%)	CCl ₄ , addition in the cold, reflux	(18)
	Br	<i>m</i> -Bromonitrobenzene (68%)	CCl ₄ , reflux	(57)
Silver <i>p</i> -nitrobenzoate.....	Br	<i>p</i> -Bromonitrobenzene (79%)	CCl ₄ , addition in the cold, reflux	(18)
	Br	<i>p</i> -Bromonitrobenzene (56.7%), <i>p</i> -nitrobenzoic acid (34.3%)		
	I	No <i>p</i> -iodonitrobenzene		(141)
Mercurous <i>p</i> -nitrobenzoate.....	Br	<i>p</i> -Bromonitrobenzene (49.3%), <i>p</i> -nitrobenzoic acid (31.6%)	CCl ₄ , addition in the cold, then reflux	(18)
Silver <i>m</i> -toluate.....	Br	<i>m</i> -Bromotoluene (27%), 3,4-dibromotoluene (13.1%), <i>m</i> -toluic acid (34.9%)	CCl ₄ , reflux	(141)
	Br		CCl ₄ , reflux	(57)
Silver <i>p</i> -toluate.....	Br	<i>p</i> -Bromotoluene (17%), 3-bromo- <i>p</i> -toluic acid (66%)		
Silver <i>o</i> -trifluoromethylbenzoate.....	Br	<i>o</i> -Bromotrifluoromethylbenzene	CCl ₄ , addition in the cold, then reflux	(18)
Silver <i>m</i> -trifluoromethylbenzoate.....	Br	<i>m</i> -Bromotrifluoromethylbenzene		(51)

Silver <i>p</i> -trifluoromethylbenzoate.....	Br	<i>p</i> -Bromotrifluoromethylbenzene			(51)
Silver 2-acetyl-3-trifluoromethylbenzoate.....	Br	2-Acetyl-1-bromo-3-trifluoromethylbenzene		CCl ₄ , reflux	(51)
Silver 3-bromo-4-methoxybenzoate.....	Br	2,4-Dibromoisole (92%)		CCl ₄ , reflux	(18)
Silver 2-carboethoxy-3-nitrobenzoate.....	Br	Ethyl 2-bromo-6-nitrobenzoate (51.1%)			(67)
Silver 2-chloro-6-trifluoromethylbenzoate.....	Br	2-Bromo-1-chloro-3-trifluoromethylbenzene			(51)
Silver 2-nitro-4-trifluoromethylbenzoate.....	Br	1-Bromo-4-trifluoromethyl-2-nitrobenzene			(51)
Silver 2-trifluoromethyl-4-nitrobenzoate.....	Br	1-Bromo-2-trifluoromethyl-4-nitrobenzene			(51)
Silver phthalate.....	Br	<i>o</i> -Dibromobenzene (10.1%), phthalic acid (29%)		CCl ₄ , reflux	(142)
Silver isophthalate.....	Br	<i>m</i> -Dibromobenzene (4.9%), recovered silver salt (78.4%)		CCl ₄ , reflux	(142)
Silver terephthalate.....	Br	Recovered silver salt (98%)		CCl ₄ , reflux	(142)
Silver 1-naphthoate.....	Br	Brominated naphthalenes, bromo-1-naphthoic acid, 1-naphthoic acid		CCl ₄ , reflux	(57)
	Br	1-Bromonaphthalene (4.5%), 4-bromo-1-naphthoic acid (14.1%), 1-naphthoic acid (78.2%)		CCl ₄ , reflux	(141)
Silver 2-naphthoate.....	Br	Brominated naphthalenes, bromo 2-naphthoic acid, 2-naphthoic acid		CCl ₄ , reflux	(57)
Silver naphthalate.....	Br	1,8-Dibromonaphthalene (38.9%), 4-bromonaphthalic acid (17.2%), naphthalic acid (36.8%)		CCl ₄ , reflux	(141)
Silver diphenate.....	Br	No 2,2'-dibromobiphenyl			(22)
Silver tropone-4-carboxylate.....	Br	No 4-bromotropone			(106)
Silver α -cycloheptatrienecarboxylate.....	Br	No bromocycloheptatriene			(107)

the production of "positive" halogen through coördination with the halogen molecule.

Intramolecular halogenation by an acyl hypobromite has been suggested (57) to account for an instance of nuclear "non-Hunsdiecker" halogenation, *viz.*:



Steric factors should dictate whether this mechanism could be operative in any specific case.

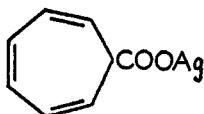
Barnes and Prochaska (18) regard the ease of bromination of the free acid (present as impurity in the silver salt or produced by hydrolysis) as the critical factor in determining the relative amounts of Hunsdiecker product and brominated acid. When bromination of the nucleus is a facile process, the yield of Hunsdiecker product is small; the same groups which discourage direct ring substitution are favorable to the degradation. Thus, appreciable amounts (>20 per cent) of both Hunsdiecker product and halogenated acid have not been obtained from the same reaction.

Among the simple aromatic dicarboxylic acid salts, only the three isomeric silver phthalates have been employed in the Hunsdiecker reaction. Oldham (142) found that these salts reacted only incompletely with bromine in refluxing carbon tetrachloride.

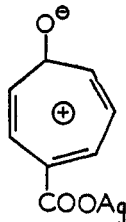
With iodine, silver phthalate was converted to phthalic anhydride (31, 184); silver terephthalate yielded only the free acid (184).

Although silver diphenate could not be degraded to 2,2'-dibromobiphenyl (22), silver naphthalate gave almost a 40 per cent yield of 1,8-dibromonaphthalene (141). The latter reaction easily represents the most successful application of the Hunsdiecker reaction to aromatic dicarboxylic acid salts.

The silver salts of 1- and 2-naphthoic acid have been treated with bromine (57, 141). The predominant reaction was bromination of the naphthalene nucleus. The poor yield (4.5 per cent) of 1-bromonaphthalene from the one partially successful experiment (141) does not recommend the Hunsdiecker reaction for the highly reactive polynuclear systems.



XVIII



XIX

TABLE 4
Heterocyclic halides prepared by the Hunsdiecker reaction

Carboxylic Acid Salt	Halogen	Products	Conditions	Reference
Silver picolinate.....	Br	2-Bromopyridine, pyridine, 2,2'-bipyridine	C ₆ H ₅ NO ₂ , 120-200°C.	(116)
Silver nicotinate.....	Br	3,5-Dibromopyridine, a dibromobipyridine, nicotinic acid	C ₆ H ₅ NO ₂ , 140-230°C.	(116)
Silver isonicotinate.....	Br	Isonicotinic acid	C ₆ H ₅ NO ₂ , 130-225°C.	(116)
Silver 2-hydroxy-4,6-dimethyl-3-pyridinecarboxylate.....	Br	3-Bromo-2-hydroxy-4,6-dimethylpyridine	CCl ₄ , reflux	(130)
Silver quinuclidine-2-carboxylate.....	Br	2-Bromoquinuclidine		(165)

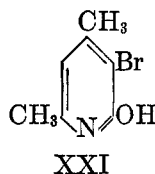
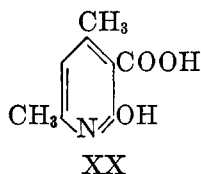
Attempts have been made to extend the Hunsdiecker reaction to "non-classical" aromatic systems. However, neither silver α -cycloheptatrienecarboxylate (XVIII) (107) nor silver tropone-4-carboxylate (XIX) (106) could be thus degraded.

D. Heterocyclic halides (table 4)

The halogenative decarboxylation reaction as carried out in basic aqueous medium has been used for the preparation of certain halogenated heterocycles (see Section V). The Hunsdiecker reaction, however, has been employed only in efforts to obtain bromopyridines.

The silver salts of the three pyridinemonocarboxylic acids have been subjected to the action of bromine at elevated temperatures, nitrobenzene being used as solvent (116). Silver nicotinate yielded only 3,5-dibromopyridine and a dibromobipyridine, while silver isonicotinate did not react. From silver picolinate was obtained a small amount of 2-bromopyridine and, in addition, some pyridine and 2,2'-bipyridine.

A highly substituted pyridinemonocarboxylic acid has been degraded to the corresponding bromide in unstated yield by means of the Hunsdiecker reaction (130). The silver salt of 2-hydroxy-4,6-dimethylnicotinic acid (XX) has been converted to 3-bromo-2-hydroxy-4,6-dimethylpyridine (XXI).



Since this reaction was carried out in refluxing carbon tetrachloride, and silver nicotinate did not react under the same conditions (116), it appears that activating groups may be necessary for reaction at moderate temperatures in the pyridine series.

The reaction of silver 2-quinuclidinecarboxylate with bromine has been noted previously (Section II,B).

III. MATERIALS AND METHODS³

The widespread use of the name "silver salt reaction" is indicative of the extensive use of silver salts of carboxylic acids in the Hunsdiecker reaction. Silver salts generally give more satisfactory results than do other salts. Possible reasons for this superiority include the facts that the silver salts are water-insoluble and thus can be precipitated from solution, that they are non-hygroscopic, and that they react under mild conditions.

From an examination of published reports⁴ it appears that the mercurous (96, 98, 99, 100, 102, 103, 141), mercuric (15, 71, 73, 96, 99, 100, 101, 102, 103, 133), and lead (15, 71, 73, 103, 133) salts of carboxylic acids are suitable in most instances but give in general lower yields than the silver salts. The mercuric and lead salts (as well as the barium salts) of the perfluoro acids are too hygroscopic for convenient use (73).

The alkali metal salts (sodium and potassium) have found limited application (15, 42, 51, 59, 71, 73, 74, 101), but there seems to be no reason to prefer them to the silver salts. The former usually are water-soluble and hence difficult to isolate; frequently they are hygroscopic. Since they are less reactive than the silver salts, they require longer reaction periods and higher temperatures, both of which may encourage side reactions.

Scanty information is available on the suitability of the barium (71, 73), thallos (96, 98, 99, 100, 102), copper (15, 103, 133, 141), calcium (3), zinc (128), cadmium (128), magnesium (3, 141), aluminum (141), and nickel (103) salts. Only the first two named appear to possess appreciable reactivity.

In the majority of Hunsdiecker reactions the halogen has been bromine. Oldham (142) has compared bromine and iodine as halogen ingredients of the reaction. Perhaps the most important drawback to the use of iodine is the tendency towards ester formation (see Section V).

Relatively few instances of the use of chlorine have been described in the literature. This may be only the reflection of the inconvenience in using a gaseous reagent and the relative lack of reactivity of the chlorine-containing products in comparison with the corresponding bromo compounds. There is no evidence to indicate that chlorine acts differently from bromine in the Hunsdiecker reaction. The use of fluorine is discussed elsewhere in this review (see Section IV).

Some workers (23, 24, 25, 145, 163) have added silver acetate to the Hunsdiecker reaction mixture. There is no reason to believe that the yields have been improved as a result.

The usual solvent⁵ for the Hunsdiecker reaction is carbon tetrachloride. Its

³ This section is not intended to be a comprehensive listing of all references pertaining to the experimental details of the Hunsdiecker reaction. The reader is referred to the tables of the review for further information and to references 4, 46, and 93 for detailed experimental procedures.

⁴ In the patent literature (51, 96, 97, 98, 99, 100, 102) it is claimed that the Hunsdiecker reaction is especially applicable to metals of the first, second, and third groups of the periodic table.

⁵ Though the term "solvent" is used in this review and quite generally in the literature of the Hunsdiecker reaction, it should be understood that complete solution of the carboxylic acid salt probably is never observed.

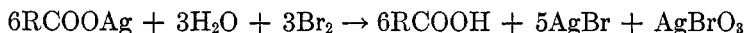
non-polar character, non-flammability, and low cost recommend it for most cases. In addition, carbon tetrachloride is easily rendered anhydrous. The low boiling point is advantageous in most cases; difficulties in isolation may arise if the product possesses a boiling point near that of the solvent. Halogen-solvent interaction is fairly common when carbon tetrachloride is used, and the removal of the by-products may require an inordinate amount of purification.

Carbon disulfide (51, 86, 101), petroleum ether (125, 185), chlorobenzene (26), nitrobenzene (86, 116, 172), ethyl bromide (23, 24, 25, 145, 163, 164), chloroform (26, 98), dichloromethane (45), dichlorodifluoromethane (159, 160, 161), *sym*-tetrachloroethane (159), trichlorotrifluoroethane (26), and trichloroethylene (176) have also been employed with success in specific instances. Carbon disulfide has been reported to be more satisfactory than carbon tetrachloride when mercury salts are used (101). Perfluorinated hydrocarbons (54, 171), amines (35, 54, 171), and ethers (54, 171) have found use in the preparation of perfluoroalkyl halides, but often these compounds are prepared in the absence of solvent (81, 82, 83, 87, 171).

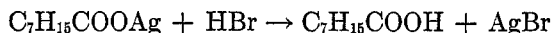
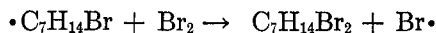
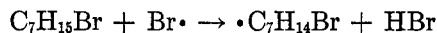
Only one comprehensive study of the effect of solvent on yield in the Hunsdiecker reaction has been published. Eleven different solvents were used for the bromination of silver palmitate. Carbon tetrachloride easily proved to be the best from the standpoint of yield of alkyl bromide (3).

For best results it is necessary that glassware and chemicals be thoroughly free from moisture. The glassware can be kept in the oven prior to the reaction; the halogen, solvent, and carboxylic acid salt are conveniently desiccated over phosphorus pentoxide. It may also be advantageous to carry out the reaction in an atmosphere of dry nitrogen.

The presence of traces of moisture presumably accounts for the accumulation of free acid which has been observed so frequently. Oldham (142) has proposed the following explanatory equation:



However, Cason, Kalm, and Mills (44) found that the free acid was formed in a Hunsdiecker reaction even when all efforts were made to exclude moisture. Taking into account the simultaneous formation of dibromoheptanes, 1-bromoheptane, and caprylic acid from silver caprylate, the latter group of workers proposed the free-radical mechanism:



The experiments of Rottenberg (164) indicate that the presence of free acid in the silver salt leads to a decreased yield of alkyl halide but is not otherwise deleterious. However, the possibility exists that the brominated acids that have been observed (18, 32, 57, 86) as by-products arose as the result of bromination of the free acid present with the silver salt.

The reaction itself usually is carried out by the addition of the halogen (if

bromine or iodine, it may be dissolved in the solvent used) to the salt suspension. The technique of "inverse addition," i.e., addition of the salt to the halogen in solution, has been recommended for use in certain cases (37, 38, 47, 50, 52, 124, 166, 182).

The salt suspension may be kept cold during the addition process and subsequently warmed, or the addition may be made at an elevated temperature. It has been demonstrated (32) that the technique used may have a significant effect on the yield of halide.

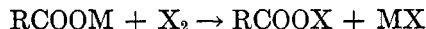
The reaction periods which have been used vary considerably in duration, and no attempt has been made to determine the optimum time for a particular Hunsdiecker reaction. In the case of bromination of silver trifluoroacetate, it was found (65) that a reaction time of 3 hr. gave a better yield (39 per cent *vs.* 21 per cent) of bromotrifluoromethane than did a time of 18 hr. From the experiments of Rottenberg (164) and Anker (49) it can be concluded that a reaction time of 20 min. or less may suffice for small-scale reactions.

Ordinarily the Hunsdiecker reaction can be run without any special safety precautions. However, in at least two cases the reaction was accompanied by a violent decomposition (50, 159).

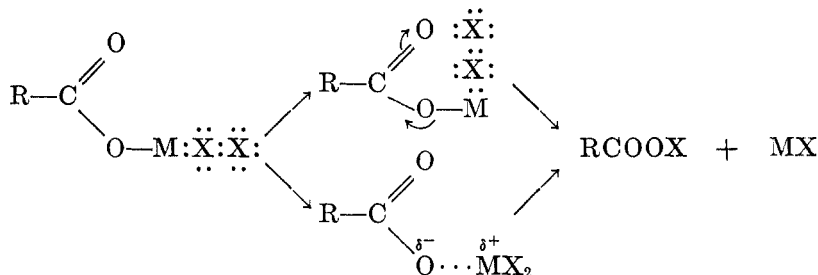
IV. MECHANISMS

Halogens (bromine, chlorine, iodine) react with salts of carboxylic acids in a number of molecular proportions (110). When an organic halide is the desired product, the reactants generally are used in equimolar amounts.

The first stage of the Hunsdiecker reaction (at least when chlorine or bromine is used) involves the formation of an acyl hypohalite and a metallic halide.



It has been suggested (46) that the coloration (not due to bromine) which may be observed at the point of contact of bromine and a silver salt suspension is indicative of the formation of a complex,⁶ $\text{RCOOAg} \cdot \text{Br}_2$. Complex formation could logically be the initial step in acyl hypohalite formation by either of two paths:



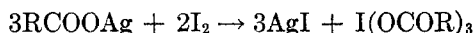
⁶ A complex of the formula $\text{CF}_3\text{COOAg} \cdot \text{I}_2$ has also been suggested (87).

Though silver salts undoubtedly have a lesser degree of ionic character than alkali metal salts, they are more satisfactory than the latter. The superiority of the silver salts can seemingly be attributed, at least in part, to their higher solubility in the usual suspending media for the Hunsdiecker reaction and the high degree of coördination of silver with halogen.

Though acyl hypohalites, excepting perhaps perfluoroacyl hypofluorites, have never been obtained in the free state but only in solution (6), there is spectroscopic evidence for their existence (5).

Chemical evidence for the existence of acyl hypohalites is limited apparently to the observation of the oxidizing power of silver salt-halogen mixtures and the nature of the product from the treatment of an olefin with the supposed hypohalite. Bockemuller and Hoffmann (32) demonstrated the "positive" or oxidizing nature of the bromine ion in a bromine-silver butyrate mixture, and as others before and since (1, 28, 62, 149, 150, 151, 152, 153, 154, 178), they showed that the acyl and halogen moieties add to the terminals of a carbon-carbon double bond.

It has been shown that iodine can react with silver salts in molar ratios other than 1:1. Oldham and Ubbelohde (143) found that the silver salts of long-chain carboxylic acids would react with a slight excess of iodine according to the equation:

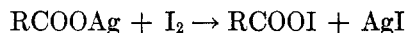


These "iodine triacyls" gave good yields of alkyl iodides when heated with an excess of iodine in dry benzene or carbon tetrachloride. The excess of iodine favored the formation of the alkyl iodide in preference to the ester, RCOOR .

A complex of the formula $(\text{RCOO})_2\text{AgI}$ results from the interaction of two moles of silver salt with one of iodine (110). Such complexes where R is a perfluoroalkyl radical have been suggested as intermediates in the degradation of silver salts of perfluorocarboxylic acids with iodine (54, 78).

Though Henne and Zimmer (88) reported that the action of bromine or iodine on silver trifluoroacetate gave the trifluoroacetyl hypohalite, Crawford and Simons (54) were unable to find evidence of such compounds. The latter workers concluded that such perfluoroacyl hypohalites are not formed as intermediates in reactions.

It is possible that the various silver salt-iodine reaction intermediates can result from a series of consecutive reactions (78):



The point at which the reaction halts is governed by the molecular ratios of the reactants and the nature of the halogen. Iodine seems to be the only halogen which forms a triacyl, perhaps owing to the fact that only iodine atoms are of the requisite size.

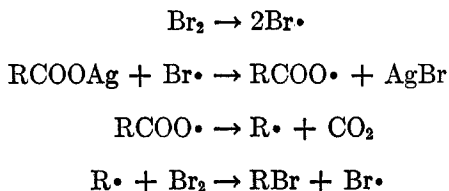
It might be expected that the vigorous oxidizing action of elemental fluorine would prevent its use in the Hunsdiecker reaction; this cannot be confirmed, since there are no reports of a fluorinative decarboxylation of a carboxylic acid salt. However, acyl hypofluorites have been reported as products of the direct fluorination of perfluorocarboxylic acids. Here the absence of hydrogen atoms in the alkyl group stabilizes the acids to fluorine.

Trifluoroacetic acid can be converted to trifluoroacetyl hypofluorite (41, 175), and pentafluoropropionic acid to pentafluoropropionyl hypofluorite (134). In addition, heptafluorobutyryl hypofluorite may have been obtained by an analogous procedure (134).

On decomposition of the first two mentioned hypofluorites, tetrafluoromethane and hexafluoroethane, respectively, were formed (among other products).

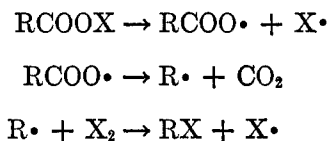
The initially formed hypohalite could conceivably decompose by either a homolytic or a heterolytic process,⁷ and indeed both processes have been considered. For the remainder of this section, it will be assumed that the Hunsdiecker intermediate has the formula RCOOX.

Price (155) suggested the sequence:

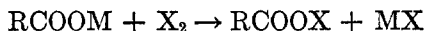


Such a mechanism (with subsidiary reactions to account for by-products) has also been postulated by Heintzeler (86).

Price's scheme has been modified somewhat by Berr (26):

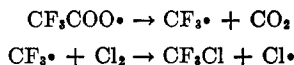


Of the two mechanisms the latter⁸ is preferable, since it indicates the hypohalite as a definite chemical entity and intermediate in the Hunsdiecker reaction. For completeness, it might be well to include an initial step:



⁷ There is, of course, the possibility that both processes are operative in the sense that the nature of the reaction is of intermediate type. Or perhaps certain salts undergo the reaction by an ionic mechanism while others follow a free-radical path, the mechanism depending on the structure of the salt and the reaction conditions.

⁸ Resembling the last two steps of Berr's mechanism is Stewart's mechanism (175) for the chlorine-inhibited decomposition of trifluoroacetyl hypofluorite.



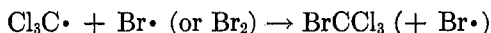
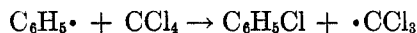
This equation implies nothing about the mechanism of hypohalite formation, but the reviewers suggest two ionic possibilities (page 250).

A number of observations which correspond to those anticipated for homolytic cleavage (89, 180) of the acyl hypohalite seem to indicate the free-radical nature of the reaction.

Interaction of the halogen reagent with the solvent has been observed in a number of instances.

Barnes and Prochaska (18) found that the bromination of silver *p*-toluate gave bromotrichloromethane and *p*-chlorotoluene in addition to *p*-bromotoluene when carbon tetrachloride was the solvent.

In the preparation of bromobenzene from silver benzoate in carbon tetrachloride, bromotrichloromethane and chlorobenzene were isolated (57). The following series of reactions was proposed to account for the by-products.



Heintzeler obtained benzhydryl chloride as a by-product of the bromination of silver diphenylacetate and some chlorine-containing material from the bromination of silver triphenylacetate (86). Both reactions were run in carbon tetrachloride.

The cyclopropyl bromide prepared from silver cyclopropanecarboxylate was contaminated with a small amount of chlorine-containing substance presumably formed as the result of a reaction of a bromine atom with *sym*-tetrachloroethane (159).

In studies of the bromination of the silver salt of 1-apocamphanecarboxylic acid, the bromoapocamphane obtained contained a chlorinated impurity when the reaction was carried out in carbon tetrachloride. However, the pure bromide was obtained when petroleum ether was used as the reaction medium (185).

When the silver salt of 2-methylpentanoic acid was brominated in dichloromethane, small amounts of bromodichloromethane were formed (45).

Recently it was found that the action of bromine on the silver salts of *cis*- and *trans*-cinnamic acid in carbon tetrachloride gave bromostyrenes which gave positive tests for chlorine on sodium fusion and analysis (156).

It seems likely that in other cases products derived from interaction of halogen with the solvent might be isolated if the reactions were carried out on a fairly large scale and a concerted effort made to isolate and identify all organic products.

If the free-radical mechanisms previously described (page 252) are truly representative of the nature of the Hunsdiecker reaction, coupling products, R—R, should be encountered. Such a side reaction has been found to occur in the bromination of silver picolinate (116). In nitrobenzene at 120–200°C. some 2,2'-bipyridine was formed. Silver nicotinate gave a dibromobipyridine.

It has often been observed that acyl hypohalites halogenate aromatic systems (27, 29, 57, 78, 88, 168), and since the positions of substitution correspond to

those expected for electrophilic attack (by positive halogen ion), an ionic mechanism is generally accepted for this operation. However, Haszeldine and Sharp were able to isolate bibenzyl from the reaction of bromine and silver trifluoroacetate with toluene (78). Attack by bromine atoms on the side chain of toluene and coupling of the resulting benzyl radicals seems indicated here.

The iodination of silver benzoate at 160–180°C. in the absence of solvent produced an iodobiphenyl in addition to benzoic acid and an iodobenzoic acid (31). Again the formation of a coupling product points to a free-radical reaction.

It has been reported that the action of nitrosyl chloride (see Section V) on silver trifluoroacetate (76) and silver heptafluorobutyrate (16) yielded small amounts of hexafluoroethane and tetradecafluorohexane, respectively.

Suggestive also of a free-radical mechanism are the apparent catalysis of the reaction by light (32, 51, 184) and the reported induction period (50, 26).⁹

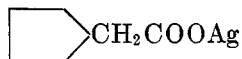
In experiments with silver *cis*- and *trans*-cinnamates, it was found that bromination in carbon tetrachloride yielded *trans*- β -bromostyrene in each case (156). The previous work (109) on the isomerization of isostilbene (*cis* isomer) to stilbene (*trans* isomer) under free-radical-promoting conditions suggests that free radicals are involved in both instances.

The bromination of the sodium salts of *cis*- and *trans*- α -phenylcinnamic acids in aqueous solution, clearly an ionic process, yielded the bromostilbenes of configuration corresponding to the original acids (157). Indications are that both the *cis* and *trans* forms of the silver salts of this acid give the same product (as determined by comparison of infrared spectra) on bromination in carbon tetrachloride, but conclusive evidence is lacking at present (156).

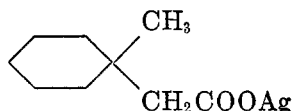
There are a few lines of evidence considered to rule out an ionic mechanism which have been cited as indications of a free-radical process.

Silver *tert*-butylacetate when treated with bromine in nitrobenzene gave neopentyl bromide exclusively (26, 172). The failure to obtain *tert*-amyl bromide indicates that a neopentyl carbonium ion is not formed during the reaction, for such would be expected to rearrange rapidly to a tertiary carbonium ion, leading to the tertiary bromide.

Significant too is the apparent lack of adjustment in ring size when XXII (98) and XXIII (145) were treated with bromine.



XXII



XXIII

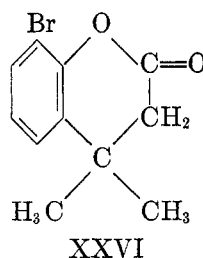
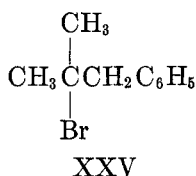
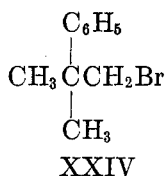
Attention has been called to the failure of the cyclobutyl system to undergo rearrangement (44). However, it has been shown through use of infrared spectra that the cyclobutyl cyclobutanecarboxylate obtained (47) as the by-product of the Hunsdiecker reaction is contaminated with a large quantity of cyclopropyl-

⁹ The reviewers have not seen any reference in the literature to the use of a free-radical initiator such as benzoyl peroxide for the starting of reluctant Hunsdiecker reactions.

carbonyl cyclobutanecarboxylate (160). Since no evidence of cyclopropylcarbonyl bromide has been found in the products of the reaction of silver cyclobutanecarboxylate with bromine, it seems likely that the rearrangement occurs subsequent to bromide formation and as part of the "Simonini ester" formation. This latter reaction does appear to proceed by an ionic process (78, 160), though such may not be the case in the fluorocarbon series (72).

The action of bromine on the silver salts of 2-methylpentanoic and 2-ethylbutanoic acids yielded only 2-bromopentane and 3-bromopentane, respectively (45). Since the anilides of these halides melted at higher temperatures than those previously reported, it was suggested that in these cases the Hunsdiecker reaction proceeds with a minimum of rearrangement (if any). The enantiomorphic composition of the 2-bromopentane and its precursor silver salt was not considered.

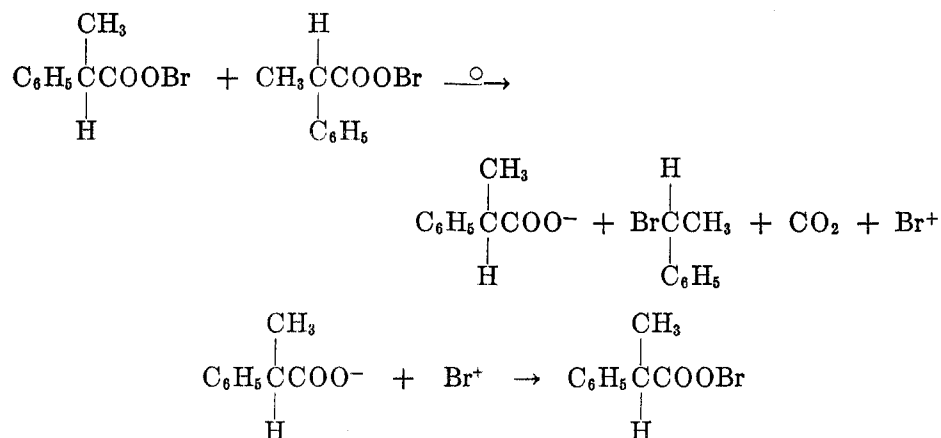
Berr (26) has found that some rearrangement occurs in the reaction of bromine with silver 3-phenylisovalerate. In his experiments the normal product (XXIV) was contaminated with about 5 per cent (estimated from solvolysis experiments)



of XXV. Also obtained were significant amounts of the lactone XXVI, the product of an "internal Simonini" esterification. Berr considers that silver bromide would not cause such a large measure of rearrangement of XXIV to XXV. If the ionic rearrangement through the agency of silver bromide is excluded, then rearrangement of the intermediate free radical or ion must account for the formation of XXV. The experiments of Urry and Kharasch (177) indicate that the neophyl (2-methyl-2-phenylpropyl) radical would be susceptible to rearrangement. On the other hand, a carbonium-ion intermediate would be expected to rearrange by analogy with the neopentyl case (see page 254).

The first suggestion that the Hunsdiecker reaction might involve an ionic process was made by Arcus, Campbell, and Kenyon (11, 12). They found that silver (+)-2-phenylpropionate was converted to (+)-1-phenylethyl bromide with a 43.1 per cent retention of asymmetry. Since the (+)-forms of the acid and the bromide could be shown to be of opposite configuration, it was concluded that the reaction proceeded with inversion of configuration. The partial racemization (10) observed was considered to be due to the action of bromine and silver bromide on the fully inverted phenylethyl bromide.

The mechanism proposed (11, 12) for this reaction was of the type S_E2 with accompanying Walden inversion (187):



Electrophilic attack by bromonium ion or the positive portion of a polarized bromine molecule on the acyl hypobromite was considered a possible subsidiary reaction.

Previously, Arnold and Morgan (13) had performed similar experiments with silver salts of the *d*- and *l*-forms of 2-ethylcaproic acid. In each case optically inactive 3-bromoheptane was obtained.

When the silver salts of 2-ethylcaproic acid and 1,2-diphenylsuccinic acid (in each case, both optical isomers) were converted to the Hunsdiecker products by Bell and Smyth (22), totally inactive bromides were obtained. Though silver (–)-2-benzylbutyrate gave a completely inactive product, the bromide from the (+) salt had a small specific rotation. The experiments were not considered to be indicative of a free-radical mechanism; this opinion was due apparently to the adherence of the authors to the ionic mechanism previously proposed (11, 12), rather than to evidence from their own work.

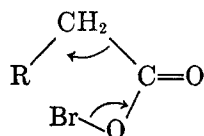
More recent attempts to determine the mechanism of the Hunsdiecker reaction by the use of optically active silver salts have included reexaminations of the original experiments (11, 12). Two other groups (26, 44) have reported failures in attempts to obtain *any* 1-phenylethyl bromide from silver 2-phenylpropionate. A repetition of the original experiments by Abbott and Arcus (2) produced only the "Simonini ester." These workers did find that the enantiomorphic forms of 2-ethylcaproic acid could be converted into bromides having a small measure of optical activity. However, the low order of activity does not rule out the possibility of contamination by optically active impurities.

The unpublished dissertation of Berr (26) records some attempts to prepare optically active halides by the Hunsdiecker reaction. The silver salts of 2-methylbutyric acid and 2-ethylcaproic acid (in each case, both optical isomers) yielded only inactive bromides and chlorides. The bromination of potassium (+)-2-methylbutyrate did result in 2-bromobutane which showed a small degree of optical activity. The rotation corresponded to inversion to the extent of 0.4 per cent.

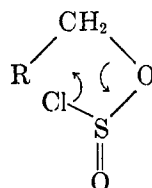
Heintzeler (86) also obtained racemic 2-bromobutane and 2-chlorobutane from silver (+)-2-methylbutyrate.

The production of racemic halides from optically active carboxylic acid salts is in accord with a free-radical mechanism. The slightly active halides which have been obtained on occasion may have contained impurities, and repetition of such experiments under more exacting conditions seems warranted.

A cyclic mechanism has been offered for the Hunsdiecker reaction (19, 162, 183). The mechanism proposed is a 1,3-intramolecular shift (XXVII) which is analogous to the S_Ni interpretation¹⁰ (XXVIII) of the conversion of alcohols to alkyl chlorides through reaction with thionyl chloride.



XXVII

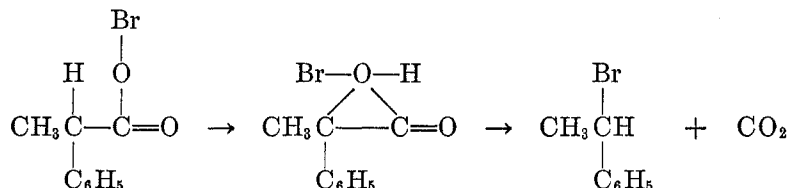


XXVIII

Though Rottenberg (162) considers this mechanism to supplement the S_E2 mechanism where the latter cannot be operative for steric reasons, Wiberg and Shryne (183) take the position that the intramolecular cyclic process explains the earlier work of Abbott and Arcus (2), as well as other cases. The conversion of silver (+)-2-ethylcaproate to (+)-3-bromoheptane is considered to involve retention of configuration; if such actually is the case, then the S_Ei mechanism proposed above can be applied. No attempt has been made to explain the results of Arcus, Campbell, and Kenyon (11, 12) on the basis of the S_Ei mechanism which predicts only retention of configuration.

It is known that the Hunsdiecker reaction proceeds very well at the bridgehead of bicyclic systems (9). The failure of Bartlett and Knox (20) to obtain 1-chloroapocamphane from thionyl chloride and the requisite alcohol suggests that an S_Ni reaction is not favored at the bridgehead. Such may well be the case with an S_Ei reaction also.

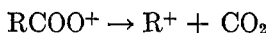
A second mechanism of a cyclic nature has been proposed in the recent literature (56). An unstable oxonium compound was considered to be the intermediate. The interpretation given to the results of the original bromination of silver 2-phenylpropionate (11, 12) is as follows:



¹⁰ A similar mechanism has been offered in explanation of the production of phenylethanol of retained configuration from the reaction of 2-phenylpropionic acid with sodium peroxide. An intermediate per acid was considered as the species undergoing cyclic decomposition (68).

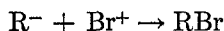
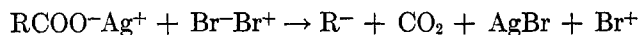
Such a process requires an intermediate in which the oxygen atom is surrounded by ten electrons (however, no charge distribution is indicated in the formula of the original article); this mechanism seems not only unlikely but also unnecessary.

Halide formation by the combination of carbonium ion with bromide ion has recently been proposed as a possible mechanism for the Hunsdiecker reaction (123):



This scheme ignores the experiments (26, 172) which tend to rule out the possibility of a carbonium-ion intermediate and also the evidence for the presence of positive halogen.

The proposal of Maekawa (128) employs a bromonium ion and a carbanion and is equivalent to the original mechanism suggested (11, 12) for an ionic Hunsdiecker reaction.



Since the original article is unavailable to the reviewers, it is not known whether there is new experimental evidence for this mechanism.

A decision as to the mechanism of the Hunsdiecker reaction cannot ignore the numerous indications of a free-radical process.¹¹ Such are halogen-solvent interaction, light catalysis, and the formation of racemic halides when an asymmetric carbon-halogen bond is formed.

On the other hand, the experiments of Arcus, Campbell, and Kenyon (11, 12) and Abbott and Arcus (2) cannot be discounted entirely. There is the possibility that under the particular conditions of their reactions, an ionic process was operative. It should be pointed out that all of the ionic mechanisms which have been formulated are predicated on the validity of the early work, and there have been no subsequent experiments which confirm the original findings.

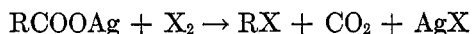
A duality of mechanism may be possible; this has been suggested by Wiberg (183). While supporting an ionic mechanism for aliphatic carboxylic acid salts, he has by implication admitted the possibility of a free-radical mechanism in the other series.

The reviewers are of the opinion that the Hunsdiecker reaction has been amply demonstrated to be free radical in character; ionic mechanisms are inadmissible unless and until there is further experimental work which warrants such an explanation.

¹¹ A more obvious free-radical process and one related to the Hunsdiecker reaction is the formation of bromobenzene by the decomposition of benzoyl peroxide in the presence of *N*-bromosuccinimide (64).

V. RELATED REACTIONS

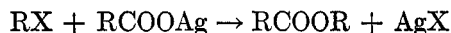
One of the most important factors affecting the nature of the product obtained from the reaction of metallic salts of carboxylic acids with halogen is the ratio of salt to halogen. For the Hunsdiecker reaction the theoretical molar ratio is 1:1.



A ratio of 2:1 favors ester formation (78, 169, 170). This reaction was developed

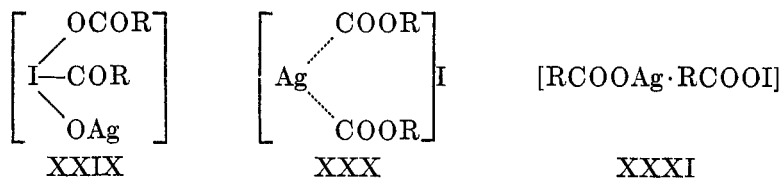


largely by Simonini and is often referred to as the Simonini reaction. While evidence indicates a free-radical mechanism for the Hunsdiecker reaction (see Section IV), an ionic mechanism is favored for the Simonini reaction (78, 160, 184). The alkyl halide formed by a Hunsdiecker-type reaction probably reacts with the excess silver salt by simple ionic means. Evidence favoring an ionic

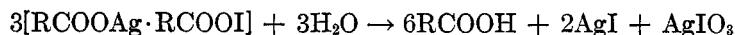
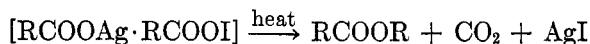


mechanism includes the failure to detect the presence of triphenylmethyl radicals from the reaction of silver triphenylacetate and iodine (184) and the fact that rearrangement products are obtained from the reaction of silver cyclobutanecarboxylate with iodine (160).

The above equation, however, represents an oversimplification of circumstances. In most cases a complex intermediate is formed (132, 169, 170, 184). Often, the intermediate complex is sufficiently stable to be isolated. Simonini (169, 170) assigned structure XXIX to the intermediate; Wieland and Fisher (184) preferred structure XXX. The exact nature of the intermediate is as yet unknown and it is perhaps best represented by formula XXXI; the iodine of the Simonini complex possesses a positive character (29, 30, 85). Treatment of the

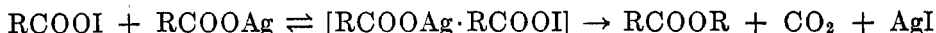
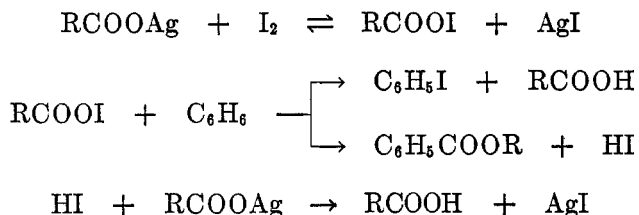


intermediate complex with water results in the formation of the corresponding acid, silver iodide, and silver iodate (30, 133, 184).



Birkenbach and Meisenheimer carried out a series of reactions with monobasic acids and iodine in the presence of benzene (29). The following reactions were

suggested:



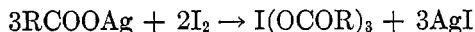
With aliphatic acids, the Simonini reaction was found to be the more rapid reaction; with benzoic acid, the substitution reaction achieved approximately the same velocity as the Simonini reaction; and with certain substituted benzoic acids, the substitution reaction was by far the more rapid.

Unlike the Hunsdiecker reaction, the Simonini reaction as a preparative tool is limited primarily to the use of iodine (133) and to silver salts of aliphatic monobasic acids.

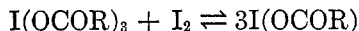
The reaction of three moles of the silver salt with two moles of halogen might be considered a combination of the Hunsdiecker and Simonini reactions. However, there is evidence that a somewhat different type of reaction takes place.



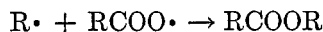
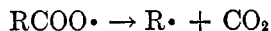
With salts of long-chain fatty acids, an iodine triacyl intermediate has been isolated (143).



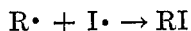
The iodine triacyl compound reacts with additional iodine to give good yields of the alkyl iodide. This may be explained (143) by an equilibrium of the type



the acyl hypoiodite then undergoing the normal Hunsdiecker reaction. The thermal decomposition of the iodine triacyl may also involve the formation of free acyl radicals according to the following scheme (143):



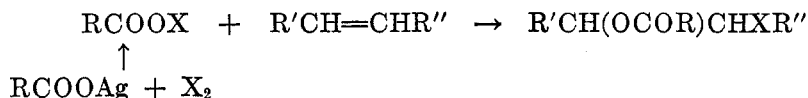
or



It is noteworthy, however, that not more than traces of the hydrocarbon, R—R, appear to be formed.

The intermediates formed in the Hunsdiecker and Simonini reactions may react with other substances present in the system. One of the most common of

such reactions is the addition of acyl hypohalites to unsaturated compounds (the Prévost reaction) (149, 150, 152, 153, 154).



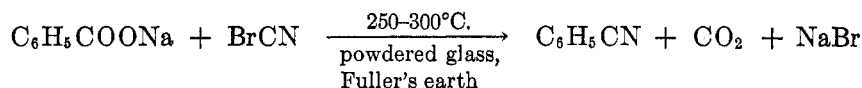
The reaction may proceed further to give the diester, from which the 1,2-glycol may be prepared. A silver 3,5-dinitrobenzoate and iodine mixture has been

$\text{R}'\text{CH}(\text{OCOR})\text{CHXR}'' + \text{RCOOAg} \rightarrow \text{R}'\text{CH}(\text{OCOR})\text{CH}(\text{OCOR})\text{R}'' + \text{AgX}$
suggested as a reagent for the identification of olefins (70). With unsymmetrical olefins, only one of the possible isomers is isolated.

It is interesting that silver acetate and iodine in aqueous acetic acid give *cis* hydroxylation of double bonds (63), while silver benzoate and iodine in benzene form *trans* glycol dibenzoates (63).

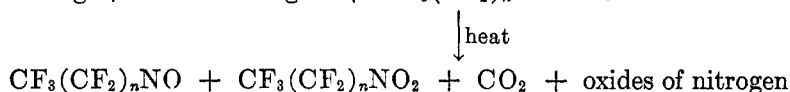
Many references to the halodecarboxylation reaction in an aqueous medium appear in the literature (42, 49, 66, 111, 112, 181). Undoubtedly, such reactions proceed *via* an ionic mechanism and conditions for these reactions definitely differ from those in non-aqueous media. The reaction of potassium acetate in water with bromine to give methyl bromide was perhaps the first use of an aqueous solution for this type of reaction (49). Under similar conditions, butyl bromide was obtained from sodium valerate. Several reports have appeared (66, 111, 112, 181) concerning the preparation of iodo-substituted heterocycles by the treatment of the sodium salts of the corresponding acids with iodine and potassium iodide in aqueous solution. Price and Berman (157) reacted a series of sodium salts of carboxylic acids with halogen and came to the conclusion that for halogen displacement of the carboxylate group, a pair of readily available π -electrons in the α, β - or β, γ -position seems to be necessary.

Another reaction which is similar to the Hunsdiecker reaction involves the synthesis of nitriles from salts of carboxylic acids (61). Benzonitrile can be prepared by heating sodium benzoate with cyanogen bromide in the presence of powdered glass and Fuller's earth.

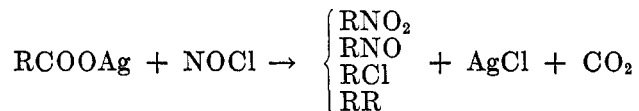


By the use of labeled carbon, it was shown that the carbon of the carbon dioxide was derived almost entirely from the cyanogen bromide; also obtained from the reaction were products tentatively identified as benzamide and the trimer of benzonitrile. Cyanogen chloride has also been employed for this reaction (188).

Haszeldine and Jander (76) report the reaction of nitrosyl chloride with silver perfluoroalkancarboxylates to give nitroso- and nitroperfluoroalkanes. Although the yields are low, the reaction is of preparative value because it obviates the

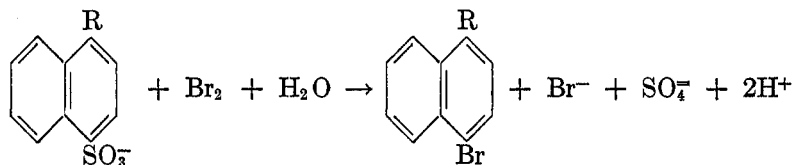
$$\text{CF}_3(\text{CF}_2)_n\text{COOAg} + \text{NOCl} \rightarrow \text{AgCl} + \text{CF}_3(\text{CF}_2)_n\text{COONO}$$


isolation of the perfluoroalkyl iodides and their subsequent irradiation in the presence of nitrosyl chloride (137). When silver trifluoroacetate was employed, hexafluoroethane was isolated, indicating that free radicals were involved. The reaction was used by Banus (16) to prepare nitrosoperfluoroalkanes in a similar manner, using heptacosafuorotributylamine as a solvent; also obtained were some of the nitro- and chloroperfluoroalkanes as well as the coupled product.



Attempts to prepare the nitro compound by heating the silver perfluoroalkane-carboxylate with dinitrogen tetroxide gave small yields of the nitro compound mixed with large quantities of decomposition products which were difficult to separate (16).

The bromodesulfonation of 1-alkylnaphthalene-4-sulfonic acids by the reaction of their salts with bromine in an aqueous solution has recently been reported (113).



The reaction of silver 2-naphthalenesulfonate with iodine in benzene gave 2-naphthalenesulfonic acid, iodobenzene, and silver iodide (114). When carbon tetrachloride or nitrobenzene was employed as a solvent rather than benzene, iodination of the naphthalene nucleus occurred.

Another closely related reaction is that of perfluoroalkancarboxylic acids, rather than their salts, with halogen at high temperatures to give the corresponding haloperfluoroalkane (41, 119, 134). When the halogen is fluorine, the hypofluorite can be isolated; the hypofluorite decomposes on warming to give the perfluoroalkane (41, 134). The formation and decomposition of the hypo-



fluorite are in accordance with the proposed free-radical mechanism for the Hunsdiecker reaction. Certain aromatic acids also undergo halodecarboxylation when the free acid is treated with halogen: for example, 3,5-dibromo-2-hydroxybenzoic acid and 3,5-dibromo-4-hydroxybenzoic acid react with bromine to give the corresponding tribromophenols (69).

VI. SUMMARY

In the aliphatic series the Hunsdiecker reaction is a useful tool for the preparation of alkyl halides and derivatives thereof from acids containing an additional carbon atom. Only when the halide produced is a primary one, is the reaction of general preparative value.

Relatively few attempts have been made to exploit the reaction in the preparation of aromatic halides. Success attends such attempts when the nucleus is substituted with electron-withdrawing groups. Electron-donating groups encourage ring substitution at the expense of halogenative decarboxylation.

Alicyclic halides can be conveniently prepared by the Hunsdiecker reaction. Particularly advantageous is the application to the preparation of bridgehead halides.

Few attempts have been made to employ the Hunsdiecker reaction in the heterocyclic series.

The reaction is most successful when the silver salt of the carboxylic acid is employed. Carbon tetrachloride has been the usual solvent for the reaction. Perfluoroalkyl halides are best prepared in the absence of solvent.

Although there are isolated bits of evidence for an ionic process, the bulk of the published information is in favor of a free-radical mechanism for the Hunsdiecker reaction.

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VIII. ADDENDUM

(added January 24, 1956)

The silver salts of palmitic, stearic, and 9,10-dibromostearic acids have been brominated in carbon tetrachloride (191). From the first, 1-bromopentadecane was obtained in 90 per cent yield after a reaction time of only 10–15 min. A series of experiments with silver stearate yielded from 60–90 per cent of bromide, 3–10 per cent of acid, and 1–10 per cent of the Simonini ester. Silver 9,10-dibromostearate yielded 50 per cent of 1,8,9-tribromoheptadecane, 30 per cent of the regenerated acid, and 1–2 per cent of the Simonini ester.

Bromination of the silver salt of D(+)-3-methylpentacosanoic acid gave D-1-bromo-2-methyltetracosane in 32 per cent yield (197).

Repetition of an earlier preparation (74) of heptafluoriodopropene from silver heptafluorobutyrate afforded the halide in 86 per cent yield (192).

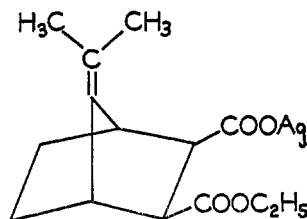
1,1,2,2-Tetrachloro-1,2-difluoroethane has been obtained by two routes (193). Chlorination of silver 2,3,3-trichloro-2,3-difluoropropionate or the disilver salt of 2,3-dichloro-2,3-difluorosuccinic acid gave the desired compound in 79 and 71 per cent yield, respectively.

Additional references to the application of the Hunsdiecker reaction to the synthesis of ω -bromo esters note the preparation of methyl 3-methyl-4-bromobutyrate (197) (60 per cent), ethyl 5-bromovalerate (199) (51 per cent), and ethyl 17-bromomargarate (198) (70 per cent).

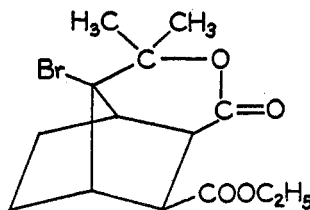
An attempt (197) to convert silver 3-methyl-4-phenoxybutyrate to the Hunsdiecker bromide produced instead a bromo acid. The formula suggested by analysis, $C_{11}H_{13}O_3Br$, would seem to indicate substitution of the aromatic nucleus by bromine with concomitant liberation of the free acid.

The silver salts of (+)-3-D,6-L-dimethylsuberic acid and (–)-3-L,6-D-dimethylsuberic acid were found to give low yields of the corresponding dibromides (194). In the case of the latter salt, some of the ω -bromo acid was formed also.

Wilder and Winston (201) treated the silver salt (XXXII) with an equimolar amount of bromine and obtained the Simonini ester (XXXIII).



XXXII



XXXIII

As the result of its recent publication (200) the dissertation material (175) of Stewart regarding trifluoroacetyl hypofluorite is now readily accessible.

The reaction of bromine with silver 3-phenylisovalerate has been studied by Wilt (202). Only neophyl bromide was obtained; no tertiary bromide was detected (*cf.* page 255). In separate experiments both neophyl bromide and the possible rearrangement product, 2-bromo-2-methyl-1-phenylpropane, were found to be stable to silver bromide under conditions of the reaction.

Levitt (196) has restated an earlier mechanism (123) considered to apply to the Hunsdiecker reaction. Though an abstract (128) of an article by Maekawa is cited in this connection, it should be pointed out that the latter details only a carbanion mechanism rather than the carbonium-ion interpretation of Levitt.

In the area of related reactions, Heynes and Stange (195) have extended their earlier study (91) on the reaction of *N*-bromosuccinimide with the silver salts of peptides.

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