Summary

1. It has been shown that certain methylenedioxy compounds are cleaved by base in spite of the fact that they are ketals.

2. A detailed mechanism has been offered for this unusual reaction.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Mechanism of the Haloform Reaction
The Preparation of Mixed Haloforms

BY J. G. ASTON, J. D. NEWKIRK, JULIAN DORSKY AND D. M. JENKINS

The present paper records a detailed investigation of the preparation of chloroform, dichlorobromomethane, chlorodibromomethane and bromoform from the dihaloacetophenone derivative by the haloform reaction with particular attention to the cleavage reaction of the corresponding trihaloacetophenone.

When dichloroacetophenone is treated with sodium hypobromite in the presence of excess alkali in the cold, dichlorobromomethane is produced practically instantaneously. When chlorobromoacetophenone is similarly treated, chlorodibromomethane is likewise instantaneously produced. In the same way dibromoacetophenone yields bromoform. In these last two cases mandelic acid is produced in 12% yield due to rearrangement of the dihaloacetophenone by alkali. Alkaline hypochlorite reacts similarly on dichloroacetophenone, chlorobromoacetophenone and dibromoacetophenone.

For a reason which will appear presently it was not convenient to prepare the intermediate mixed trihaloacetophenones which would yield, respectively, the mixed haloforms on cleavage. It is a simple matter, however, to prepare trichloroacetophenone and tribromoacetophenone and to study their cleavage to chloroform and bromoform, respectively.

In the preparation of these two compounds it was merely necessary to add sodium acetate to obtain smooth replacement of the last alpha hydrogen by halogen. Without the sodium acetate the equilibrium favors the reverse reaction, a fact which seems to have been overlooked and is possibly the reason why tribromoacetophenone has never been prepared until now.

We were considerably surprised to find that tribromoacetophenone can be recovered unchanged from 5 *N* alkali at zero degrees. In addition warming to 80° with one normal alkali did not effect rapid cleavage. The cleavage was not noticeably increased in the presence of alkaline hypobromite.

Fuson and co-workers[1] found that acetophenones with both alpha positions occupied do not yield the corresponding substituted benzoic acids on treatment with sodium hypobromite solution. Instead the corresponding α,α,α-tribromo derivative could be recovered from the solution. In some cases the α-bromo and the α,α-dibromo acetophenones were isolated. The substituted α,α,α-trihaloacetophenones could then be cleaved under conditions primarily involving solubility. Fuson concluded that, in the haloform reaction alpha substitution of halogen occurs until the trihaloacetyl group is formed, which then immediately cleaves in the presence of alkali yielding the sodium salt of the carboxylic acid and the haloform, providing the cleavage is not sterically hindered.

To explain the results the possibility was considered that during the action of sodium hypobromite on the dihaloacetophenone, the trihaloacetophenone was formed in highly supersaturated solution and then cleaved due to its high concentration. Accordingly the action of sodium hypobromite at zero degrees on dibromoacetophenone was investigated in the presence of crystalline tribromoacetophenone which would presumably tend to remove any supersaturation. No additional tribromoacetophenone was produced; in fact that originally added disappeared.

However, it was found that the cleavage of tribromoacetophenone proceeds practically instantaneously by the action of one mole of sodium hydroxide per mole of tribromoacetophenone in aqueous dioxane (1 volume of water to 2 volumes of dioxane) when the solution is 0.13 volume formal with respect to each. This indicates that

(1) Fuson and Bull, *Chem. Rev.*, **15**, 275 (1934).

the slow cleavage of the tribromoacetophenone by aqueous alkali is due to the slow rate of solubility probably caused by precipitation of the liquid bromoform on the unreacted substance.

It was also observed that the two-phase reaction of trichloroacetophenone with alkali at zero degrees is more rapid than that of tribromoacetophenone. Nevertheless, 77% of the trichloroacetophenone can be recovered unchanged after stirring with 5.2 *N* alkali for ten minutes, while after thirty minutes 41% still can be recovered. On the other hand, the reaction of one mole of dichloroacetophenone with one mole of sodium hypochlorite and three moles of sodium hydroxide in 2.6 *N* solution is 68% complete in twelve minutes. Besides the products of the haloform reaction, 3% of trihaloacetophenone is formed. This result is probably due to the low rate of solubility of the trichloroacetophenone as was the case for the tribromoacetophenone.

It is interesting to note that if the excess sodium hydroxide is reduced to one mole per mole of dichloroacetophenone, the reaction to yield haloform is almost entirely prevented at 0° and more trichloroacetophenone results.

Several attempts were made to prepare chlorodibromoacetophenone by brominating chloroacetophenone in the presence of sodium acetate. The chlorodibromoacetophenone was not isolated although it was formed. It was found that the product was a mixture of roughly 30% chlorodibromoacetophenone and 70% tribromoacetophenone apparently due to the reaction of chlorodibromoacetophenone with the sodium bromide formed in the solution. Inasmuch as dichloroacetophenone could be converted to chlorobromoacetophenone by stirring with sodium bromide in glacial acetic acid, the above result is probably due to a similar reaction.

Experimental

Reaction of Sodium Hypobromite Solution with Dichloroacetophenone, Chlorobromoacetophenone, and Dibromoacetophenone.—Twenty grams (0.50 mole) of sodium hydroxide was dissolved in 95 cc. of water and 26.7 g. (0.167 mole) of bromine was added to the chilled solution. Thirty grams (0.159 mole) of dichloroacetophenone was added with constant stirring. The temperature was maintained at 0°. The mixture was stirred fifteen minutes after addition was completed.

The alkaline solution was extracted with three 50-cc. portions of cold ether. The combined ether extracts were dried and distilled, yielding 10.2 g. (0.62 mole) of dichlorobromomethane; b. p. 89–94° (735 mm.) (39% of theoretical).

The alkaline aqueous solution was acidified and yielded 11.0 g. (0.09 mole) of benzoic acid (56% of theoretical).

Repetition on a large scale (1.50 moles of dichloroacetophenone) produced 45% of the theoretical yield of dichlorobromomethane and 92% of benzoic acid.

Treatment of chlorobromoacetophenone and of dibromoacetophenone with sodium hypobromite solution under similar experimental conditions and in the same molecular proportions yielded 35% of the theoretical amount of chlorodibromomethane and 47% of bromoform, respectively.

While the amounts of mandelic acid formed were not investigated in the first case here considered, in the last two reactions it was formed in 12% yields. The mandelic acid was obtained by ether extraction of the water layer after filtering off the precipitated benzoic acid, and subsequent crystallization from benzene.

Reaction of Dichloroacetophenone with Sodium Hypochlorite and Sodium Hydroxide.—(a) Twenty-one and nine-tenths grams (0.528 mole) of sodium hydroxide was dissolved in 340 cc. of water and cooled in an ice–salt mixture. The apparatus was tared and 18.8 g. (0.264 mole) of chlorine was admitted from a cylinder. The temperature varied from 0 to +3° during admission. To this solution was added 31.8 g. (0.795 mole) of pellet sodium hydroxide. When the temperature had dropped to −3°, 50 g. (0.264 mole) of chilled dichloroacetophenone was added at once. The mixture was well stirred and the average temperature was 2°. The reaction was interrupted at the end of twelve minutes, and extracted with two 100-cc. portions of cold ether in a cold separatory funnel, this operation requiring five to six minutes. The ether extracts were combined, dried, the ether was distilled and 16.0 g. of "dichloroacetophenone" was recovered which on dissolving in excess warm sodium hydroxide solution and acidifying yielded 0.83 g. of benzoic acid. On this basis the recovered dichloroacetophenone consisted of 1.5 g. (0.0068 mole) of trichloroacetophenone and 14.5 g. (0.0768 mole) of dichloroacetophenone. Twenty and eight-tenths grams (0.171 mole, 65% of theoretical) of benzoic acid was found in the original basic solution.

(b) Thirty-two and eight-tenths grams (0.819 mole) of sodium hydroxide was dissolved in 170 cc. of water and cooled in an ice–salt mixture. After taring 18.8 g. (0.264 mole) of chlorine was admitted. The procedure followed was exactly similar to the experiment above, except that the time interval of reaction was ten minutes. Forty-six grams of "dichloroacetophenone" was recovered from the ether extracts. On the basis of the 2.9 g. of benzoic acid yielded on treating with warm sodium hydroxide as above, 5.3 g. (0.0236 mole) of the recovered dichloroacetophenone was trichloroacetophenone and 40.7 g. (0.215 mole) was dichloroacetophenone. In the original basic aqueous layer 0.5 g. (0.0041 mole, 1.6% of theoretical) of benzoic acid was found.

Preparation of Tribromoacetophenone.—To 60 cc. (0.50 mole) of acetophenone and 110 cc. of glacial acetic acid was added, with stirring, a solution of 240 g. (1.5 mole) of bromine and 50 cc. of glacial acetic acid. The addition was made sufficiently rapidly to cause refluxing.

When the bromine ceased to decolorize addition was interrupted and 70 g. of fused sodium acetate was added,

the addition of bromine was completed and the reaction mixture was stirred for fifteen minutes.

The flask containing the reaction mixture was then placed in an ice-bath and stirred until crystallization occurred. After pouring the reaction mixture into cold water the crystals were filtered off and recrystallized from 95% methyl alcohol; yield 75 g. (67% of theoretical) of tribromoacetophenone; after repeated recrystallization from methyl alcohol, m. p. 65–66°. *Anal.* Calcd. for $C_8H_5OBr_3$: Br, 67.20; mol. wt., 357. Found: Br, 67.04; mol. wt., 352.

Reaction of Tribromoacetophenone with Sodium Hydroxide at 0°.—Twenty-seven grams (0.076 mole) of tribromoacetophenone, m. p. 57–58°, was stirred with 11.2 g. (0.28 mole) of sodium hydroxide in 53.5 cc. of water for one hour with the temperature between −5 and 0°. The 24 g. of recovered tribromoacetophenone had a melting point of 57–58° after one recrystallization from methyl alcohol.

Reaction of Tribromoacetophenone with Sodium Hydroxide in Aqueous Dioxane.—The sodium hydroxide solution was prepared by adding 25 cc. of 0.2664 *N* aqueous solution to 25 cc. of dioxane and cooling to 0° by immersion in an ice-bath. The tribromoacetophenone (2.378 g.) was dissolved in 25 cc. of dioxane and cooled to about 10° (just above the freezing point) before adding to the alkaline solution. After mixing, 10-cc. aliquots were pipetted into excess standard alkali at approximately one-minute intervals. The excess acid was back titrated.

It was found that the reaction was complete in less than one minute using up one mole of base per mole of compound. That an insignificant quantity of bromine was hydrolyzed was shown by the constancy of the volume of base required for back titration.

Reaction of Tribromoacetophenone with Sodium Hypobromite at 0°.—Ten grams of tribromoacetophenone was stirred for one hour at 0° with 11.2 g. of sodium hydroxide and 53.5 cc. of water to which had been added 1.5 cc. of bromine.

Seven grams of unreacted tribromoacetophenone was recovered, m. p. 61–62° after recrystallization from methyl alcohol, mixed melting point with tribromoacetophenone 61–62°.

Reaction of Dibromoacetophenone with Sodium Hypobromite Solution in the Presence of Tribromoacetophenone.—Twenty-seven and eight-tenths grams of dibromoacetophenone (0.1 mole, m. p. 35°) and 3 g. of tribromoacetophenone (0.0084 mole, m. p. 65°) were suspended in 50 cc. of cold water. A sodium hypobromite solution was prepared by dissolving 8.8 g. (0.22 mole) of sodium hydroxide in 50 cc. of water, cooling and adding 16 g. of bromine (0.10 mole). This mixture was added at once with stirring to the dibromoacetophenone suspension, followed by a cold solution of 4.4 g. (0.11 mole) of sodium hydroxide in 20 cc. of water added dropwise. Stirring was continued for one hour after addition was completed. The temperature was maintained at 0°.

The oil layer was separated and the water solution extracted with two 30-cc. portions of ether. The ether extracts were combined with the oil layer, dried and distilled.

A total of 15.4 g. (0.06 mole, of bromoform 61% of theoretical) b. p. 148–151°, was recovered. The high boiling residue of 4 g. consisted essentially of unreacted dibromoacetophenone.

Preparation of Trichloroacetophenone.—We were not able to obtain a satisfactory yield of this substance by the method described by Gautier.[2] Only by the use of sodium acetate could satisfactory yields be obtained. Seventy-six grams (0.402 mole) of freshly distilled dichloroacetophenone, b. p. 134° (18–20 mm.), was dissolved in 100 cc. of glacial acetic acid and 50 g. of fused sodium acetate added. Chlorine was added until a change in weight of 30.0 g. occurred (0.423 mole chlorine), when excess chlorine failed to be decolorized. The temperature was maintained between 95 and 100° throughout.

Finally the reaction mixture was poured into 600 cc. of cold water, and a solution of 6 g. of sodium sulfite was added to destroy excess chlorine.

The milky oil layer was separated, dried and fractionated through a column (10 plates). A fraction of 72.5 g. (0.317 mole) boiling at 135° (18–20 mm.) was collected (79% of theoretical). Curiously enough this compound is non-lachrymatory.

Reaction of Trichloroacetophenone with 5.25 *N* Sodium Hydroxide at 0°.—Two identical experiments were run. One was interrupted at the end of ten minutes; the other at the end of thirty minutes. The procedure was identical. To an ice-cold solution of 35.7 g. of sodium hydroxide (0.893 mole) dissolved in 170 cc. of water was added at once 50 g. (0.224 mole) of trichloroacetophenone. The mixture was stirred well. An ice-salt bath was used to maintain the temperature at from −3 to 0°.

After the desired time interval the reaction was interrupted, and the unreacted trichloroacetophenone was separated from the basic solution with two 150-cc. portions of cold ether in a cold separatory funnel. The time consumed in this operation from the time when the reaction was interrupted to the time when the unreacted trichloroacetophenone was completely separated was from five to six minutes.

Subsequently the ether extracts were combined, dried and the ether was distilled. The resulting trichloroacetophenone was dried under a vacuum of 20 mm. of mercury for half an hour and weighed. The basic solution was acidified, the benzoic acid filtered and reprecipitated and dried to constant weight.

After the ten-minute interval 38.6 g. (0.173 mole) of trichloroacetophenone (77%) and 5.2 g. (0.043 mole) of benzoic acid (19% of theoretical) were recovered.

After the thirty-minute interval 20.7 g. (0.0924 mole) of trichloroacetophenone (41%) and 16.1 g. (0.132 mole) of benzoic acid (59%) were recovered.

Reaction of Chloroacetophenone with Bromine and Excess Sodium Acetate.—To a solution of 100 g. (0.65 mole) of chloroacetophenone in 110 cc. of glacial acetic acid was added with stirring a solution of 208 g. (2.6 moles) of bromine in 50 cc. of glacial acetic acid until the bromine was no longer decolorized (*i. e.*, until about half had been added). The solution was refluxed for five minutes and then 80 g. (1 mole) of fused sodium acetate was added and the addition of the bromine solution continued with stirring. The solution was refluxed for ten minutes after addition was complete.

(2) Gautier, *Ann. chim. phys.*, [6] **14**, 396 (1888).

After cooling, the reaction mixture was poured into 600 cc. of ice and water. The excess bromine was decolorized with a little sodium sulfite solution. The precipitated material after drying weighed 216 g. (93% if all tribromoacetophenone). After one recrystallization from methyl alcohol it melted between 57 and 58°. After repeated recrystallization from methyl alcohol the material melted at 61° and did not lower the melting point of tribromoacetophenone (m. p. 65–66°). The original material was shown to consist of roughly 30% of chlorodibromoacetophenone and 70% of tribromoacetophenone by cleavage which was accomplished by refluxing 50 g. (0.16 mole) with sodium acetate (2 g.)[3] in ordinary methyl alcohol 120 cc.) for one and one-half hours and finally distilling. The chlorodibromomethane (0.022 mole) and the bromoform (0.054 mole) came over after the alcohol had been distilled from the reaction mixture. The last fraction was methyl benzoate (0.09 mole). A similar experiment using methyl alcohol containing 20% water and twenty times the concentration of sodium acetate indicated 40% of chlorodibromomethane.

Summary

1. Acetophenone can be completely halogenated in the alpha position in good yields by using sodium acetate to remove the halogen acid and shift the otherwise unfavorable equilibrium.

2. α,α,α-Tribromoacetophenone has been prepared for the first time and its cleavage to bromoform by aqueous alkali found to be very slow, but very rapid in aqueous dioxane solution.

3. Haloforms (including bromoform) can be prepared in good yield by the action of alkaline sodium hypochlorite and hypobromite on the appropriate dihaloacetophenone at 0°.

4. Chloroform is formed more rapidly by the action of alkaline sodium hypochlorite on dichloroacetophenone than by the cleavage of trichloroacetophenone in the same medium.

5. The slow rate of cleavage of the trihaloacetophenone by aqueous alkali is due to slow rate of solubility.

(3) Jackson and Adams [THIS JOURNAL, **37**, 2529 (1915)] have used aqueous sodium acetate to cleave hexabromoacetone. The use of methyl alcohol as solvent is new.

STATE COLLEGE, PENNSYLVANIA
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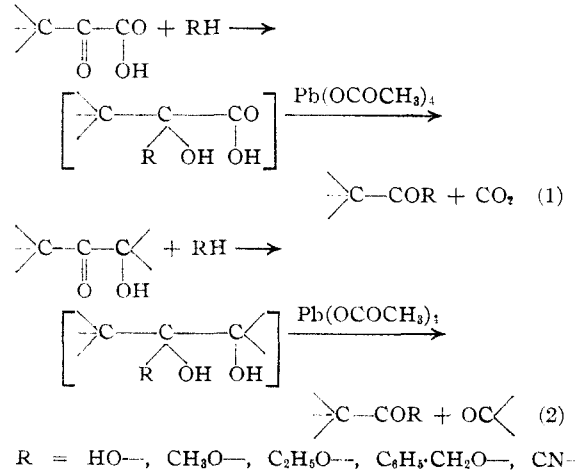
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BANTING INSTITUTE, UNIVERSITY OF TORONTO]

Oxidative Cleavage of Cyclic α-Keto Alcohols by Means of Lead Tetraacetate. II

BY ERICH BAER

The oxidative cleavage of 1,2-glycols[1] and polyalcohols[2] by means of lead tetraacetate is today a well investigated and frequently used method for effecting the cleavage of a carbon–carbon linkage. The ease with which the procedure is carried out and its quantitative nature have contributed to its rapid acceptance. The more recently discovered[3] cleavage of α-keto alcohols and α-keto acids by lead tetraacetate in the presence of hydroxyl-forming substances, however, is a comparatively new reaction about which more had to be learned.

In the first paper on this subject, in which the investigation was limited to compounds containing the reactive group in an aliphatic chain, evidence has been presented to support the conception that the reaction might be considered as a glycol cleavage in a wider sense. The formation of the pseudoglycols, found to be indispensable for the progress of the cleavage reaction, takes place by the addition of water or alcohol to the keto group (Equations 1 and 2).



R = HO—, CH_3O—, C_2H_5O—, $C_6H_5CH_2O$—, CN—

As a result of experience gained in the investigation of acyclic and alicyclic α-keto alcohols and α-keto acids, the expectation was expressed that the oxidative cleavage of α-keto alcohols may be

(1) Criegee, Kraft and Rank, *Ann.*, **507**, 159 (1933); Baer, Grosheintz and Fischer, THIS JOURNAL, **61**, 2607 (1939).

(2) Grosheintz, *ibid.*, **61**, 3379 (1939); McClenahan and Hockett, *ibid.*, **60**, 2061 (1938).

(3) Baer, *ibid.*, **62**, 1597 (1940).