THE HALOFORM REACTION

REYNOLD C. FUSON AND BENTON A. BULL

Department of Chemistry, University of Illinois, Urbana, Illinois

Received September 28, 1934

CONTENTS

I. Introduction 275
II. The early history of the haloform reaction 276
III. The haloform reaction in qualitative organic analysis 277
IV. Structural determination by means of the haloform degradation 281
V. Quantitative methods based on the haloform reaction 286
VI. The use of the haloform reaction in synthesis 287
A. The haloforms 287
B. Saturated aliphatic acids 288
C. Unsaturated acids 289
D. Aromatic acids 290
VII. The mechanism of the haloform reaction 291
A. The halogenation phase of the haloform reaction 292
B. The cleavage phase of the haloform reaction 295
VIII. Reactions related to the haloform reaction 298
A. Modifications of the haloform reaction 299
B. Reactions analogous to the haloform reaction 299
IX. Summary 304
X. References 304

I. INTRODUCTION

The haloform reaction comprises those processes whereby the haloforms are derived from organic compounds by the action of hypohalites. It represents one of the most interesting and useful types of organic reactions and, since its discovery more than a century ago, has engaged the attention of investigators in a wide variety of ways. The theoretical problem involved is unique; and, in spite of the large amount of study which has been expended upon its various aspects, the mechanism of the process is not yet fully understood. On the practical side, the haloform reaction has furnished indispensable methods of detection, estimation, synthesis, and degradation. The literature of the subject is extensive, but is made up chiefly of observations incidental to other studies. This review represents the first general survey which has been made of the work in this field. The fact that many of the examples of the haloform reaction have been carried out incidentally in connection with other work has made the literature

survey peculiarly difficult. No attempt has been made to present here a complete bibliography, but the most significant contributions to the subject have been cited.

II. THE EARLY HISTORY OF THE HALOFORM REACTION

The history of the haloform reaction dates from 1822, when Serullas (167) made the accidental discovery that iodine and alkali convert alcohol into iodoform, which he called a "hydroiodide of carbon." Chloroform was not known until Guthrie (72) in 1831 isolated an "impure chloric ether" formed by the action of bleaching powder on alcohol, and Soubeiran (173) prepared "bichloric ether" by the same method. This compound was discovered almost simultaneously by these investigators and by Liebig (126), who prepared it by the action of alkali on chloral, under circumstances which led to the celebrated dispute regarding priority in this connection—a dispute which was carried on throughout the life-time of these investigators (128), and which is still the subject of much discussion (37, 42, 174, 30).

In 1834, Dumas (44) prepared bromoform by the action of hypobromite on alcohol. He determined the composition of the haloforms and gave them their present names, which refer to the fact that they yield formic acid on hydrolysis.

In extending the reaction Dumas and Peligot (45) reported the formation of chloroform by the action of hypochlorite on methyl alcohol; Lefort (121) also claimed that this alcohol gave the iodoform test. Bonnet (19) asserted that acetic acid gave chloroform when treated with bleaching powder. The error with methyl alcohol occurred repeatedly in the literature until acetone-free methanol became available in comparatively recent times. As a matter of fact, Lieben (125) showed in 1870 that pure methyl alcohol, obtained by hydrolysis of dimethyl oxalate, did not give iodoform,—a result which was confirmed by Belohoubek (11) in 1873.

The reports contained in the early literature did not afford any useful generalization. Bouchardat (21), using hypoiodite, reported positive tests with ethyl acetate and ethyl ether, and a negative test with methyl ethyl ketone, while Schlagdenhauffen (158) reported the formation of chloroform from the ethyl esters of formic, acetic, tartaric, benzoic, and nitrous acids, as well as from methyl tartrate. Likewise, Millon (134) in 1845 reported the formation of iodoform when sucrose, glucose, gums, dextrin, or albuminoids were treated with iodine and potassium bicarbonate.

It was not until 1870 that any systematic study of the reaction was made. In this year Lieben (124) showed that the "iodoform test" was given by a wide variety of compounds, including acetaldehyde, ethyl alcohol, acetone, ethyl acetate, *secondary*-butyl alcohol, acetophenone, 2-hexanone, lactic acid, and capryl alcohol. He also reported positive tests with amylene,

butyraldehyde, *n*-butyl alcohol, quinic acid, dulcin, sugars, meconic acid, methyl butyrate, propionaldehyde, and *n*-propyl alcohol; in these cases we now believe the production of iodoform must have been due to the presence of impurities such as alcohol and acetone. He proved, however, that pure ether and pure acetic acid do not respond to the test. He also reported negative tests for benzene, ethyl chloride, ethyl bromide, ethylene dichloride, amyl alcohol, benzaldehyde, anisic acid, benzoic acid, malic acid, formic acid, succinic acid, butyric acid, chloral hydrate, carbon tetrachloride, citric acid, glycerol, glycol, urea, oxalic acid, phenol, and picric acid.

From this study Lieben announced a general rule regarding the significance of this reaction with respect to molecular structure. The rule which is used at the present time is essentially the same as that of Lieben, and may be stated as follows: *A positive iodoform test is given by compounds containing the aceto (CH_3CO—) group joined to either carbon or hydrogen, and by compounds which are oxidized under the conditions of the test to derivatives containing this structural unit.*

That this rule is subject to considerable revision is indicated by the results of subsequent experiments, not only with hypoiodite but with the other hypohalites as well. Thus, with hypoiodite certain acetylides (118) yield iodoform; and with hypobromite, dihydroresorcinol (196), citric acid (26), certain olefins and tertiary alcohols (179), and many sugars and alkaloids (32) are reported to yield bromoform or carbon tetrabromide.[1] The formulation of a more general rule has been accomplished in connection with the use of Lieben's test in qualitative organic analysis.

III. THE HALOFORM REACTION IN QUALITATIVE ORGANIC ANALYSIS

Since 1870, when Lieben laid down the general rule regarding the structural implications of the haloform reaction, the "iodoform test" has become one of our most useful tools in the identification of alcohols and ketones which are soluble in water. The original procedure involved the treatment of the compound to be tested with iodine in an excess of dilute *aqueous* alkali. In some cases it was advisable to heat the mixture, and sometimes long standing was advantageous.

That this procedure is widely applicable is evident from an examination of the following list of compounds, all of which have been shown to give a positive iodoform test:[2] ethyl alcohol (124), acetaldehyde (124,

[1] It is probable that the carbon tetrabromide in these cases is formed by the action of the hypobromite on bromoform (32).

[2] As has been indicated, exceptions to the Lieben rule are not unknown. Thus, acetoacetic acid (35) does not give the iodoform test. It should be mentioned in this connection that Hurd and Thomas found that acetoacetic ester with bleaching

112),[3] acetone (124), isopropyl alcohol (112, 190), 2-butanone (112, 35), *secondary*-butyl alcohol (124), 2-pentanone (35), 2-hexanone (124, 35), 2-octanol (124), 2-octanone (112, 35), acetophenone (124, 112, 35), levulinic acid (190), pyruvic acid (35), lactic acid (124, 190), mesityl oxide (34), 6-ethyl-3,4-dimethoxyacetophenone (168), 6-ethyl-3-ethoxy-4-methoxyacetophenone (109), 1-diethylaminobutanone-3 (172), and certain methyl sugars (14).

For water-insoluble compounds, however, the Lieben test is uncertain and likely to be misleading. A more useful form of the test has been developed by Fuson and Tullock (62), who found that dioxan could be used as a solvent. This modified test is carried out by dissolving the compound to be tested in 5 cc. of dioxan, adding dilute aqueous alkali, and a slight excess of iodine–potassium iodide solution, and then warming the mixture for two minutes at 60°C. After the excess iodine is discharged by means of alkali, the iodoform is precipitated by the addition of water.

The new procedure has been tried with a large number of compounds with results as indicated below.

Alcohols

Positive: isopropyl alcohol, methyl-*n*-amylcarbinol, 2-octanol, methylisopropylcarbinol, 2,3-butanediol, methylbenzylcarbinol.

Negative: methyl alcohol, allyl alcohol, trimethylene glycol, mannitol, isobutyl alcohol.

Aliphatic ketones

Positive: acetone, methyl ethyl ketone, methyl propyl ketone, 2-hexanone, methyl isobutyl ketone, 2-heptanone, 2-octanone, methyl isohexyl ketone, 4-methyl-2-heptanone, methyl cyclohexyl ketone, methyl γ-phenoxypropyl ketone, benzylacetone, benzohydrylacetone.

Mixed ketones

Positive: acetophenone, methyl *p*-tolyl ketone, *p*-chloroacetophenone, *p*-bromoacetophenone, methyl *p*-anisyl ketone, 2,4-dimethoxyacetophenone, 2-methyl-4-methoxyacetophenone, 5-methyl-2-methoxyaceto-

---

powder gave dichloroacetic acid in a yield of 60 per cent (94). Pinacolone (39) and many similar compounds involving steric hindrance fail to respond to the Lieben test. On the other hand, many compounds which do not possess either of the groupings CH_3COC— and $CH_3CH(OH)C$— give a positive Lieben test. Examples of this type are acetoxime, 2-methyl-2-butene, and pulegone (147).

[3] It is interesting to note that the corresponding acetal, $CH_3CH(OC_2H_5)_2$, does not give a positive iodoform test. However, if the acetal is shaken with a drop of hydrochloric acid it will then give the test (71).

phenone, acetocymene, 2,4,5-trimethylacetophenone, *o*-hydroxyacetophenone, *m*-hydroxyacetophenone, *p*-hydroxyacetophenone, 3-methoxy-4-hydroxyacetophenone, *o*-nitroacetophenone, *m*-nitroacetophenone, *p*-nitroacetophenone, *o*-aminoacetophenone, *m*-aminoacetophenone, *p*-aminoacetophenone, 2-aceto-1-naphthoxyacetic acid, 2-aceto-4-bromo-1-naphthoxyacetic acid.

Negative: α-chloroacetophenone, propiophenone, acetomesitylene, 3,5-dinitroacetomesitylene, 2,4,6-tribromoacetophenone, 3-amino-2,4,6-tribromoacetophenone, 1-aceto-2-naphthoxyacetic acid, 2-methoxy-1-acetonaphthone.

Unsaturated ketones

Positive: mesityl oxide, benzalacetone, 2-methyl-1-phenyl-1-buten-3-one, furfuralacetone.

Diketones

Positive: acetylacetone, acetonylacetone, benzoylacetone, *p*-bromobenzoylacetone, dibenzoylmethane, 1,3-diketohydrindene, 2,6-dimethyl-4-acetylacetophenone.

Negative: ω-acetylacetomesitylene, ω-benzoylacetomesitylene, di(β-isoduryloyl)methane.

Acids and acid derivatives

Positive: ethyl lactate, α-aminoisobutyric acid, levulinic acid, ethyl levulinate, γ-acetylbutyric acid, diethyl acetylsuccinate, diethyl α,α'-diacetylsuccinate.

Negative:[4] alanine,* *secondary*-butyl acetate,* *secondary*-amyl acetate,* diethyl phthalate,* diethyl adipate.*

Miscellaneous

Positive: acetoxime, diacetyl monoxime, α-phenylethylamine.

Negative: 2-pentene, 1,1-diphenyl-1-propene, 1-chloro-2,3-dihydroxypropane, propionitrile, isoeugenol, phenylacetylene, rhamnose, acetophenone oxime,* anethole, resorcinol, phloroglucinol.

The foregoing results of Fuson and Tullock were summarized in the following rule: *The test is positive for compounds which contain the grouping* CH_3CO—, CH_2ICO—, or CHI_2CO—[5] *when joined to a hydrogen atom or to a carbon atom which does not carry highly activated hydrogen atoms or groups*

[4] Compounds marked with an asterisk give iodoform, but require a longer period of heating than that specified in the procedure given.

[5] Compounds containing the CI_3CO— group would undoubtedly give a positive test also, but as yet no such compound is known in a pure state.

which provide an excessive amount of steric hindrance. The test will, of course, be positive also for any compound which reacts with the reagent to give a derivative containing one of the requisite groupings. Conversely, compounds which contain one of the requisite groupings will give a negative test in case this grouping is destroyed by the hydrolytic action of the reagent before iodination is complete.

A theoretical basis for the foregoing generalization is to be found in the three fundamentally different types of effects produced by the reagent. It is capable of oxidizing alcohols and amines, of replacing active hydrogen atoms by iodine atoms, and of cleaving certain types of carbon chains. For example, these three types of processes undoubtedly take place in the order mentioned when 2,3-butanediol is converted to iodoform:

$$\begin{matrix} CH_3CHOH \\ | \\ CH_3CHOH \end{matrix} \xrightarrow{\text{oxidation}} \begin{matrix} CH_3CO \\ | \\ CH_3CO \end{matrix} \xrightarrow{\text{iodination}} \begin{matrix} CI_3CO \\ | \\ CI_3CO \end{matrix} \xrightarrow{\text{cleavage}} \begin{matrix} CHI_3 \\ \\ CHI_3 \end{matrix} + \begin{matrix} COOH \\ | \\ COOH \end{matrix}$$

It is important to note, however, that the iodination will occur, not necessarily on an active methyl group, but rather at the point in the molecule where the most active hydrogen atoms are found. Thus, β-diketones having the grouping —$COCH_2CO$— are iodinated first at the methylene group. Apparently in these cases chain cleavage then occurs. The soundness of this explanation is attested by the fact that dibenzoylmethane and 1,3-diketohydrindene give a positive test; here the iodoform obviously derives from the methylene group, and diiodomethyl ketones—compounds containing one of the requisite groupings—must be postulated as intermediates. Similarly, although acetylacetone, benzoylacetone, and *p*-bromobenzoylacetone contain the acetyl group, the iodoform comes rather from the methylene group. This conclusion is, in turn, supported by the fact that ω-acetylacetomesitylene ($CH_3COCH_2COC_9H_{11}$) gives a negative test; this is to be expected, since diiodoacetomesitylene, on account of the hindrance involved, would not yield iodoform (147, 60).

Numerous compounds which do not contain one of the requisite groupings give a positive test presumably because, under the influence of the reagent, they give rise to products which do contain such groupings. Many alcohols are oxidized to the corresponding carbonyl compounds and so lead to the formation of iodoform. Amines of similar structures apparently undergo analogous transformations. In the case of certain esters and oximes the production of iodoform must be traced to hydrolysis products.

The iodoform reaction is greatly retarded by steric hindrance. The test is negative for all compounds which contain one of the requisite groupings joined to an aryl radical carrying two ortho substituents. The question as to what is actually formed in the case of hindered methyl ketones has

been solved by Poggi (147), who has shown very recently that when the procedure of Lieben is used pinacolone does not give iodoform[6] but is converted to diiodopinacolone, $(CH_3)_3CCOCHI_2$. Similar results have been been obtained by Fuson, Johnson, and Bull, who isolated diiodoacetomesitylene ($C_9H_{11}COCHI_2$) and 3-diiodoacetyl-2,4,6-trimethylbenzoic acid ($HOOCC_9H_{10}COCHI_2$) by the action of hypoiodite on acetomesitylene and 3-acetyl-2,4,6-trimethylbenzoic acid, respectively (60).

IV. STRUCTURAL DETERMINATION BY MEANS OF THE HALOFORM DEGRADATION

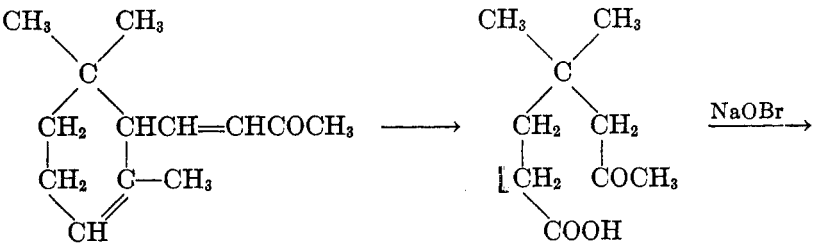
The great utility of the haloform reaction in the proof of structure depends primarily on the fact that it effects simultaneously the detection and oxidative degradation of a methyl ketone group. Moreover, it is highly specific for this grouping, and as a consequence can often be used safely with compounds which would be profoundly altered by ordinary oxidizing agents. It is impracticable to tabulate all of the compounds whose structures have been elucidated with the aid of the haloform reaction; several examples of its application to the field of terpene chemistry, wherein it has been of especial value, have been selected to illustrate its wide use as a degradative procedure.

The methyl heptenones, together with isoprene, are commonly regarded as key substances in the chemistry of the terpenes, not only because they are frequently isolated in degradative studies, but also because they are often the basis of synthetic work. The relation between the three most common methyl heptenones was demonstrated by Wallach, who found that they were all reduced to the same heptanone, and that the latter compound gave isoheptoic acid when treated with sodium hypobromite (207):

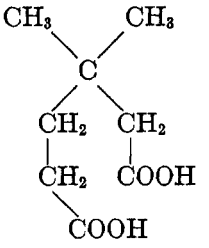
$$\left.\begin{array}{l}(CH_3)_2C{=}CHCH_2CH_2COCH_3\\(CH_3)_2CHCH{=}CHCH_2COCH_3\\(CH_3)_2CHCH_2CH{=}CHCOCH_3\end{array}\right\}\rightarrow(CH_3)_2CH(CH_2)_3COCH_3\rightarrow (CH_3)_2CH(CH_2)_3COOH$$

The haloform degradation has played a part in the structural studies of nearly every type of mono- and di-cyclic terpene. The ionones may be cited as typical examples. The positions of the double bonds in these compounds were established by the brilliant investigations of Tiemann, who oxidized the ionones to the corresponding ketonic acids, which were then converted by means of the haloform reaction to dimethyladipic acids (187, 186):

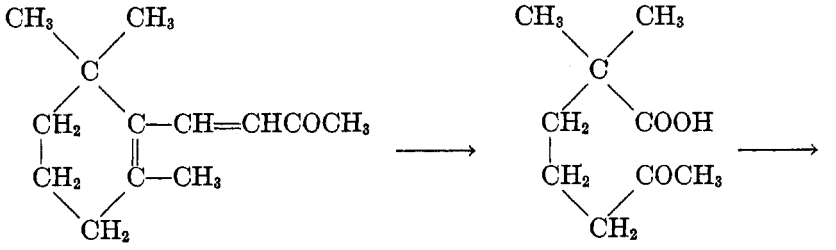
[6] The course of the reaction in the case of pinacolone is apparently dependent on the conditions, for with the procedure of Fuson and Tullock iodoform is obtained (62).



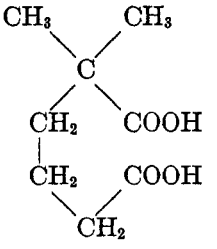
α-Ionone Isogeronic acid



β,β-Dimethyladipic acid

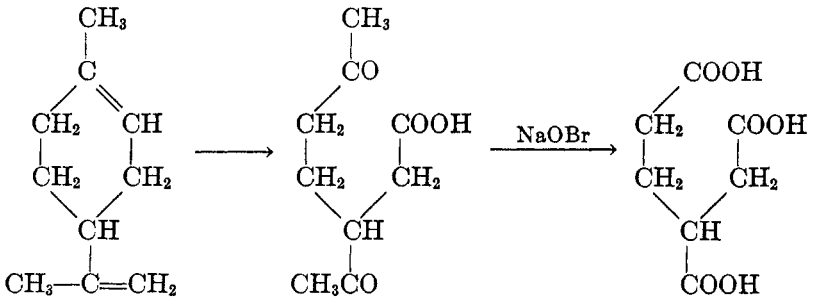


β-Ionone Geronic acid



α,α-Dimethyladipic acid

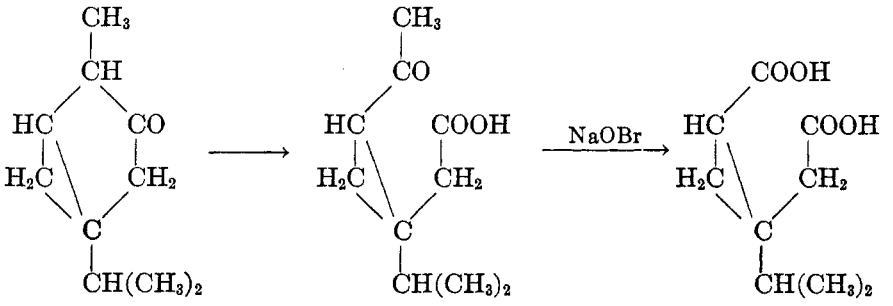
In a similar manner the structure of limonene (dipentene) was established by Tiemann and Semmler (188):



Limonene

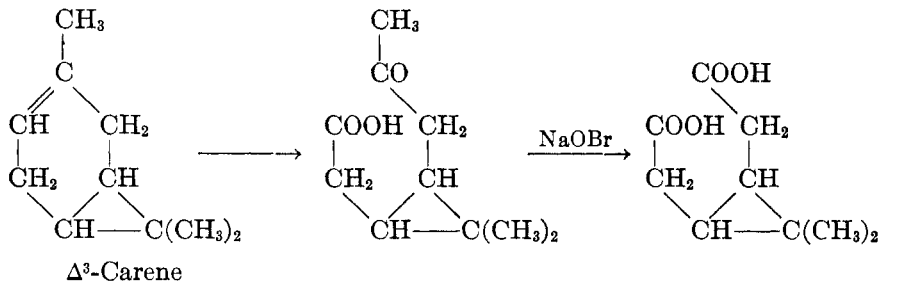
The β,δ-diacetylvaleric acid obtained by oxidation of limonene is converted by sodium hypobromite into the corresponding tribasic acid.

A similar degradation was involved in the chain of evidence which enabled Semmler (162) to arrive at the correct structure of thujone. Oxidation of thujone gave α-thujaketonic acid and this was converted to the cyclopropanedicarboxylic acid by means of hypobromite:

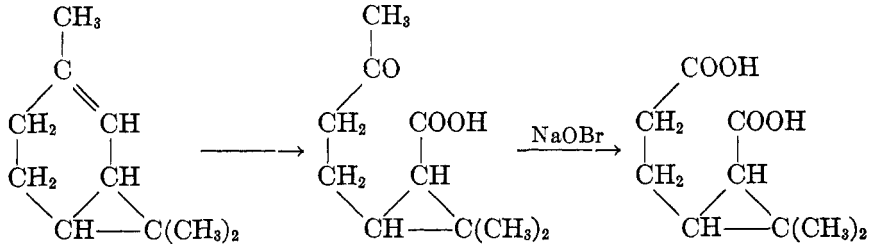


Thujone α-Thujaketonic acid

In the carane series, the positions of the double bonds in Δ^3-carene (166) and Δ^4-carene (170) were determined by oxidation, followed by treatment with hypobromite:

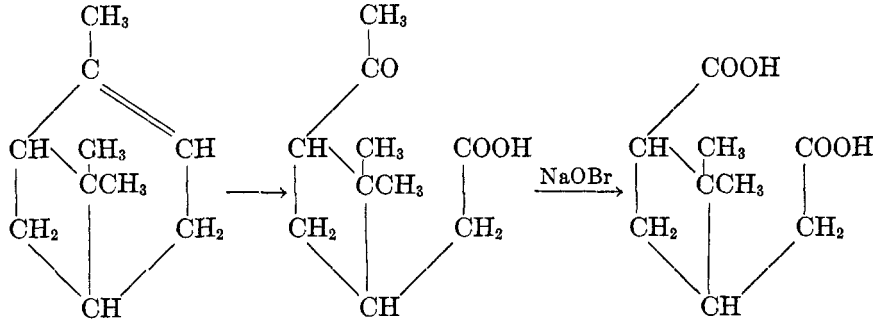


Δ^3-Carene



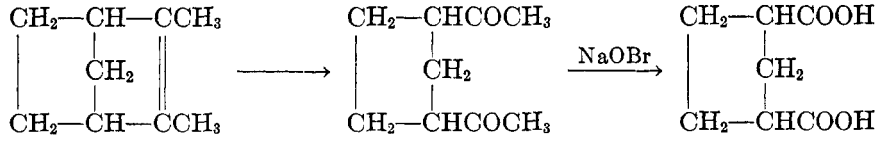
Δ^4-Carene

A similar procedure was used in the classical investigation by Baeyer of the structure of the pinanes. The pinonic acid resulting from the oxidation of α-pinene with permanganate was degraded to pinic acid by means of hypobromite (5, 7).



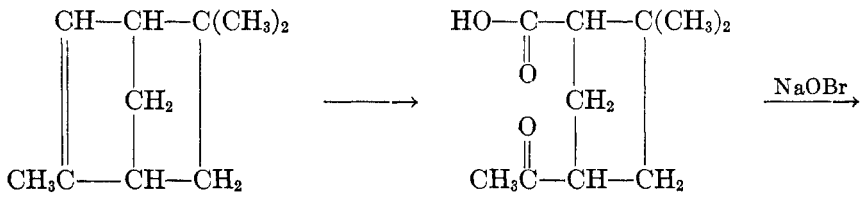
α-Pinene Pinonic acid Pinic acid

Semmler and Bartelt determined the structure of santene by ozonization followed by treatment with hypobromite (163):

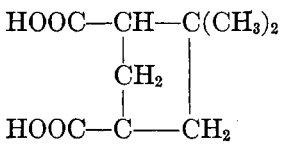


Santene

γ-Fenchene of the fenchane series, when subjected to ozonolysis, gave a keto aldehyde and a keto acid; the latter, when treated with hypobromite, was converted into apofenchocamphoric acid (107):

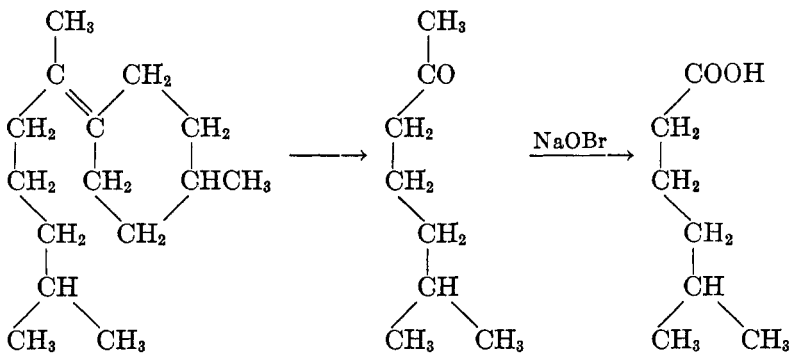


γ-Fenchene



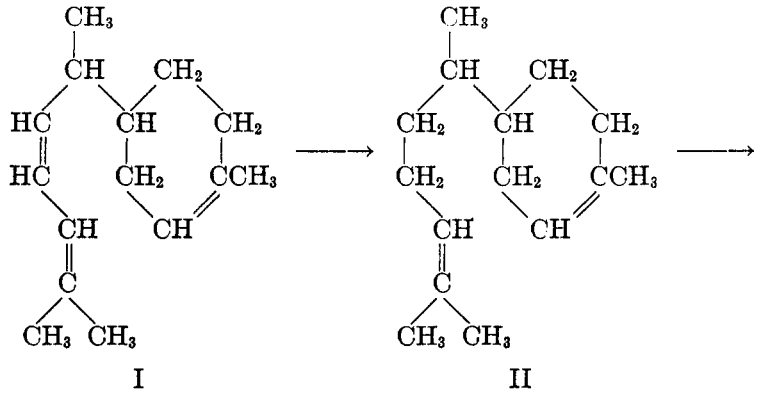
Apofenchocamphoric acid

Investigators of the sesquiterpenes have repeatedly used the haloform reaction but, in most cases, it is too early to estimate the significance of this work, since the structural problems involved are not entirely solved. Mention may be made, however, of the work of Ruzicka and van Veen, who oxidized tetrahydrobisabolene and then treated the acyclic ketonic fragment with hypobromite, which gave isoheptoic acid (155):

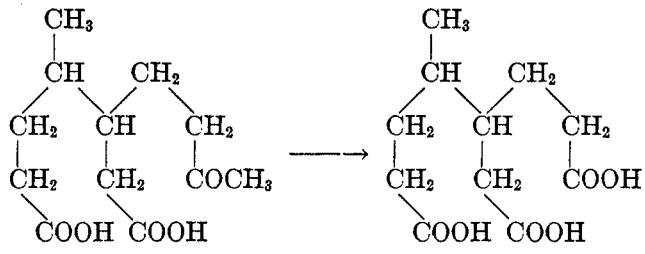


Isoheptoic acid

Zingiberene (I) may be mentioned also, as the haloform degradation has been particularly useful in the elucidation of its structure (156). Partial reduction followed by oxidation with permanganate converts zingiberene into a keto acid (III) which, with hypobromite, gives the corresponding tribasic acid (IV):



I II



III IV

V. QUANTITATIVE METHODS BASED ON THE HALOFORM REACTION

The fact that iodoform is a solid which is easy to isolate has led to many attempts to use the iodoform reaction in the quantitative estimation of compounds which undergo the reaction. As early as 1870 Lieben, by this means, was able to detect alcohol in water in dilutions as high as 1 part in 2000 (124). Krämer (112) subsequently developed a gravimetric procedure based on the iodoform reaction, in which the iodoform was extracted with ether and weighed after the evaporation of the volatile solvent. This original gravimetric method has been used by several investigators in the estimation of acetone in the presence of methanol (82, 2, 194, 104).

An excellent volumetric method was developed by Messinger (133, 195), which consisted in liberating the excess iodine used in the formation of iodoform, absorbing the free halogen in excess thiosulfate, and back-titrating with iodine, using starch as an indicator. Various modifications of this method have been suggested for the estimation of acetone in the presence of water (33, 66, 80, 148, 69), methanol (152, 148, 69, 10), ethanol (152, 175, 219, 148, 69, 105), urine (85), or glycerol (12). In addition, Elliott and Dalton used Messinger's iodometric method for estimating the amount of acetone in air (48). Hatcher and Mueller (79) state, however,

that with pyruvic acid, acetaldehyde, and acetone, sodium hypoiodite does not give a quantitative yield of iodoform under any conditions. The Messinger method has been studied also by Kebler (99), Vaubel and Scheuer (193), Keppeler (101), and Marriott (131).

van der Lee (119) found that the formation of iodoform from acetone takes place at a much lower pH than from alcohol. Thus, in testing acetone, sodium carbonate may be used, but with ethyl alcohol caustic alkali is necessary. Similarly, levulinic acid reacts more rapidly than does isopropyl alcohol or lactic acid. Upon this fact Kolthoff (105) has based a very sensitive test for acetone in the presence of alcohol by control of the pH used. An extremely sensitive form of this test was discovered by Kunz (115), who found that the presence of potassium persulfate imparted a red or orange color to the precipitated iodoform. Ammonium persulfate may also be used (161). With this reagent the formation of iodoform may be detected in concentrations as low as 1 part in 200,000 by the turbidity which appears.

The haloform reaction has also been employed in the quantitative estimation of lactic acid (96), levulinic acid (157), and pyruvic acid (79).

VI. THE USE OF THE HALOFORM REACTION IN SYNTHESIS

A. The haloforms

The synthesis of the haloforms themselves has almost always been accomplished by the action of hypohalites on ethyl alcohol or acetone. Chloroform, the most important commercially, is generally prepared by the action of bleaching powder on alcohol. Bromoform and iodoform, on the other hand, are best prepared by the electrolytic process (68). Iodoform is best prepared electrolytically from alcohol (181, 117) and bromoform from acetone, while the corresponding method of preparing chloroform is uneconomical (68).[7]

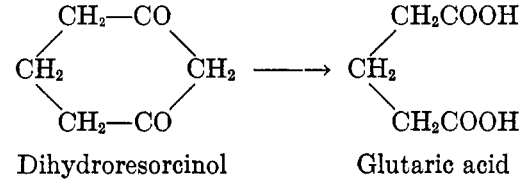
The haloforms, when prepared by the haloform reaction, are contaminated to a greater or less degree by the corresponding tetrahalomethanes. This is due to the action of the hypohalites on the haloforms by which the latter are converted into the corresponding tetrahalogen compounds: $CHX_3 + NaOX = CX_4 + NaOH$. This is a general reaction (83, 73, 8, 38); it often becomes the principal reaction when dilute solutions are used. Thus, Wallach (198) found that in the formation of bromoform from hypobromite and acetone in very dilute solutions, the reaction was slow and that carbon tetrabromide was the chief product. This influence of the pH on the course of reactions involving hypohalites is frequently noticed (105, 119, 79).

[7] For excellent reviews of the electrolytic methods, see Feyer (53) and Glasstone (68).

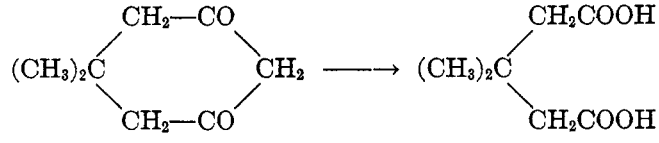
B. Saturated aliphatic acids

The saturated aliphatic acids are occasionally prepared by means of the haloform degradation of alcohols and ketones. The formation of trimethylacetic acid from pinacolone by the action of potassium hypochlorite (17) or potassium hypobromite (151, 67) is a synthesis of this type. Similarly, *tertiary*-butylacetic acid is made by the action of sodium hypobromite on 4,4-dimethyl-2-pentanone (86). A very large number of similar preparations is known, but in most cases the acid is more readily obtainable than the corresponding secondary alcohol or methyl ketone, and, as a consequence, the method has limited value in the synthesis of the fatty acids. Among the monobasic acids which have been made in this way are α,α-diphenylbutyric (132), α-methyl-α-ethylbutyric (141), β-phenylisovaleric (84), δ-phenylvaleric (20), α,α-dimethylcaproic (120), isoheptoic (207), caprylic (183), and capric (183, 74). Methyl ketonic acids are frequently encountered—especially among the oxidation products of terpenes—and in many instances these have been further degraded to the corresponding dibasic acids by means of the haloform method. Examples of these acids are methylsuccinic (145), isopropylsuccinic (199), isobutylsuccinic (13), α,α-dimethylsuccinic (185, 102, 210, 116), trimethylsuccinic (129), α,α-dimethylglutaric (184), α-isopropylglutaric (199, 209, 164), β-isopropylglutaric (22, 201), α-methyl-β-isopropylglutaric (199), β-methyladipic (206), α-isopropyladipic (212), β-isopropyladipic (202), α,α-dimethyladipic (187), pimelic (123, 200), and β,β-dimethylpimelic (122, 211). Lactonic acids have been made from the lactones of certain δ-acetyl-γ-hydroxyvaleric acids (81).

Of especial interest is the formation of glutaric acid from dihydroresorcinol (196) and of β,β-dimethylglutaric acid from dimethyldihydroresorcinol or its monobromo derivative (106, 196):



Dihydroresorcinol — Glutaric acid



Dimethyldihydroresorcinol — β,β-Dimethylglutaric acid

The haloform degradation appears to be generally applicable to diketones of this type.

As has been indicated in section IV, many alicyclic acids have also been made by the haloform degradation. Other examples are hexahydrobenzoic acid (204), the hexahydrotoluic acids (165, 213, 153), cyclopentanecarboxylic acid (138) and certain of its homologues (203, 139), norpinic acid (197, 103), cyclohexylacetic acid (205) and hexahydrotolylacetic acids (153), β-(2,2′,6-trimethylcyclohexyl)propionic acid (154), and 3-carboxy-1,1-dimethylcyclopropane-2-propionic acids (170, 144).

C. Unsaturated acids

Perhaps the most elegant application of the haloform reaction is in connection with unsaturated methyl ketones with which the usual oxidizing agents cannot be used. Hypohalites convert the acetyl group into a carboxyl group without altering the rest of the molecule. An early patent (46) sets forth a method for preparing cinnamic acid and its nuclear substitution products by the action of hypohalites on the corresponding benzalacetones:

$$ArCH{=}CHCOCH_3 \rightarrow ArCH{=}CHCOOH$$

α-Methyl-*p*-isopropylcinnamic acid (78) and nitrocinnamic acids (46) have been prepared in this way. Stoermer and Wehln (177), working with sodium hypochlorite, prepared a number of substituted cinnamic acids from the corresponding unsaturated methyl ketones, and stated that the method was general.

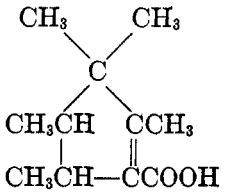
The method is also useful in the degradation of cinnamylideneacetone (40) and its derivatives:

$$ArCH{=}CHCH{=}CHCOCH_3 \rightarrow ArCH{=}CHCH{=}CHCOOH$$

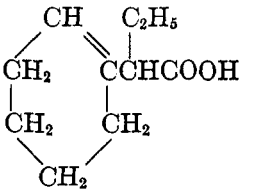
However, in the case of *p*-nitrocinnamylideneacetone, Einhorn and Gehrenbeck (47) found it necessary to use a hot concentrated solution of sodium hypochlorite, and that the yield of acid was small.

In the aliphatic series Doeuvre (43) has prepared α-bromo-β-methylcrotonic acid from the corresponding ketone by the action of potassium hypobromite. Similarly, Cuculescu (34) obtained β-methylcrotonic acid in a 75 per cent yield from mesityl oxide, using iodine in alkali. Likewise, the hexenoic acid, $(CH_3)_2C{=}CBrCH_2CH_2COOH$, was made from the corresponding bromomethylheptenone (208).

Examples of cyclene acids which have been synthesized by this method are tetrahydrotoluic acid (153), β-campholytic acid (16), and α-ethyl-Δ^1-cyclohexenylacetic acid (108).

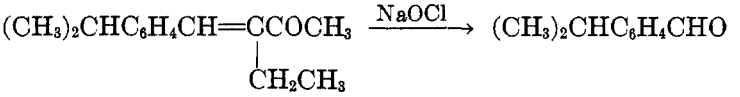


β-Campholytic acid

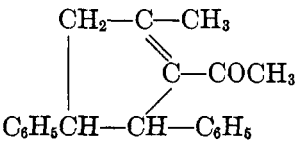


α-Ethyl-Δ¹-cyclohexenyl-acetic acid

That the method is not universally applicable to unsaturated methyl ketones is indicated by the experience of Warunis and Lekos (214), who found that the condensation product of cuminaldehyde and methyl propyl ketone was reconverted to the aldehyde by the action of sodium hypochlorite.



Similarly, Harries and Hübner (77) found that 1-acetyl-2-methyl-4,5-diphenyl-1-cyclopentene



resisted degradation by the hypobromite method. It was suggested that this may be due to steric hindrance.

D. Aromatic acids

More useful in general is the preparation of aromatic acids by the haloform degradation of the corresponding acetophenones. This method has been widely used and owes its importance to the fact that the introduction of a carboxyl group on an aromatic ring is usually much more difficult than the introduction of the acetyl group. By this method Mills (135) obtained durylic acid from acetylpseudocumene in an 80 per cent yield (171). Van Arendonk and Cupery (191) have worked out the optimum conditions for degrading acetophenones to the corresponding benzoic acids and have obtained yields which vary from 85 to 96 per cent of the theoretical amounts. According to these investigators, hypochlorite is much superior to hypobromite or hypoiodite. They found, however, that hydroxyl or

nitro groups interfere with the reaction.[8] An interesting application of this method is the preparation of 2,2′,6,6′-tetramethoxy-3,3′-dicarboxydiphenyl from the corresponding diacetyl compound (192).

VII. THE MECHANISM OF THE HALOFORM REACTION

Since alcohols which give the haloform reaction are capable of being oxidized to methyl ketones or acetaldehyde, it has been assumed that in all these cases either acetaldehyde or a methyl ketone is formed as an intermediate. There is no example of the haloform reaction in which such carbonyl compounds may not be involved. It seems justifiable, then, to limit the discussion of mechanism to compounds which contain the acetyl group united with either hydrogen or carbon.

From the work of Liebig (142), Orndorff and Jessel (143), Zincke (222), Abbott (1) and others it is clear that the generalized equation for the reaction is of the form

$$RCOCH_3 + 3MOX = RCOOM + CHX_3 + 2MOH$$

where R may be hydrogen or any group of atoms, provided only that the group contains a carbon atom to which the carbonyl group is joined directly. MOX represents a hypohalite. An inspection of the equation shows that two distinctly different types of processes are involved in the haloform reaction—halogenation and chain cleavage. That the halogenation precedes the cleavage was assumed by Orndorff and Jessel (143), Zincke (222), Noyes (140), and others, who advanced the hypothesis that a trihalomethyl derivative was formed as an intermediate and that this was then cleaved by the alkali. In the case of the formation of iodoform from acetone the equations took the following form:

$$CH_3COCH_3 + 3NaOI = CH_3COCI_3 + 3NaOH$$
$$CH_3COCI_3 + NaOH = CHI_3 + CH_3COONa$$

That this represents the actual sequence is now beyond question,[9] and it is

[8] *m*-Nitroacetophenone, *p*-hydroxyacetophenone, resacetophenone, and nitroresacetophenone cannot be converted to acids by this method (191). However, since compounds of these types do give iodoform when treated according to the procedure of Fuson and Tullock (62), it is clear that the difficulty in the above cases is not due to the failure of the haloform reaction to take place.

[9] In the case of acetone the hexahalo derivative has also been suggested as an intermediate (222, 159). Since, however, Weidel and Gruber (215) found that hexabromoacetone reacts almost quantitatively with sodium hydroxide according to the equation

$$CBr_3COCBr_3 + 2NaOH = 2CHBr_3 + Na_2CO_3$$

it is clear that the hexabromoketone cannot be an intermediate in the main reaction, for sodium acetate is always a principal product.

certain that in the haloform reaction we have to deal with halogenation followed by chain cleavage. It will be convenient to consider the two processes separately.

A. The halogenation phase of the haloform reaction

That the trihaloacetyl derivatives actually are intermediates seems certain, inasmuch as it has been possible in certain cases to interrupt the reaction before chain cleavage occurs. This has been accomplished in the case of pinacolone (151) and with a number of methyl aryl ketones carrying

TABLE 1

Trihalomethyl phenyl ketones prepared by the use of hypohalites

POSITIONS ON THE PHENYL GROUP						REFERENCE
1	2	3	4	5	6	
$COCCl_3$	CH_3		CH_3		CH_3	63
$COCBr_3$	CH_3		CH_3		CH_3	63
$COCCl_3$	OCH_3		OCH_3		OCH_3	59
$COCBr_3$	OCH_3		OCH_3		OCH_3	59
$COCBr_3$	Br		Br		Br	61
$COCCl_3$	Br		Br		Br	61
$COCCl_3$	CH_3	NO_2	CH_3	NO_2	CH_3	63
$COCBr_3$	CH_3	NO_2	CH_3	NO_2	CH_3	63
$COCBr_3$	Cl		Cl		Cl	57
$COCBr_3$	CH_3	Br	CH_3	Br	CH_3	55
$COCCl_3$	CH_3	Br	CH_3	Br	CH_3	55
$COCCl_3$	CH_3	$COCCl_3$	CH_3		CH_3	70
$COCBr_3$	CH_3	$COCBr_3$	CH_3		CH_3	70
$COCCl_3$	CH_3	CH_3		CH_3	CH_3	70
$COCBr_3$	CH_3	CH_3		CH_3	CH_3	70
$COCCl_3$	CH_3	CH_3	CH_3		CH_3	70
$COCBr_3$	CH_3	CH_3	CH_3		CH_3	70
$COCCl_3$	CH_3	CH_3	CH_3	$COCCl_3$	CH_3	70
$COCBr_3$	CH_3	CH_3	CH_3	$COCBr_3$	CH_3	70

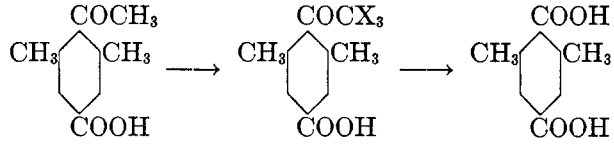
two ortho substituents. Thus, with solutions of hypohalites, acetomesitylene is converted to α,α,α-trihaloacetomesitylene (63). Table 1 lists the trihalomethyl phenyl ketones which have been prepared by the use of hypohalites.

A study has been made of the influence of various ortho substituents on the stability of the trihalomethyl ketones. As table 1 shows, the substituents which were used in this study are methyl (63, 70), bromine (61), chlorine (57), and methoxyl (59). Of these, the methoxyl group seems to have the least effect in retarding the cleavage phase, although even in this

case the trihalomethyl ketones are sufficiently stable toward alkalies to make it possible to prepare them in alkaline solution.

Without exception, the trihalomethyl ketones mentioned above were insoluble in the alkaline media used in their preparation. Experiments with alcohol and pyridine as solvents indicated, however, that the great stability of these compounds was due in part, at least, to their insolubility in alkali. To demonstrate clearly the effect of solubility on the stability of hindered trihalomethyl ketones, Bull and Fuson synthesized 3,5-dimethyl-4-acetylbenzoic acid and converted it to the corresponding trihalomethyl ketonic acids (24). These compounds were all soluble in alkali, hence the insolubility factor was eliminated.

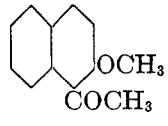
The synthesis of these compounds in alkaline solutions demonstrates that they are moderately stable toward alkalies. Moreover, when dissolved in sodium hydroxide solutions at 0°C. they could be recovered unchanged. However, if these solutions were allowed to stand, or were warmed, the trihalomethyl ketonic acid underwent rapid cleavage to dimethylterephthalic acid:



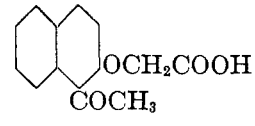
These results indicated that the solubility factor is of considerable importance to the stability of the trihalomethyl ketones in alkali. The ease with which cleavage takes place is greatly increased by the solubility of the ketone in alkali, and, conversely, the stability of trihalomethyl ketones is greatly enhanced by their insolubility in aqueous alkali.

A more striking demonstration of this fact has been furnished by the same authors; they compared the reactions of methyl aryl ketones in which (a) the solubility factor was changed while the steric factor remained constant, and (b) the steric factor was changed while the solubility factor remained constant (25).

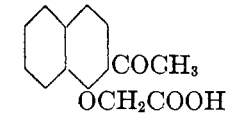
Such a comparison was satisfactorily afforded by the study of the three ketones 1-aceto-2-naphthyl methyl ether (I), 1-aceto-2-naphthoxyacetic acid (II), and 2-aceto-1-naphthoxyacetic acid (III).



I



II



III

In the first two, the solubility factor is changed while the steric factor remains approximately constant, since the molecular volume of the acetoxy group, while unknown, would certainly not be less than that of the methoxyl group. In the last two the steric factor is changed while the solubility factor remains approximately constant, since the solubility of these position isomers in alkali may be assumed to be the same.

1-Aceto-2-naphthyl methyl ether (I) and the corresponding trihalomethyl derivatives were prepared by Fuson, Farlow, and Stehman (59), who found it necessary to reflux the trihaloacetyl derivatives for four hours with 20 per cent alkali before the cleavage to the corresponding acid was complete.

The hindered ketone (II), when dissolved in solutions of sodium hypohalite, gave 1-trihaloacetyl-2-naphthoxyacetic acid (25). The synthesis of these compounds in alkaline solutions demonstrates that they are moderately stable toward alkalies. Moreover, when dissolved in sodium hydroxide solutions at 0°C., they could be recovered unchanged. Yet the effect of the solubility on the stability of these trihalomethyl ketonic acids was indicated by their conversion into the dibasic acid when warmed with dilute alkali for half an hour, *or in approximately one-eighth the time required for the cleavage of the alkali-insoluble trihalomethyl ketones derived from 1-aceto-2-naphthyl methyl ether* (I) (59). Hence the cleavage of these two types of trihalomethyl ketones possessing approximately equal steric factors, and differing essentially only in solubility, indicates that the introduction of a solubilizing group leads to an increase in the ease of cleavage, and, conversely, that the insolubility of the trihalomethyl ketones in alkali greatly enhances their apparent stability.

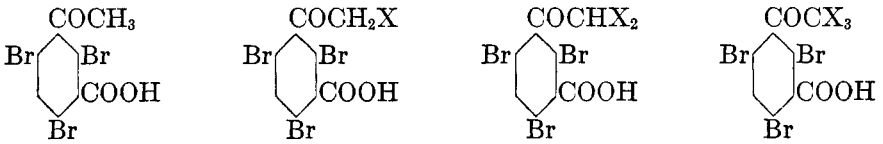
When the unhindered ketone (III) was treated with ice-cold solutions of hypohalites, quantitative cleavage to the dibasic acid resulted (25). This result was observed under conditions identical with those obtaining when the trihalomethyl ketones of the hindered acid were prepared. Even when the reaction time was reduced to five minutes and when, in addition, an attempt was made to salt out any trihalomethyl ketonic acids which might have been formed,[10] cleavage to the dibasic acid was quantitative. In sharp contrast to this behavior is the fact that the hindered trihalomethyl ketonic acids are readily prepared in cold dilute alkaline hypohalite solutions and, indeed, can be recovered unchanged from dilute alkali at room temperature.

It was, of course, highly probable that these trihaloacetyl derivatives were formed by a stepwise halogenation of the corresponding ketones, but

[10] These trihaloacetylbenzoic acids are relatively insoluble in alkali. Indeed, the isolation of the insoluble sodium salt has been used as a convenient means of purifying these derivatives (24).

because of the rapidity of the reaction, this aspect of the halogenation phase had heretofore eluded demonstration. An intermediate monohalogen derivative was isolated by Fuson, Bertetti, and Ross (57), who succeeded in preparing the monochloroacetyl derivative of 2,4,6-trichloroacetophenone in sodium hypochlorite solution.

The isolation of all the intermediate haloacetyl derivatives has recently been accomplished (60) by the treatment of 2,4,6-tribromo-3-acetylbenzoic acid with alkaline hypohalites for various periods of time, ranging from fifteen minutes to twenty-four hours.



The isolation of these compounds clearly demonstrates that the halogenation phase of the haloform reaction involves a step-by-step halogenation to the trihaloacetyl derivatives.

The mechanism of the halogenation reaction still remains obscure. This process is often assumed[11] to proceed through the enol form of the methyl ketone in order to account for the fact that the iodoform and bromoform reactions are pseudo-unimolecular.[12] Bartlett (9) and others have assumed that the rate-controlling reaction is the enolization, and that all subsequent reactions are extremely rapid.

B. The cleavage phase of the haloform reaction

The evidence for the final step in the haloform reaction was set forth by Liebig, who prepared chloroform by the action of alkali on chloral (126, 127):

$$CCl_3CHO + NaOH = CHCl_3 + HCOONa$$

Many compounds containing the trihaloacetyl grouping (CX_3CO—) joined to hydrogen or to carbon are now known and, except in certain special cases already noted which involve steric hindrance, these are readily cleaved by alkalies to give a haloform and the salt of an acid: $RCOCX_3 + NaOH = CHX_3 + RCOONa$. Tables 2, 3, and 4 contain lists of such compounds.

[11] See, for example, Pieroni and Tonniolo (146), Bartlett (9), Sukhnevich and Chilingaryan (180).

[12] The reaction of acetone with hypochlorite is a bimolecular reaction, according to Bartlett (9); in this connection it is interesting to note that Böttiger and Kötz (18) have found the alkaline decomposition of chloral hydrate is itself a second-order reaction when a great excess of alkali is present.

Trihaloacetyl derivatives of more complex types have also been prepared and subjected to cleavage with alkali. Among these are derivatives of α-naphthol (87), tetralin (89), β-naphthyl methyl ether (59), β-naphthoxyacetic acid (25), and pyrrole (54).

In most cases strong alkalies such as sodium, potassium, calcium, and barium hydroxides are used to bring about the cleavage, but sodium carbonate (217) and ammonium hydroxide (29) have been employed also. That sodium carbonate is not always sufficient is shown by the work of Zincke and Egly (223), who carried out the following reaction in *hot* sodium carbonate solution:

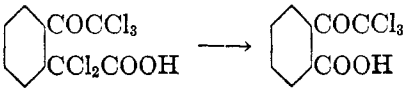


TABLE 2

Trihalomethyl aldehydes and ketones (aliphatic)

COMPOUND	REFERENCE	COMPOUND	REFERENCE
CCl_3CHO	127, 149, 216, 49	CCl_3COCH_2Br	29
		CBr_3COCBr_3	215, 75
CBr_3CHO	130	$CCl_2BrCOCClBr_2$	76
CCl_3COCH_3	111, 136, 29	CBr_3COCCl_2Br	76
		$CBr_3COCClBr_2$	76
CBr_3COCH_3	50	$CBr_3COCHBr_2$	28
$(CH_3)_2CHCOCCl_3$	97	$CBr_3COCOCBr_3$	95
CCl_3COCH_2Cl	29	$CCl_3COCCl{=}CHCHCl_2$	221
$CCl_3COCHCl_2$	29	$CCl_3COCCl{=}CClCHCl_2$	225
CCl_3COCCl_3	29	$(CH_3)_3CCOCBr_3$	151
CBr_3COCH_2Cl	29		

TABLE 3

Trihalomethyl ketonic acids (aliphatic)

COMPOUND	REFERENCE
$CBr_3COCH{=}CHCOOH$	217
$CBr_3COCBr{=}CHCOOH$ (?)	217
$CCl_3COCH{=}CHCOOH$	100
$CCl_3COCCl{=}CHCOOH$	221, 226
$CCl_3COCHBrCHBrCOOH$	100
$CCl_3COCCl{=}CClCOOH$	231, 227
$CCl_3COCCl{=}C(CH_3)COOH$	176, 100, 221, 220
$CCl_3COCCl{=}CHCCl_2COOH$	221
$CCl_3COCCl{=}CClCCl_2COOH$	225
$CCl_3CO(CH_2)_8COOH$	137
$CCl_3COCCl_2CHClCCl_2COOH$	231

TABLE 4

Trihalomethyl aryl ketones and ketonic acids

POSITIONS ON THE PHENYL GROUP						REFERENCE
1	2	3	4	5	6	
$COCI_3$						31
$COCCl_3$						65, 41
$COCBr_3$						137
$COCCl_3$			CCl_3			52
$COCCl_3$	CCl_3		CCl_3			51
$COCCl_3$	COOR		CCl_3			51
$COCCl_3$	COOR			CCl_3		51
$COCCl_3$	CCl_3		CCl_3	$COCCl_3$		51
$COCCl_3$	CH_3	$COCCl_3$	CCl_3		CCl_3	51
$COCCl_3$	CCl_3			CCl_3		51
$COCCl_3$			OCH_2CH_3			87
$COCCl_3$		SO_3H	OCH_2CH_3			87
$COCCl_3$			OCH_3			87
$COCCl_3$	CH_3		OCH_3			87
$COCCl_3$		CH_3	OCH_2CH_3			87
$COCCl_3$	OCH_3			CH_3		87
$COCCl_3$		OCH_3	OCH_3			87
$COCCl_3$		Br	OCH_3			87
$COCCl_3$			OC_6H_5			87
$COCCl_3$	CH_3		OH	CH_3		89
$COCCl_3$	CH_3		OH	$CH(CH_3)_2$		89
$COCCl_3$		CH_3	OH		$CH(CH_3)_2$	89
$COCCl_3$		CH_3	OH			88
$COCCl_3$			OH			88
$COCCl_3$	OH		CH_3			88
$COCCl_3$	CH_3		OH			88
$COCCl_3$	OCH_3			CH_3		88
$COCCl_3$	OH			CH_3		88
$COCCl_3$	COOH		COOH			51
$COCCl_3$	COOH			COOH		51
$COCCl_3$	Cl	Cl	Cl	Cl	COOH	230
$COCCl_3$			COOH			52
$COCCl_3$	COOH					229
$COCCl_3$			$COOCH_3$			52
$COCCl_2Br$	COOH					229
$COCClBr_2$	COOH					229
$COCCl_3$	COOH		COOH		Br	224
$COCCl_3$	CCl_2COOH					223
$COCBr_3$	COOH					229, 64

However, the resulting ketonic acid was decomposed by alkali into chloroform and phthalic acid.

An entirely new light was thrown on the nature of the cleavage of trihalomethyl ketones by an experiment of Jackson and Adams (95). Working with hexabromodiacetyl, they found that cleavage was induced by sodium acetate:

$$CBr_3COCOCBr_3 + H_2O \xrightarrow{CH_3COONa} 2CHBr_3 + (COOH)_2$$

Houben and Fischer have subsequently demonstrated that the process is catalytic. In the presence of sodium as a catalyst, trichloromethyl ketones react with alcohols to give chloroform and esters: $RCOCCl_3 + ROH = RCOOR + CHCl_3$ (90). Even more significant is the discovery that trichloroacetophenone, although unchanged by seven hours' heating with water at 170°C., is immediately decomposed by the addition of one drop of potassium hydroxide solution to a methyl alcohol solution of the ketone (91). That the cleavage is catalytic is clearly proved by the fact that the ketone is smoothly decomposed by being heated for several hours with water containing a little potassium acetate:

$$C_6H_5COCCl_3 + H_2O \rightarrow C_6H_5COOH + CHCl_3 \text{ (91)}$$

We may conclude with certainty that the mechanism of the haloform reaction involves a stepwise halogenation of compounds which undergo the reaction, followed by chain cleavage of the trihaloacetyl derivatives thus formed, according to the following scheme:

$$\begin{aligned} RCOCH_3 &\rightarrow RCOCH_2X \\ RCOCH_2X &\rightarrow RCOCHX_2 \\ RCOCHX_2 &\rightarrow RCOCX_3 \\ RCOCX_3 &\rightarrow RCOOH + HCX_3 \end{aligned}$$

VIII. REACTIONS RELATED TO THE HALOFORM REACTION

From what has gone before, it is evident that the haloform reaction involves several types of processes—halogenation, chain cleavage, and, if we include alcohols and amines, oxidation. Moreover, each of these represents a very large group of reactions of which the one under consideration is but a single type. It is beyond the scope of the present article to attempt a survey of the work which has been done on reactions which are related to the haloform reaction, yet there are a few degradation processes which resemble the haloform reaction so closely as to warrant mention in this connection. Those mentioned below not only have a formal similarity to the haloform reaction, but resemble it also in the great ease with which they proceed.

A. Modifications of the haloform reaction

One of the most interesting modifications of the haloform reaction was reported by Chattaway and Baxter (27), who found that nitrogen triiodide reacted with acetophenone to give benzamide and iodoform. The triiodoacetophenone was postulated as an intermediate:

$$C_6H_5COCH_3 + NI_3 \rightarrow (C_6H_5COCI_3) \rightarrow C_6H_5CONH_2 + CHI_3$$

The cleavage in this case appears to be produced by ammonia. Amide formation by the action of ammonia was reported as early as 1886 by Cloëz (29), who carried out the following reaction

$$CHBr_2COCBr_3 + NH_3 \rightarrow CHBr_2CONH_2 + HCBr_3$$

and many others of the same type. Similarly, Weidel and Gruber (215) obtained tribromoacetamide from hexabromoacetone by the action of ammonia.

$$CBr_3COCBr_3 + NH_3 \rightarrow CBr_3CONH_2 + HCBr_3$$

Similar results were obtained by Hantzsch (76) with other hexahaloacetones. Likewise, ammonia and aniline were found to act upon hexabromodiacetyl to give, respectively, oxamide and oxanilide (95). Cloëz (29) states that similar decompositions can be accomplished by the action of toluidine, allylamine, diethylamine, ethylene diamine, and urea on trihaloacetyl compounds. A result of especial interest has been reported by Datta and Prosad (36) who, by using iodine and ammonia, obtained iodoform from di- and tri-ethylamine.

As has already been mentioned, Houben and Fischer discovered a modification of the haloform reaction in which the trihaloacetyl compound is decomposed by alcohol in the presence of a small amount of sodium (90). Esters and a haloform are formed in this reaction according to the equation:

$$RCOCCl_3 + R'OH \rightarrow RCOOR' + HCCl_3$$

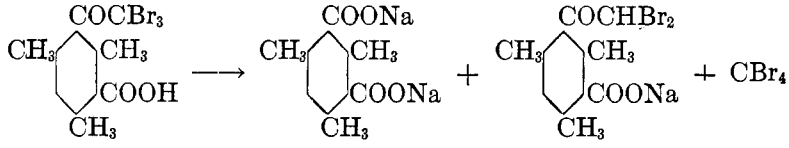
B. Reactions analogous to the haloform reaction

It is a well-known fact that hypohalites react with compounds containing active hydrogen atoms in such a manner as to replace the latter by halogen atoms. In this review, however, we shall mention only examples of this type of reaction in which *hydrogen on carbon* is replaced. Examples are known of the replacement of the hydrogen atoms of methylene (58, 56) and methine (114) groups by halogen by the action of hypohalites. It is especially noteworthy that in these types of halogenation the methylene and the methine groups are not necessarily adjacent to a carbonyl group.

Of the examples in which a carbonyl group is not involved, the most striking are the acetylenes (15), cyclopentadiene (178), and the haloforms (198, 32, 8). As has already been stated, the conversion of a haloform to the corresponding tetrahalomethane is a general reaction and takes place quantitatively (83, 73, 38, 8).

From these facts emerges the generalization that mobile or active hydrogen atoms on carbon are replaced by halogen in the treatment with hypohalites. It has been suggested (146) that this process involves enolization, followed by addition of the hypohalite to the enol form. From the foregoing examples, however, it is clear that replacement of hydrogen takes place in some compounds which are incapable of enolization. Moreover, no proof has yet been found that an enol form is involved in any of these cases. Further, it is worth noting that a halogen atom which has replaced an active hydrogen atom has certain peculiar properties, such as that of being itself a halogenating agent, *and this property is shared by the carbon tetrahalides in which enolization to a hypobromite structure cannot be assumed to account for the unusual reactivity of the atom involved* (93).

An interesting example of this peculiar behavior was discovered by Johnson and Fuson (98), who found that 2,4,6-trimethyl-4-tribromoacetylbenzoic acid was converted by alkali into the salts of 2,4,6-trimethylisophthalic acid and *2,4,6-trimethyl-4-dibromoacetylbenzoic acid*, according to the following scheme:



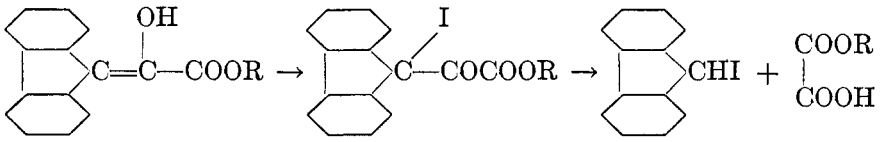
Carbon tetrabromide was also formed in the reaction, and it must be supposed that it results from the brominating action of the tribromomethyl ketone on bromoform.

An interesting extension of the haloform reaction is seen in the formation of iodoform by the action of hypoiodite on silver, copper, and mercury acetylides (118). Here the results suggest hydration to give a methyl ketone, which thereafter undergoes the normal haloform reaction. Recent work on this interesting reaction indicates that this behavior of acetylides may be general (137).

Another reaction, clearly of the haloform type, was observed by Reissert (150), who found that *o*-nitrophenylpyruvic ester is converted by sodium hypobromite into *o*-nitrobenzal bromide, a compound which may be regarded as bromoform in which one atom of bromine is replaced by an aryl group.

$$o\text{-}NO_2C_6H_4CH_2COCOOR \rightarrow o\text{-}NO_2C_6H_4CHBr_2 + \begin{matrix}COOR\\|\\COOH\end{matrix}$$

A similar case was discovered by Kuhn and Levy (114), in which a biphenylene radical replaces two of the halogen atoms of the haloform. These investigators obtained 9-iodofluorene by the action of hypoiodite on α-hydroxy-β-diphenyleneacrylic ester:



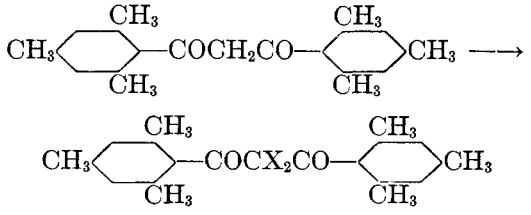
Another interesting and synthetically important variation of the haloform degradation is the catalytic decomposition which occurs when solutions of imides of trichloromethyl ketones are allowed to stand over alkalies. Chloroform and the corresponding nitrile are produced.

A number of examples of this type have been found by Houben and Fischer, who state that the reaction is general (92).

The action of hypohalites on *β-diketones* has already been discussed; it gives rise to the formation of a haloform or of a closely related type of compound. Thus, acetyl-*p*-bromoacetophenone (218), dihydroresorcinol (196), methone (196, 106), and bromomethone (106) yield bromoform with hypobromite. The process has been formulated as follows (218):

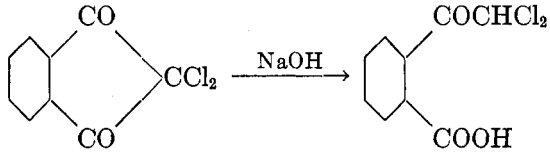
$$RCOCH_2COR' + 2NaOX \rightarrow RCOCX_2COR' + 2NaOH \quad (1)$$
$$RCOCX_2COR' + NaOH \rightarrow RCOONa + R'COCX_2H \quad (2)$$
$$R'COCX_2H + NaOX \rightarrow R'COCX_3 + NaOH \quad (3)$$
$$R'COCX_3 + NaOH \rightarrow R'COONa + HCX_3 \quad (4)$$

The first step is exemplified by the case of di(β-isoduryloyl)methane, which is transformed by hypohalites into the corresponding dihalodiketone (218):

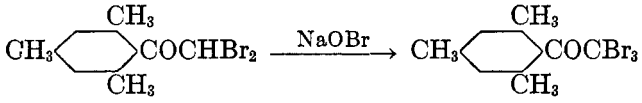


Here the hindrance offered by the mesityl groups arrests the reaction at the first stage.

The second step—the cleavage of the dihalodiacylmethanes by alkalies—is illustrated by the reaction of dichlorodiketohydrindene with alkali to give *o*-dichloroacetylbenzoic acid (228):

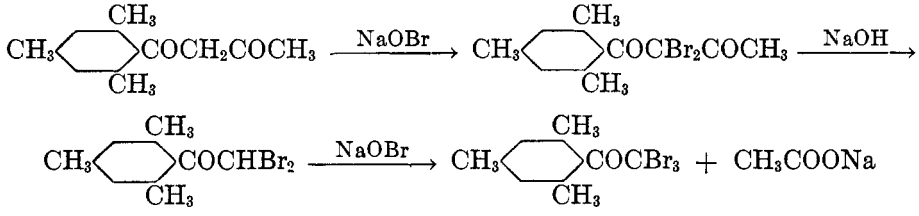


The third step is illustrated by the reaction of α,α-dibromoacetomesitylene with hypobromite, the corresponding trihaloacetyl derivative being produced (56):



The last step—the cleavage of trihaloacetyl compounds—is, of course, illustrated by a great number of known compounds.[13]

A combination of the first three steps is illustrated in the reaction of α-acetylacetomesitylene, which is converted by alkaline hypobromite to α,α,α-tribromoacetomesitylene (218):



It is interesting to note that this is also an example of a methyl ketone which does not give the haloform reaction; the acetyl group is eliminated in the form of acetic acid.

Closely similar to the behavior of β-diketones is that of β-ketonic esters. In the case of acetoacetic ester the product with calcium hypochlorite is dichloroacetic acid, formed as follows (94):

$$CH_3COCH_2COOR \rightarrow CH_3COCCl_2COOR \rightarrow CH_3COOH + CHCl_2COOH + ROH$$

[13] See tables 2, 3, and 4.

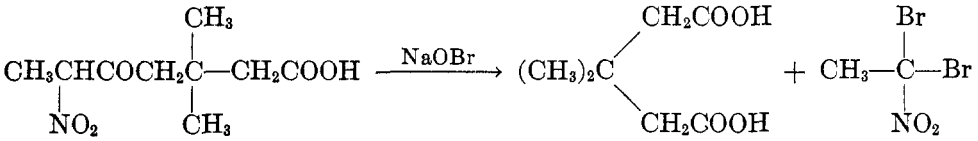
That this correctly represents the mechanism is supported by Brühl's observation (23) that bromine in alkali converts ethyl acetoacetate to ethyl α-bromoacetoacetate and ethyl α,α-dibromoacetoacetate:

$$CH_3COCH_2COOC_2H_5 \xrightarrow{NaOBr} CH_3COCHBrCOOC_2H_5 \xrightarrow{NaOBr} CH_3COCBr_2COOC_2H_5$$

The behavior of methyl ketones is paralleled by that of nitromethyl ketones. Thiele and Haeckel (182) found that α-nitroacetophenone gives dibromonitromethane and bromopicrin with hypobromite:

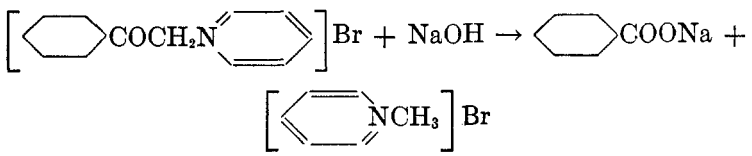
$$C_6H_5COCH_2NO_2 \rightarrow C_6H_5COONa + HCBr_2NO_2 + CBr_3NO_2$$

A similar degradation was observed by Toivonen, Osara, and Ollila (189):



It is interesting to note at this point that methyl sulfones and sulfoxides do not give haloforms with hypohalites (169).

One of the outstanding characteristics of the haloform type of reaction is the ease with which it takes place. In this respect it is set off sharply from the cleavage by alkali of ordinary ketones, β-diketones, β-ketonic esters, and the like. A reaction very similar to the haloform reaction in this respect is the cleavage of keto quaternary ammonium salts of the type illustrated by phenacylpyridinium bromide (6). Schmidt and van Ark (160) have shown that the reaction takes place according to the equation:



Kröhnke (110), Krollpfeiffer and Müller (113), and others (4) have confirmed and extended these results.[14] It appears that this cleavage of β-keto pyridinium halides is a general reaction of potential synthetic importance.

[14] Auwers and Lämmerhirt (3) showed that certain α-halogen ketones could be degraded to acids by treatment with pyridine; it seems probable that here also the pyridinium halide is formed as an intermediate.

IX. SUMMARY

1. Methyl ketones and acetaldehyde yield haloforms when treated with hypohalites. The process involves stepwise halogenation followed by chain cleavage of the resulting trihalomethyl derivative.

2. A few methyl ketones fail to react normally. This is sometimes due to the presence of a group which is very sensitive to the reagent and which diverts the reaction from the normal course. More frequently, however, the interference is steric. If the acetyl group is joined to a radical which is highly branched the reaction may be interrupted at the cleavage phase, the product being a trihalomethyl ketone.

3. The haloform reaction occurs also with certain alcohols, amines, β-diketones, olefins, oximes, esters, and acetylides. In all of these cases, however, the compounds are convertible to methyl ketones (or acetaldehyde) by processes such as oxidation, hydrolysis, and halogenation,—processes which are known to be brought about by hypohalite solutions. In other words, it would appear that all of the compounds which undergo the haloform reaction do so by first being transformed into methyl ketones (or acetaldehyde).

4. Considerable differences have been observed in the results obtained with the various hypohalites. Thus, hypochlorite and hypobromite often attack compounds which are unaffected by hypoiodite. In particular, the triiodomethyl derivatives, postulated as intermediates, have never been prepared. Even in those cases in which the corresponding trichloro and tribromo compounds are readily obtainable the iodination does not go to completion but yields only diiodomethyl derivatives.

The authors are indebted to Professors Mario Passerini and Raoul Poggi of the Royal University of Florence, Italy, for permission to use the libraries of that institution.

X. REFERENCES

(1) ABBOTT: J. Phys. Chem. **7**, 84 (1903).
(2) ARACHEQUESNE: Compt. rend. **110**, 642 (1890).
(3) AUWERS AND LÄMMERHIRT: Ber. **53**, 433 (1920).
(4) BABCOCK, NAKAMURA, AND FUSON: J. Am. Chem. Soc. **54**, 4407 (1932).
BABCOCK AND FUSON: J. Am. Chem. Soc. **55**, 2946 (1933).
(5) BAEYER: Ber. **29**, 25 (1896).
(6) BAMBERGER: Ber. **20**, 3344 (1887).
(7) BARBIER AND GRIGNARD: Compt. rend. **147**, 597 (1908).
(8) BARTAL: Chem.-Ztg. **29**, 377 (1909).
(9) BARTLETT: J. Am. Chem. Soc. **56**, 967 (1934).
(10) BATES, MULLALY, AND HARTLEY: J. Chem. Soc. **123**, 401 (1923).
(11) BELOHOUBEK: Ann. **165**, 350 (1873).
(12) BENESCH: Chem.-Ztg. **50**, 98 (1926).

(13) BENTLEY AND PERKIN: J. Chem. Soc. **73**, 52 (1898).
(14) BERGMANN, ZERVAS, AND ENGLER: Ann. **508**, 25 (1933).
(15) BILTZ AND KÜPPERS: Ber. **37**, 4412 (1904).
(16) BLANC: Bull. soc. chim. [4] **5**, 24 (1909).
(17) BÖESEKEN: Rec. trav. chim. **29**, 99 (1910).
(18) BÖTTIGER AND KÖTZ: J. prakt. Chem. [2] **65**, 481 (1902).
(19) BONNET: J. prakt. Chem. **10**, 207 (1837).
(20) BORSCHE: Ber. **44**, 2595 (1911).
(21) BOUCHARDAT: J. Pharm. Chem. **23**, 1 (1837); Ann. **22**, 225 (1837).
(22) BOUVEAULT AND LEVALLOIS: Compt. rend. **146**, 180 (1908).
(23) BRÜHL: Ber. **36**, 1731 (1903).
(24) BULL AND FUSON: J. Am. Chem. Soc. **55**, 3424 (1933).
(25) BULL AND FUSON: J. Am. Chem. Soc. **56**, 736 (1934).
(26) CAHOURS: Ann. chim. [3] **19**, 488 (1847).
(27) CHATTAWAY AND BAXTER: J. Chem. Soc. **103**, 1986 (1913).
(28) CLOËZ: Ann. **122**, 121 (1862).
(29) CLOËZ: Ann. chim. [6] **9**, 145 (1886).
(30) COHEN: Pharm. Weekblad **69**, 363 (1932).
(31) COLLET: Bull. soc. chim. [3] **23**, 831 (1900).
(32) COLLIE: J. Chem. Soc. **65**, 262 (1894).
(33) COLLISCHONN: Z. anal. Chem. **29**, 562 (1890).
(34) CUCULESCU: Bul. Fac. Stiinte Cernauti **1**, 53 (1927).
(35) CUCULESCU: Bul. Fac. Stiinte Cernauti **2**, 137 (1928).
(36) DATTA AND PROSAD: J. Am. Chem. Soc. **39**, 441 (1917).
(37) DAVIS: Archeion **13**, 11 (1931).
(38) DEHN: J. Am. Chem. Soc. **31**, 1227 (1909).
(39) DELANGE: Bull. soc. chim. [4] **3**, 914 (1908). Cf. DENIGÈS: Bull. soc. chim. [3] **29**, 598 (1903).
(40) DIEHL AND EINHORN: Ber. **18**, 2324 (1885).
(41) DINESMANN: Compt. rend. **141**, 202 (1905).
(42) DOBBIN: Chemist and Druggist **115**, 761 (1931).
(43) DOEUVRE: Bull. soc. chim. [4] **39**, 1594 (1926).
(44) DUMAS: Ann. chim. **56**, 113, 122 (1834).
(45) DUMAS AND PELIGOT: Ann. **15**, 9 (1835).
(46) Dyeworks, Höchst-on-the-Main: D. R. P. 21162; Friedländer **1**, 28 (1882). See also EINHORN AND GRABFIELD: Ann. **243**, 363 (1888).
(47) EINHORN AND GEHRENBECK: Ann. **253**, 357 (1889).
(48) ELLIOTT AND DALTON: Analyst **44**, 132 (1919).
(49) ENKLAAR: Rec. trav. chim. **23**, 419 (1904); **24**, 419 (1905); **25**, 297 (1906); **29**, 173 (1910).
(50) ÉTARD: Compt. rend. **114**, 753 (1892).
(51) FEIST: Ann. **496**, 99 (1932).
(52) FEIST: Ber. **67B**, 938 (1934).
(53) FEYER: Z. Elektrochem. **25**, 115 (1919).
(54) FISCHER AND VIAUD: Ber. **64B**, 193 (1931).
(55) FISHER: J. Am. Chem. Soc. **55**, 4241 (1933).
(56) FISHER, SNYDER, AND FUSON: J. Am. Chem. Soc. **54**, 3665 (1932).
(57) FUSON, BERTETTI, AND ROSS: J. Am. Chem. Soc. **54**, 4380 (1932).
(58) FUSON AND BEVERIDGE: J. Am. Chem. Soc. **53**, 1985 (1931).
(59) FUSON, FARLOW, AND STEHMAN: J. Am. Chem. Soc. **53**, 4097 (1931).
(60) FUSON, JOHNSON, AND BULL: Unpublished work.

(61) FUSON, LEWIS, AND DU PUIS: J. Am. Chem. Soc. **54**, 1114 (1932).
(62) FUSON AND TULLOCK: J. Am. Chem. Soc. **56**, 1638 (1934).
(63) FUSON AND WALKER: J. Am. Chem. Soc. **52**, 3269 (1930).
(64) GABRIEL AND MICHAEL: Ber. **10**, 1551 (1877).
(65) GAUTIER: Ann. chim. [6] **14**, 396 (1888).
(66) GEELMUYDEN: Z. anal. Chem. **35**, 503 (1896).
(67) GILMAN: Organic Syntheses, Coll. Vol. I, p. 512. John Wiley and Sons, New York (1932).
(68) GLASSTONE: Ind. Chemist **7**, 315 (1931).
(69) GOODWIN: J. Am. Chem. Soc. **42**, 39 (1920).
(70) GRAY, WALKER, AND FUSON: J. Am. Chem. Soc. **53**, 3494 (1931).
(71) GRODZKI: Ber. **16**, 512 (1883).
(72) GUTHRIE: Am. J. Sci. and Arts **21**, 64 (1832). See also reference 37.
(73) HABERMANN: Ann. **167**, 174 (1873).
(74) HALLER AND LASSIEUR: Compt. rend. **150**, 1015 (1910).
(75) HANTZSCH: Ber. **20**, 2040 (1887); **21**, 244 (1888).
(76) HANTZSCH: Ber. **22**, 1238 (1889).
(77) HARRIES AND HÜBNER: Ann. **296**, 301 (1897).
(78) HARRIES AND WARUNIS: Ann. **330**, 264 (1904).
(79) HATCHER AND MUELLER: Trans. Roy. Soc. Can. [3] **23**, Sect. 3, 35 (1929).
(80) HEIKEL: Chem.-Ztg. **32**, 75 (1908).
(81) HENRY AND PAGET: J. Chem. Soc. **130**, 72 (1928).
(82) HINTZ: Z. anal. Chem. **27**, 182 (1888).
(83) HLASIWETZ AND HABERMANN: Ann. **159**, 322 (1871).
(84) HOFFMAN: J. Am. Chem. Soc. **51**, 2542 (1929).
(85) HOFMEISTER: Z. anal. Chem. **29**, 632 (1890).
(86) HOMEYER, WHITMORE, AND WALLINGFORD: J. Am. Chem. Soc. **55**, 4209 (1933).
(87) HOUBEN AND FISCHER: Ber. **60B**, 1759 (1927).
(88) HOUBEN AND FISCHER: J. prakt. Chem. [2] **123**, 262 (1929).
(89) HOUBEN AND FISCHER: Ber. **63B**, 2455 (1930).
(90) HOUBEN AND FISCHER: Ber. **64B**, 240 (1931).
(91) HOUBEN AND FISCHER: Ber. **64B**, 2636 (1931).
(92) HOUBEN AND FISCHER: Ber. **66B**, 339 (1933).
(93) HUNTER AND EDGAR: J. Am. Chem. Soc. **54**, 2025 (1932).
(94) HURD AND THOMAS: J. Am. Chem. Soc. **55**, 1646 (1933).
(95) JACKSON AND ADAMS: J. Am. Chem. Soc. **37**, 2529 (1915).
(96) JERUSALEM: Biochem. Z. **12**, 361 (1908).
(97) JOCICZ: J. Russ. Phys.-Chem. Soc. **29**, 104 (1897).
(98) JOHNSON AND FUSON: J. Am. Chem. Soc. **56**, 1417 (1934).
(99) KEBLER: J. Am. Chem. Soc. **19**, 316 (1897).
(100) KEKULÉ AND STRECKER: Ann. **223**, 170 (1884).
(101) KEPPELER: Z. angew. Chem. **18**, 464 (1905).
(102) KERP AND MÜLLER: Ann. **299**, 224 (1898).
(103) KERSCHBAUM: Ber. **33**, 891 (1900).
(104) KLAR: Z. anal. Chem. **35**, 595 (1896).
(105) KOLTHOFF: Pharm. Weekbald **62**, 652 (1925).
(106) KOMPPA: Ber. **32**, 1423 (1899); Ann. **368**, 135 (1909). Cf. MAYURANATHAN AND GUHA: J. Indian Inst. Sci. **15A**, 131 (1932).
(107) KOMPPA AND ROSCHIER: Ann. **470**, 151 (1929).
(108) KON AND NARAYANAN: J. Chem. Soc. **1927**, 1536.
(109) KONDO, NOTO, AND TANAKA: J. Pharm. Soc. Japan **48**, 1163 (1928).

(110) KRÖHNKE: Ber. **66B**, 604, 1386 (1933).
(111) KRAEMER: Ber. **7**, 252 (1874).
(112) KRÄMER: Ber. **13**, 1000 (1880).
(113) KROLLPFEIFFER AND MÜLLER: Ber. **66B**, 739 (1933).
(114) KUHN AND LEVY: Ber. **61B**, 2240 (1928).
(115) KUNZ: Z. anal. Chem. **59**, 302 (1920).
(116) LAPWORTH: J. Chem. Soc. **85**, 1222 (1904).
(117) LAZZARINI: Industria chimica **4**, 771 (1929).
(118) LE COMTE: J. pharm. chim. [6] **16**, 297 (1902).
(119) VAN DER LEE: Chem. Weekblad **23**, 444 (1926).
(120) LEERS: Bull. soc. chim. [4] **39**, 651 (1926).
(121) LEFORT: Compt. rend. **23**, 229 (1846).
(122) LESER: Bull. soc. chim. [3] **21**, 548 (1899).
(123) LESER: Compt. rend. **141**, 1033 (1905).
(124) LIEBEN: Ann. Spl. Bd. **7**, 218 (1870).
(125) LIEBEN: Ann. Spl. Bd. **7**, 377 (1870).
(126) LIEBIG: Ann. Physik Chem. **23**, 444 (1831).
(127) LIEBIG: Ann. **1**, 182 (1832).
(128) LIEBIG: Ann. **162**, 161 (1872).
(129) LOCQUIN: Compt. rend. **153**, 285 (1911).
(130) LÖWIG: Ann. **3**, 296 (1832).
(131) MARRIOTT: J. Biol. Chem. **16**, 281 (1913).
(132) MEERWEIN: Ann. **419**, 158 (1919).
(133) MESSINGER: Ber. **21**, 3366 (1888).
(134) MILLON: Compt. rend. **21**, 828 (1845).
(135) MILLS: J. Chem. Soc. **101**, 2191 (1912).
(136) MORAWSKY: J. prakt. Chem. **12**, 388 (1875).
(137) MYDDLETON, BARRETT, AND SEAGER: J. Am. Chem. Soc. **52**, 4405 (1930).
(138) NENITZESCU AND CANTUNIARI: Ber. **65B**, 807 (1932).
(139) NENITZESCU AND IONESCU: Ann. **491**, 207 (1931).
(140) NOYES: Ber. **57B**, 1238 (1924).
(141) NYBERGH: Ber. **55B**, 1960 (1922).
(142) OCHI: J. Chem. Ind. Japan **24**, 209 (1921).
(143) ORNDORFF AND JESSEL: Am. Chem. J. **10**, 363 (1888).
(144) OWEN AND SIMONSEN: J. Chem. Soc. **134**, 1424 (1932).
(145) PAULY, GILMOUR, AND WILL: Ann. **403**, 123 (1914).
(146) PIERONI AND TONNIOLI: Gazz. chim. ital. **43, II**, 620 (1913).
(147) POGGI: Atti soc. ital. progresso sci., XXI Riunione, **2**, 376 (1933).
(148) RAKSHIT: Analyst **41**, 246 (1916).
(149) REICHER: Rec. trav. chim. **4**, 347 (1885).
(150) REISSERT: Ber. **30**, 1043 (1897).
(151) RICHARD AND LANGLAIS: Bull. soc. chim. [4] **7**, 464 (1910).
(152) ROBINEAU AND ROLLIN: Mon. sci. [4] **7**, Pt. I, 272 (1893).
(153) RUPE AND KUENZY: Helv. Chim. Acta **14**, 701 (1931).
(154) RUZICKA: Helv. Chim. Acta **2**, 361 (1919).
(155) RUZICKA AND VAN VEEN: Ann. **468**, 133 (1929).
(156) RUZICKA AND VAN VEEN: Ann. **468**, 143 (1929).
(157) SAVARÈ: Gazz. chim. ital. **36, II**, 345 (1906).
(158) SCHLAGDENHAUFFEN: J. Pharm. [3] **36**, 199 (1859).
(159) SCHLENK AND BERGMANN: Ausführliches Lehrbuch der organischen Chemie, Vol. 1, p. 109. Franz Deuticke, Leipsic and Vienna (1932).

(160) SCHMIDT AND VAN ARK: Arch. Pharm. **338**, 321 (1900).
(161) SCHOORL: Pharm. Weekblad **58**, 209 (1921).
(162) SEMMLER: Ber. **33**, 273 (1900).
(163) SEMMLER AND BARTELT: Ber. **41**, 386 (1908).
(164) SEMMLER AND MCKENZIE: Ber. **39**, 1164 (1906).
(165) SEMMLER AND RIMPEL: Ber. **39**, 2585 (1906).
(166) SEMMLER AND VON SCHILLER: Ber. **60**, 1591 (1927).
(167) SERULLAS: Ann. chim. **20**, 165 (1822); **22**, 172, 222 (1823); **25**, 311 (1824).
(168) SHINODA AND SATO: J. Pharm. Soc. Japan, No. **548**, 860 (1927).
(169) SHRINER, UPTON, AND ROLAND: Private communication.
(170) SIMONSEN: J. Chem. Soc. **121**, 2292 (1922).
(171) SMITH AND BYRKIT: J. Am. Chem. Soc. **55**, 4305 (1933).
(172) SOHL AND SHRINER: J. Am. Chem. Soc. **55**, 3828 (1933).
(173) SOUBEIRAN: Ann. chim. **48**, 131 (1831).
(174) SPETER: Chem.-Ztg. **55**, 781 (1931); Pharm. Zentralhalle **72**, 628 (1931).
(175) SQUIBB: J. Am. Chem. Soc. **18**, 1068 (1896).
(176) STENHOUSE: Ber. **6**, 575 (1873).
(177) STOERMER AND WEHLN: Ber. **35**, 3549 (1902).
(178) STRAUS, KOLLEK, AND HEYN: Ber. **63B**, 1868 (1930).
(179) STRAUS AND KÜHNEL: Ber. **66B**, 1834 (1933).
(180) SUKHNEVICH AND CHILINGARYAN: J. Gen. Chem. **2**, 783 (1932).
(181) TEEPLE: J. Am. Chem. Soc. **26**, 170 (1904).
(182) THIELE AND HAECKEL: Ann. **325**, 11 (1902).
(183) THOMS: Ber. deut. pharm. Ges. **11**, 3 (1901).
(184) TIEMANN: Ber. **28**, 2176 (1895).
(185) TIEMANN: Ber. **30**, 598 (1897).
(186) TIEMANN: Ber. **33**, 3703 (1900).
(187) TIEMANN AND SCHMIDT: Ber. **31**, 883 (1898).
(188) TIEMANN AND SEMMLER: Ber. **28**, 2141 (1895).
(189) TOIVONEN, OSARA, AND OLLILA: Acta Chem. Fennica **6B**, 67 (1933).
(190) TOLLENS: Ber. **14**, 1950 (1881).
(191) VAN ARENDONK AND CUPERY: J. Am. Chem. Soc. **53**, 3184 (1931).
(192) VAN ARENDONK, CUPERY, AND ADAMS: J. Am. Chem. Soc. **55**, 4228 (1933).
(193) VAUBEL AND SCHEUER: Z. angew. Chem. **18**, 215 (1905).
(194) VIGNON: Compt. rend. **110**, 534 (1890).
(195) VINCENT AND DELACHANAL: Bull. soc. chim. [3] **3**, 681 (1890).
(196) VORLÄNDER AND KOHLMANN: Ber. **32**, 1878 (1899).
(197) WAGNER AND ERTSCHIKOWSKY: Ber. **29**, 881 (1896).
(198) WALLACH: Ann. **275**, 149 (1893).
(199) WALLACH: Ber. **30**, 427 (1897).
(200) WALLACH: Ann. **345**, 142 (1906).
(201) WALLACH: Ann. **379**, 187 (1911).
(202) WALLACH: Ann. **381**, 83 (1911); **414**, 286 (1918).
(203) WALLACH: Ann. **384**, 202 (1911).
(204) WALLACH: Ann. **389**, 193 (1912).
(205) WALLACH: Ann. **394**, 362 (1912).
(206) WALLACH: Ann. **395**, 85 (1913); **397**, 194 (1913).
(207) WALLACH: Ann. **408**, 190 (1915).
(208) WALLACH AND BLEMBEL: Ann. **319**, 103 (1901).
(209) WALLACH, COLLMANN, AND THEDE: Ann. **327**, 139 (1903).
(210) WALLACH AND KEMPE: Ann. **329**, 99 (1903).

(211) WALLACH AND KÖHLER: Ann. **339**, 110 (1905).
(212) WALLACH AND KÖHLER: Ann. **339**, 113 (1905).
(213) WALLACH AND RITTER: Ann. **381**, 92 (1911).
(214) WARUNIS AND LEKOS: Ber. **43**, 654 (1910).
(215) WEIDEL AND GRUBER: Ber. **10**, 1137 (1877).
(216) WERNER: J. Chem. Soc. **85**, 1377 (1904).
(217) WOLFF AND RÜDEL: Ann. **294**, 199 (1897).
(218) WOODWARD AND FUSON: J. Am. Chem. Soc. **55**, 3472 (1933).
(219) ZETZSCHE: Pharm. Zentralhalle **44**, 505 (1903).
(220) ZINCKE: Ber. **26**, 322 (1893).
(221) ZINCKE: Ber. **26**, 498 (1893).
(222) ZINCKE: Ber. **26**, 501 (1893).
(223) ZINCKE AND EGLY: Ann. **300**, 184 (1898).
(224) ZINCKE AND FRANCKE: Ann. **293**, 147 (1896).
(225) ZINCKE AND FUCHS: Ber. **25**, 2694 (1892).
(226) ZINCKE AND FUCHS: Ber. **26**, 506 (1893).
(227) ZINCKE AND FUCHS: Ber. **26**, 1666 (1893).
(228) ZINCKE AND GERLAND: Ber. **21**, 2391 (1888).
(229) ZINCKE AND GERLAND: Ber. **21**, 2396 (1888).
(230) ZINCKE AND GÜNTHER: Ann. **272**, 243 (1893).
(231) ZINCKE AND LÖHR: Ber. **25**, 2219 (1892).