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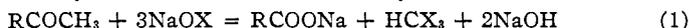
THE HALOFORM REACTION. IV. THE INFLUENCE OF ORTHO METHOXY GROUPS

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The haloform reaction (1) characteristic of methyl ketones is of great interest theoretically because it involves not only



the cleavage of a carbon chain, but also halogenation by means of hypohalite solutions. In the ordinary case the process does not permit the isolation of any intermediate products and hence the mechanism is conjectural. A step in the solution of the problem of mechanism has been made by a study of the steric effect of ortho substituents in the case of methyl aryl ketones. The assumption that the cleavage phase involved an additive step led to the expectation that the process might be slowed down at this point by introduction of steric hindrance. Experiment has shown that this is the case. Acetomesitylene and certain of its derivatives when treated with solutions of hypohalites gave the corresponding trihalomethyl ketones—compounds which are comparatively stable to the action of alkalis.¹

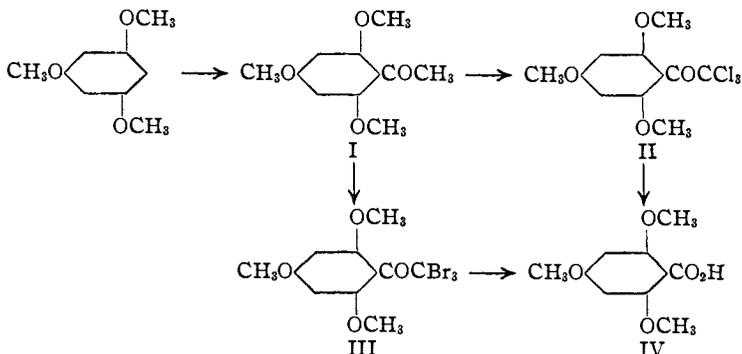
It has subsequently been shown that this interruption of the haloform reaction by steric hindrance is general for ketones of the type under consideration. The present article is a report of a study of the influence of ortho methoxy groups on the course of the haloform reaction. The ketones used in this work were the trimethyl ether of phloroacetophenone (I) and 2-methoxy-1-acetonaphthone (V). Mention should be made at this point of the effect of a single ortho methoxy group. In no case has it been found possible to isolate the trihalomethyl intermediate in the case of acetophenones with only one ortho substituent.

Derivatives of the Trimethyl Ether of Phloroacetophenone.—The trimethyl ether of phloroacetophenone was prepared from the trimethyl ether of phloroglucinol by the method of Kostanecki and Tambor.²

When treated with solutions of sodium hypochlorite and sodium hypobromite this ketone gave good yields, respectively, of the corresponding trichloromethyl ketone (II) and the tribromomethyl ketone (III). The preparation of the tribromo compound, α,α,α -tribromo-2,4,6-trimethoxyacetophenone, was carried out both in dilute alkali and in a 40% solution of alkali in order to determine whether the concentration of the alkali would affect the reaction. The result was the same in the two cases, but the reaction time was much longer when the concentrated solution of alkali was employed.

¹ Fuson and Walker, *THIS JOURNAL*, **52**, 3269 (1930).

² Kostanecki and Tambor, *Ber.*, **32**, 2262 (1899).

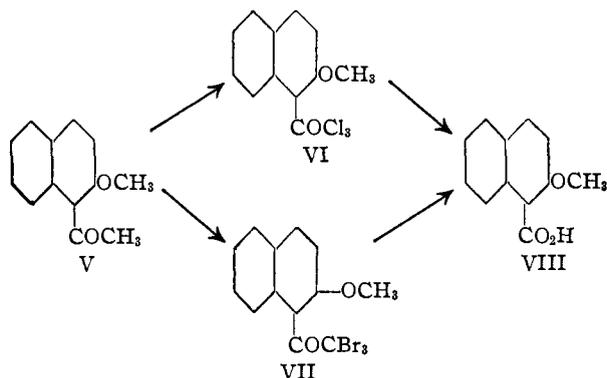


As compared with the previously reported halogenation of acetomesitylene, that of the trimethyl ether of phloroacetophenone differed widely in the apparent rate of the reaction. Whereas with acetomesitylene two days were required for the halogenation to go to completion, in the case of the trimethyl ether of phloroacetophenone the halogenation required only about an hour. This significant difference in the rates of reaction corresponds qualitatively at least with the experience in other cases in which the hindrance of methyl and methoxy groups has been compared. Whatever the mechanism of the halogenation may be, it would appear from these results that it suffers less hindrance from the methoxy groups than from the methyl groups.

The effect of the methoxy groups on the cleavage by alkali of the trihalomethyl ketones showed a similar difference as compared with that found with the methyl groups. Both α,α,α -trichloro-2,4,6-trimethoxyacetophenone and α,α,α -tribromo-2,4,6-trimethoxyacetophenone were found to be much less stable to the action of hot alkali than were the α,α,α -trihaloacetomesitylenes. In the former case whether the starting material was the trichloro or the tribromo compound the acid obtained was the same, namely, 2,4,6-trimethoxybenzoic acid (IV).

Derivatives of 2-Methoxy-1-acetonaphthone (V).—The halogenation of 2-methoxy-1-acetonaphthone was first carried out in aqueous hypohalite solutions but it was later discovered that the use of a solution of one part methyl alcohol in four to six parts of hypohalite solution caused the reaction to go more rapidly and in better yields.

1-Trichloroacetyl-2-methoxynaphthalene (VI), melting at 131–131.5°, and 1-tribromoacetyl-2-methoxynaphthalene (VII), melting at 136.5–137°, were the products of chlorination and bromination, respectively. The cleavage was effected by hot 30% sodium hydroxide solution and more easily by use of a 30% sodium hydroxide solution made up in 20% methyl alcohol. The trichloro compound was found to undergo the cleavage more rapidly than the tribromo compound. In each case the acid obtained was 2-methoxy-1-naphthoic acid (VIII).



In the case of the tribromo compound a careful study was made of the cleavage products. In addition to the methoxy naphthoic acid there was obtained an oil which was identified as bromoform. This was accomplished by treating the oil with a solution of sodium hypobromite and in this way converting it into carbon tetrabromide, a solid which was identified by the method of mixed melting points.

From these results it appears that the retardation of the haloform reaction in the case of 2-methoxy-1-acetonaphthone is of the same order of magnitude as that observed in the case of the trimethyl ether of phloroacetophenone. Since the effect observed with 2-methoxy-1-acetonaphthone is to be ascribed to the combined influences of the methoxy and the benzo groups, it is evident that the separate effect of the benzo group is similar to that of the methoxy group.

Experimental

α,α,α -Tribromo-2,4,6-trimethoxyacetophenone

(a) **Preparation in Dilute Alkali.**—A dilute sodium hypobromite solution was prepared by dissolving 15 g. of sodium hydroxide in 50 cc. of water, adding 100 g. of ice and, when the solution was cold, 15 g. of bromine.

To the above solution in a 250-cc. round-bottomed flask was added 1 g. of very finely powdered 2,4,6-trimethoxyacetophenone. The flask was then stoppered tightly and attached to a mechanical shaker, by means of which it was shaken violently for seventy-five minutes. At the end of this time the solid had ceased to be dispersed evenly throughout the liquid; instead, a light froth-like solid floated upon the surface of the liquid. This solid was removed by filtration. After five recrystallizations from aqueous alcohol the melting point was constant at 102.5–103° (corr.), and the product was in the form of long, flat, pale green needles. The yield was 67% of the theoretical.

Anal. Calcd. for C₁₁H₁₁O₄Br₃: Br, 53.7. Found: Br, 53.9.

(b) **Preparation in Concentrated Alkali.**—This reaction was run in the same manner as in (a) with the exception that an equal volume of 40% sodium hydroxide solution was substituted for the more dilute solution. The appearances of the two mixtures during the course of the reactions were identical. In the case of the more concentrated alkali, however, the time required was approximately six times that in dilute alkali.

A mixed melting point showed the products in each case to be identical. The yield was 58% of the theoretical.

α,α,α -Trichloro-2,4,6-trimethoxyacetophenone.—A dilute sodium hypochlorite solution was prepared as follows: 15 g. of sodium hydroxide was dissolved in 50 cc. of water and to this solution 100 g. of cracked ice was added. Ten cubic centimeters of this solution was removed, and the remainder was saturated with chlorine. The 10 cc. was then replaced, and 1 g. of finely powdered 2,4,6-trimethoxyacetophenone was added. The mixture was placed in a 250-cc. round-bottomed flask, which was then stoppered tightly and attached to a mechanical shaker. After a few minutes of shaking the solid collected into a plastic mass which appeared to be unchanged by prolonged shaking. No solid could be obtained by attempts to recrystallize this substance. A faint odor of free chlorine was noticeable above the hypochlorite solution.

Another hypochlorite solution was prepared as above except that in this case 50 cc. of the sodium hydroxide solution was removed before saturation with chlorine. In this instance a light solid collected on the surface of the hypochlorite solution after ninety minutes' shaking. This solid was removed by filtration. After four recrystallizations from aqueous alcohol the product was in the form of long, flat, colorless needles, melting at 119–120° (corr.). The yield was 68% of the theoretical.

Anal. Calcd. for $C_{11}H_{11}O_4Cl_3$: Cl, 34.0. Found: Cl, 34.0.

Decomposition of α,α,α -Trichloro-2,4,6-trimethoxyacetophenone by Alkali.—To 2 g. of finely powdered α,α,α -trichloro-2,4,6-trimethoxyacetophenone in a 50-cc. Erlenmeyer flask was added 20 cc. of a 10% sodium hydroxide solution. A reflux condenser was attached and the entire mixture was heated on a wire gauze for two hours. At the end of this time the solid had completely dissolved. The solution was filtered, cooled to 0° and acidified with dilute sulfuric acid, care being taken to keep the solution from becoming warm. The colorless solid which separated was filtered. After two recrystallizations from water it was found to melt at 144–145°, with decomposition. This corresponds to the melting point given for 2,4,6-trimethoxybenzoic acid.³ The yield was small.

Decomposition of α,α,α -Tribromo-2,4,6-trimethoxyacetophenone by Alkali.—Two grams of finely powdered α,α,α -tribromo-2,4,6-trimethoxyacetophenone was decomposed by alkali, by the method used above. The time required was three hours. The alkaline reaction mixture became scarlet in color upon acidification in this instance, with the precipitation of a small amount of 2,4,6-trimethoxybenzoic acid.

1-Tribromoacetyl-2-methoxynaphthalene

(a) **Preparation in Aqueous Solution.**—To an ice-cold solution of 30 g. of sodium hydroxide in 300 cc. of water in a 500-cc. round-bottomed flask was added rapidly 30 g. of bromine. The bromine went immediately to the bottom, and was gradually dissolved by swirling the mixture gently in the flask. To this hypobromite solution was added 2 g. of 2-methoxy-1-acetonaphthone which had previously been pulverized in a mortar along with an equal amount of amorphous silica. The reaction mixture was stirred at room temperature for a period of twelve hours, at the end of which time the mixture of solid substances was separated by filtering. After this solid mass had dried, the crystalline substance was extracted with boiling methyl alcohol. The solid obtained was purified by recrystallization from methyl alcohol, and separated finally as thick yellow rhombic crystals, melting at 136.5–137° (corr.). The yield was 2.2 g., or 51% of the theoretical.

Anal. Calcd. for $C_{13}H_9O_2Br_3$: Br, 54.9. Found: Br, 54.7.

³ Herzig and Wenzel, *Monatsh.*, **23**, 97 (1902); **24**, 873 (1903).

(b) **Preparation in 20% Alcoholic Solution.**—To an ice-cold solution of 150 g. of sodium hydroxide in 1500 cc. of water in a three-liter round-bottomed flask was added 150 g. of bromine, in the same way as above. To this hypobromite solution was added 300 cc. of methyl alcohol containing 10 g. of 2-methoxy-1-acetonaphthone. A fine yellowish precipitate immediately appeared. The reaction mixture was stirred at room temperature for five hours, at the end of which time the yellow crystals were separated from the solution by filtration. The bright yellow rhombic crystals formed on recrystallization were the same as in (a). The yield was 14 g., or 64% of the theoretical. In both of the above methods of preparation, a red-brown product was obtained by evaporating the mother liquor from the first recrystallization. The melting point of this impure substance was 140–145°.

1-Trichloroacetyl-2-methoxynaphthalene

(a) **Preparation in Aqueous Solution.**—Chlorine gas was bubbled through an ice-cold solution of 25 g. of sodium hydroxide in 250 cc. of water in a 500-cc. round-bottomed flask until it was evident that no more chlorine was being absorbed (fifteen to thirty minutes). To this solution, which contained an excess of chlorine, was added a solution containing 5 g. of sodium hydroxide in 50 cc. of water. To this hypochlorite solution was added 2 g. of 2-methoxy-1-acetonaphthone which had previously been pulverized in a mortar along with an equal amount of amorphous silica. The reaction mixture was stirred at room temperature for a period of twelve hours, at the end of which time the mixture of solid substances was separated by filtering. After this solid mass had dried, the crystalline substance was extracted with boiling methyl alcohol. The solid obtained was purified by recrystallization, and separated finally as fine yellow-green crystals, melting at 131–131.5° (corr.). The yield was 1.98 g., or 65% of the theoretical.

Anal. Calcd. for $C_{13}H_9O_2Cl_3$: Cl, 35.1. Found: Cl, 34.9.

(b) **Preparation in 20% Alcoholic Solution.**—Chlorine gas was bubbled through an ice-cold solution of 25 g. of sodium hydroxide in 250 cc. of water in a 500-cc. round-bottomed flask until it was evident that no more chlorine was being absorbed (fifteen to thirty minutes). To this solution, which contained an excess of chlorine, was added a solution containing 5 g. of sodium hydroxide in 50 cc. of water. To this hypochlorite solution was added 60 cc. of methyl alcohol containing 2 g. of 2-methoxy-1-acetonaphthone. A fine precipitate, almost colorless, appeared. The reaction mixture was stirred at room temperature for three hours, at the end of which time the crystals were separated from the solution by filtration. Upon recrystallization from methyl alcohol the fine yellow-green crystals were found to be the same as in (a). The yield was 2.19 g., or 72% of the theoretical.

The Cleavage of 1-Tribromoacetyl-2-methoxynaphthalene by Alkali

(a) **In Aqueous Solution.**—Two grams of the tribromo compound was placed in a 200-cc. round-bottomed flask, and 50 cc. of 20% sodium hydroxide added. A 75-cm. air-cooled reflux condenser was attached to the mouth of the flask, and the upper opening of the air-cooled condenser connected to a water-cooled condenser, to catch any bromoform given off in the decomposition. The mixture was boiled, gently at first, and then more vigorously, for four hours. A fairly large drop of bromoform was collected in the receiver, along with 20 cc. of water which distilled. It appeared that most of the decomposition occurred during the third hour, and at this time the strength of the sodium hydroxide in the flask was approximately 30%, calculating from the amount of water distilled by that time. The bromoform obtained was identified by making from it the solid derivative, carbon tetrabromide. This was done by placing the entire

distillate (including the 20 cc. of water) on the shaker in a small flask, along with 30 cc. of a hypobromite solution made up from 40 cc. of ice-cold water, 10 g. of sodium hydroxide and 9 g. of bromine. After two hours a good yield of carbon tetrabromide was obtained. After one recrystallization from ethyl alcohol, the melting point of the compound was 92° , as compared with 92.5° given in the literature for carbon tetrabromide. Using a known sample of carbon tetrabromide melting at 92.0° , a mixed melting point of 92.0° was obtained.

The mixture remaining in the original flask was filtered, and the filtrate was acidified. A cloudiness appeared, but the precipitate could not be filtered. This mixture was extracted with ether, the extraction layer washed and dried, and the ether evaporated. A colorless crystalline substance was obtained after one recrystallization from acetic acid. The melting point of this substance was $173\text{--}174^\circ$; the melting point given in the literature for 2-methoxy-1-naphthoic acid is 176° .⁴

In a later trial 3 g. of 1-tribromoacetyl-2-methoxynaphthalene was placed in a 200-cc. round-bottomed flask, with 20 g. of sodium hydroxide dissolved in 60 cc. of water. After the mixture had been boiled vigorously under a reflux condenser for four hours, most of the yellow tribromo compound had disappeared. The alkaline mixture was then acidified, and a colorless, finely divided precipitate was obtained. The yield of the acid was 0.8 g., or 57% of the theoretical.

(b) In 20% Alcoholic Solution.—Two grams of the tribromo compound was placed in a 200-cc. round-bottomed flask, with 15 g. of sodium hydroxide dissolved in 40 cc. of water and 10 cc. of methyl alcohol. After being boiled vigorously under a reflux condenser for two hours, the solution was cooled, water was added to make a total volume of 100 cc. of solution and the mixture was acidified. A yield of 0.4 g. of the acid was obtained, or 44% of the theoretical.

The Cleavage of 1-Trichloroacetyl-2-methoxynaphthalene by Alkali.—One and nine-tenths grams of the trichloro compound was placed in a 200-cc. Erlenmeyer flask, and 60 cc. of 10% sodium hydroxide and 10 cc. of methyl alcohol added. A reflux condenser was attached to the flask, and the mixture was boiled for four hours, at the end of which time all of the solid had disappeared. The reaction mixture, which smelled strongly of chloroform, was evaporated on the steam-bath to one-half of its volume, and cooled. To this solution was added 20 cc. of concentrated hydrochloric acid. When the solution had cooled, the acid which precipitated was removed by filtration. When recrystallized from dilute acetic acid, this acid gave a melting point of 176° , which is the melting point given in the literature for 2-methoxy-1-naphthoic acid.

Summary

The effect of ortho methoxy groups on the haloform reaction has been studied in the case of the trimethyl ether of phloroacetophenone (I). When treated with solutions of sodium hypochlorite and sodium hypobromite, this ketone has been shown to give, respectively, α,α,α -trichloro-2,4,6-trimethoxyacetophenone (II) and α,α,α -tribromo-2,4,6-trimethoxyacetophenone (III). Both of these compounds have been converted into 2,4,6-trimethoxybenzoic acid by the action of hot solutions of alkali.

A similar retardation of both the halogenation and the cleavage phases of the haloform reaction has been observed with 2-methoxy-1-acetonaphthone. In this case the intermediate compounds, 1-trichloroacetyl-2-methoxynaphthalene (VI) and 1-tribromoacetyl-2-methoxynaphthalene

⁴ Rousset, *Bull. soc. chim.*, [3] 17, 311 (1897).

(VII), have been prepared and converted by the action of alkali into 2-methoxy-1-naphthoic acid.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN AND THE BAKER LABORATORY OF CHEMISTRY OF CORNELL UNIVERSITY]

MONOARYLGUANIDINES. III. BENZOTHAIOLEGUANIDINE^{1,2}

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Introduction

In a previous communication it has been shown that benzoxazoleguanidine is formed from dicyandiamide and *o*-aminophenol through a process of deammonation. The present paper describes an application of this nitrile property of dicyandiamide in the preparation of benzothiazoleguanidine from *o*-aminothiophenol.

This investigation was undertaken in order that certain pharmacological properties of benzothiazoleguanidine might be studied and compared with those of the oxy and imide analogs and of other guanidine derivatives,³ and its properties as an accelerator of vulcanization of rubber might be examined.⁴

Properties of Benzothiazoleguanidine

Benzothiazoleguanidine is a white crystalline solid whose aqueous solution is a weak base which forms salts with the common acids. It differs from benzimidazoleguanidine⁵ and benzoxazoleguanidine^{1b} in that an anhydrous as well as a hydrated base is formed. The anhydrous crystals are obtained as plates when a hot saturated solution of the base is chilled and the crystals immediately separated from the mother liquor, or when either variety is crystallized from 95% ethanol. The crystals of the monohydrate separate as prismatic needles when the hot solution is slowly cooled

¹ For earlier articles of this series see (a) Smith, *THIS JOURNAL*, **51**, 476 (1929); (b) Smith, Kane and Mason, *ibid.*, **51**, 2522 (1929).

² The substances described were prepared by Mr. Carroll and a part of this paper is constructed from the thesis submitted by Mr. Carroll in partial fulfilment of the requirements for the degree of Bachelor of Science in Chemistry at the Polytechnic Institute of Brooklyn in June, 1930. This paper was presented at the eighty-second meeting of the American Chemical Society before the Division of Organic Chemistry at Buffalo, N. Y., August 31 to September 4, 1931.

³ Bischoff, Sahyun and Long, *J. Biol. Chem.*, **81**, 325 (1929); Bischoff and Long, *J. Pharm. and Exptl. Therap.*, **41**, 127 (1931).

⁴ Smith and Weiss, *Ind. Eng. Chem.*, **20**, 298 (1928); an extension of this study is projected.

⁵ (a) Ziegelbauer, *Monatsh.*, **17**, 653 (1896); (b) Pellizzari, *Gazz. chim. ital.*, **I**, **51**, 89, 140 (1921); see *C. A.*, **15**, 3076, 3078 (1921).