[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

THE HALOFORM REACTION. V. THE INFLUENCE OF ORTHO BROMINE ATOMS

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The presence in methyl aryl ketones of two ortho methyl groups[1] or two ortho methoxy groups[2] has been found to effect a retardation of the haloform reaction of these ketones such that the trihalomethyl compounds formed as intermediates may be isolated. Although in all of these cases the trihalomethyl ketones have been found to be stable to the action of cold aqueous alkalies, the cleavage has been effected in a number of cases by use of hot concentrated aqueous solutions of alkali. In the case of the methoxy compounds the cleavage is fairly rapid under these conditions but the methyl compounds offer much more resistance to the hydrolytic action of the alkali solutions. The possibility of introducing still larger groups at once suggests itself as a means of studying the effect of hindrance.

Of the ortho disubstituted acetophenones easily obtainable the dibromo would be expected to offer the greatest hindrance and would, therefore, be most suitable for the purpose in view. Actually, 2,4,6-tribromoacetophenone has been found to be the ortho-dibromoacetophenone easiest to prepare and, accordingly, it and its derivatives have been used in this study. In this preparation *m*-nitroacetophenone was used as the starting material. It was reduced by the method of Ullmann and Consonno[3] and the resulting amino compound (I) was brominated by the method of Fuchs.[4] For the removal of the amino group from the tribromo amino ketone (II) the diazotization procedure of Witt[5] using fuming nitric acid and sodium meta-bisulfite was found to be excellent.

2,4,6-Tribromoacetophenone (III) was treated with a solution of sodium hypobromite and after several days was found to have been completely converted into α,α,α,2,4,6-hexabromoacetophenone (IV).

The preparation of the corresponding trichloromethyl ketone (V) was, however, much more difficult to accomplish. Long treatment of 2,4,6-tribromoacetophenone with aqueous solutions of sodium hypochlorite caused no change. However, the desired α,α,α-trichloro-2,4,6-tribromoacetophenone was eventually obtained by two different methods.

The first method rests upon the plausible but unproved assumption that in the hypohalite halogenations the second and third halogen atoms

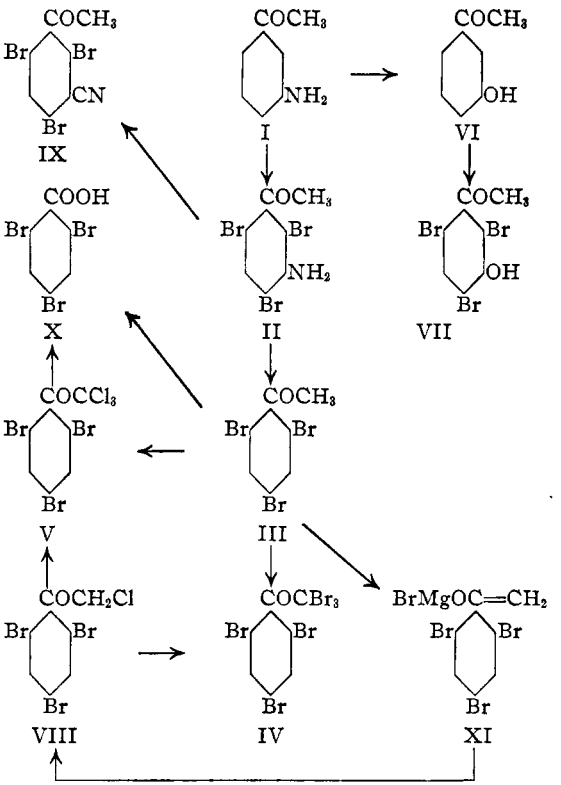
[1] Fuson and Walker, THIS JOURNAL, **52**, 3269 (1930); Gray, Walker and Fuson, *ibid.*, **53**, 3494 (1931).

[2] Fuson, Farlow and Stehman, *ibid.*, **53**, 4097 (1931).

[3] Ullmann and Consonno, *Ber.*, **35**, 2803 (1902).

[4] Fuchs, *Monatsh.*, **36**, 113 (1915).

[5] Witt, *Ber.*, **42**, 2953 (1909).



enter the molecule with greater readiness than does the first. The evidence for this is that in no case of halogenation of methyl ketones by the action of hypohalite solutions has either the mono- or the dihalomethyl derivative been isolated. This would seem to show that halogenation once started proceeds rapidly to completion. In order to test this idea in the present instance 2,4,6-tribromophenacyl chloride (VIII) was prepared and treated with solutions of hypohalites. To prepare the phenacyl chloride 2,4,6-tribromoacetophenone was added to a solution of ethylmagnesium bromide and in this way converted into its bromomagnesium enolate (XI). The enolate was converted into the phenacyl chloride by treatment with chlorine. The results of the halogenation experiments with 2,4,6-tribromophenacyl chloride fully supported the speculations presented above. When treated with solutions of sodium hypochlorite and sodium hypobromite the phenacyl chloride was converted into the α,α,α-trichloro-2,4,6-tribromoacetophenone (V) and α,α,α,2,4,6-hexabromoacetophenone (IV), respectively.

The second plan for preparing α,α,α-trichloro-2,4,6-tribromoacetophenone rests on the idea that the apparent rates of these reactions may be

dependent on solubility factors. Accordingly, pyridine was added to the reaction mixture consisting of 2,4,6-tribromoacetophenone and an aqueous sodium hypochlorite solution. Under these conditions the methyl ketone gave the desired α,α,α-trichloro-2,4,6-tribromoacetophenone.

Cleavage of the Trihalomethyl Ketones by Alkalies.—Neither the trichloromethyl nor the tribromomethyl ketone could be cleaved by treatment with hot aqueous alkali. However, it seemed likely here also that the rate of reaction might depend on the solubilities of the ketones in water.[6] To test this suggestion methyl alcoholic potassium hydroxide was used. In both cases this treatment produced a reaction but only in the case of α,α,α-trichloro-2,4,6-tribromoacetophenone was the expected 2,4,6-tribromobenzoic acid (X) obtained. The tribromomethyl ketone, although it was completely changed, gave neither of the normal cleavage products. However, it was found possible to convert 2,4,6-tribromoacetophenone into 2,4,6-tribromobenzoic acid directly by treatment with aqueous sodium hypobromite in the presence of pyridine and this would seem to indicate the intermediate formation of and subsequent cleavage of α,α,α,2,4,6-hexabromoacetophenone.

Another method of getting around the insolubility difficulty in the case of the halogenation was to introduce into the molecule solubilizing groups such as hydroxyl and carboxyl. The first attempt of this sort was to prepare 3-hydroxy-2,4,6-tribromoacetophenone (VII) from *m*-hydroxyacetophenone (VI) by bromination. When this phenolic compound was treated with a hypobromite solution it was slowly transformed into a colorless, alkali-insoluble mass from which no pure compound could be isolated.[7]

In the hope of effecting the desired result in another way the amino group in 3-amino-2,4,6-tribromoacetophenone (II) was replaced by a cyano group to give 3-cyano-2,4,6-tribromoacetophenone (IX) which on hydrolysis should yield the corresponding acid—a compound which would be soluble in alkali. This hydrolysis has as yet not been effected.

Experimental

2,4,6-Tribromophenacyl Chloride (VIII).—To a solution of ethylmagnesium bromide, prepared from 1.5 g. of magnesium and 19 cc. of ethyl bromide, was added

[6] This suggestion is supported by the work of Zincke and his collaborators [Zincke and Günther, *Ann.*, **272**, 250 (1893); Zincke and Francke, *ibid.*, **293**, 147 (1896)], who have prepared alkali-soluble di-ortho substituted trihalomethylacetophenones which were readily cleaved by alkali.

[7] In view of the interesting cleavage results obtained by Lock [*Monatsh.*, **55B**, 307 (1930)] with halogen derivatives of *m*-hydroxybenzaldehyde, it seemed worth while to try the action of concentrated alkali on the tribromo-*m*-hydroxyacetophenone to see if the acetyl group would be removed as is the aldehyde group from the phenolic aldehyde. Although a hot concentrated potassium hydroxide solution was found to change the tribromohydroxy ketone slowly no reaction products could be isolated.

a solution of 17 g. of 2,4,6-tribromoacetophenone dissolved in 100 cc. of anhydrous ether. Heat was evolved during the addition and when all of the ketone had been added a colorless precipitate separated from the solution. After the mixture had been stirred for an hour in an ice–salt bath, the solid was filtered and washed with dry ether. It was then suspended in about 100 cc. of absolute ether and into this mixture chlorine gas was passed for about two hours. The resulting mixture was filtered and the filtrate was evaporated. The residue was pressed on a clay plate to remove oily impurities and then was recrystallized several times from methyl alcohol. The compound melted at 98.0–98.5°; the yield was 7 g. or 38% of the theoretical.

Anal.[8] Equivalents of halogen per gram of substance. Calcd. for $C_8H_4OBr_3Cl$: X, 0.0102. Found: X, 0.0101.

α,α,α,2,4,6-Hexabromoacetophenone (IV). (a) From 2,4,6-Tribromoacetophenone.—Five grams of tribromoacetophenone was placed in a solution of sodium hypobromite made by dissolving 50 g. of bromine in 500 cc. of 10% aqueous sodium hydroxide at 0°. The mixture was heated over a steam cone in a 500-cc. round-bottomed flask equipped with a mercury-sealed stirrer and a thermometer. The temperature was kept at 40–50° for twenty-four hours, and then at 60–70° for forty hours. The product was washed with water twice, and after crystallization from ethyl alcohol melted at 115–115.5°. The yield was nearly quantitative.

Anal. Calcd. for $C_8H_2OBr_6$: Br, 80.8. Found: Br, 80.6.

(b) **From 2,4,6-Tribromophenacyl Chloride (VIII).**—One-half gram of 2,4,6-tribromophenacyl chloride was placed in a flask with 50 cc. of 10% sodium hypobromite solution and stirred for thirteen hours, throughout which time it was heated on a steam-bath. The solid was then filtered and recrystallized from ethyl alcohol. It was shown by the method of mixed melting points to be identical with an authentic specimen of α,α,α,2,4,6-hexabromoacetophenone.

Attempted Chlorination of 2,4,6-Tribromoacetophenone with Sodium Hypochlorite Solution.—Two grams of the tribromo ketone was placed in 200 cc. of hypochlorite solution made by passing chlorine gas into 200 cc. of a 10% aqueous sodium hydroxide solution at 0°. The mixture was stirred for three days at room temperature, but no reaction took place. An additional quantity of chlorine was passed into the mixture, which was then allowed to stand at room temperature for four days, but there was still no reaction. Another 2-g. sample was then placed in a flask with 200 cc. of hypochlorite solution, kept at 40° without shaking for two days, and then kept at 50–60° for twelve days. At the end of that time the original substance was recovered unaltered, along with a small amount of silica.

α,α,α-Trichloro-2,4,6-tribromoacetophenone (V). (a) From 2,4,6-Tribromoacetophenone.—One-half gram of 2,4,6-tribromoacetophenone was placed in a flask with 10 cc. of pyridine and 30 cc. of a 10% solution of sodium hypochlorite. After being on the shaker for fifteen hours the flask was removed and the small amount of red solid which had separated from the reaction mixture was removed and purified by recrystallization from ligroin. A larger quantity of the product was obtained from the red pyridine layer by acidification and extraction with ether. The product melted at 73–73.5°.

Anal. Equivalents of halogen per gram of substance. Calcd. for $C_8H_2OBr_3Cl_3$: X, 0.0130. Found: X, 0.0130.

[8] This and other analyses reported in this paper for compounds containing both chlorine and bromine were carried out by the Parr bomb method in which the total halogen was determined by titration.

(b) **From 2,4,6-Tribromophenacyl Chloride.**—Two grams of 2,4,6-tribromophenacyl chloride was placed in a flask with 200 cc. of a 10% solution of sodium hypochlorite. The mixture was stirred and heated for six days. The solid material was then filtered, pressed on a clay plate to remove some tarry material and crystallized several times from methyl alcohol. The α,α,α-trichloro-2,4,6-tribromoacetophenone prepared in this way was shown by the mixed melting point method to be identical with that obtained in (a).

Reaction of α,α,α,2,4,6-Hexabromoacetophenone with Alkali.—The hexabromoacetophenone was heated for long periods of time with (a) 50% aqueous sodium hydroxide, (b) with methyl alcoholic potassium hydroxide and (c) with a mixture of pyridine and 20% aqueous sodium hydroxide. In all cases the hexabromo compound was decomposed but the only products isolated were tarry substances which could not be purified.

2,4,6-Tribromobenzoic Acid. (a) **From 2,4,6-Tribromoacetophenone by Treatment with a Hypochlorite Solution.**—One gram of 2,4,6-tribromoacetophenone was placed in a flask with 25 cc. of pyridine and 25 cc. of a 10% solution of sodium hypochlorite and shaken for four days at room temperature. The red upper layer was then removed and acidified with hydrochloric acid and extracted with ether. The ether was evaporated under diminished pressure and the residue which remained was crystallized from methyl alcohol. The compound melted at 189–190°. The melting point of 2,4,6-tribromobenzoic acid is 188–189°.[9]

(b) **From 2,4,6-Tribromoacetophenone by Treatment with a Hypobromite Solution.**—One gram of 2,4,6-tribromoacetophenone was placed in a flask with 25 cc. of pyridine and 25 cc. of a 10% solution of sodium hypobromite. The mixture was shaken for two days at room temperature and then heated on the steam-bath for two days. It was then acidified and extracted with ether. The ether was evaporated and the 2,4,6-tribromobenzoic acid which was left as a residue was purified by recrystallization from aqueous methyl alcohol. It melted at 189–190° and the melting point showed no lowering when the acid was mixed with a sample of that prepared in (a).

(c) **From α,α,α-Trichloro-2,4,6-tribromoacetophenone.**—Two-tenths gram of the trichloromethyl ketone was placed in a test-tube with 15 cc. of a solution of 30% potassium hydroxide in 30% aqueous methyl alcohol. The solution was refluxed in the steam-bath for one day, removed and acidified. After standing for several days the solution deposited a small amount of material melting at 184–186° which was shown to be impure 2,4,6-tribromobenzoic acid.

***m*-Hydroxyacetophenone (VI).**—Fourteen grams of *m*-aminoacetophenone was dissolved in 140 cc. of water and 18 cc. of concentrated sulfuric acid in an 800-cc. beaker. The solution was stirred and cooled in an ice–salt bath, and the amine was diazotized by adding a concentrated solution of 7.2 g. of sodium nitrite. After the addition the solution was boiled until all the nitrogen was driven off. It was then cooled, and the crystals and dark material which separated were boiled with 800 cc. of norite and filtered. The product crystallized after two to three hours in a colorless fluffy mass. The yield of *m*-hydroxyacetophenone was 11 g. or 78.5% of the theoretical. The melting point was 94–94.5°.[10]

2,4,6-Tribromo-3-hydroxyacetophenone (VII).—Three grams of pure *m*-hydroxyacetophenone was placed in an 800-cc. beaker with 250 cc. of water. The solution was stirred and heated to 50°, at which temperature bromine was added (about 4 cc.) very slowly until a yellow color persisted in the solution. The product separated as a light tan precipitate. This was washed with dilute sodium bisulfite solution and with

[9] Wegscheider, *Monatsh.*, **18**, 217 (1897).

[10] Rupe and Majewski [*Ber.*, **33**, 3407 (1900)] give the melting point as 95°.

water, and after numerous crystallizations from aqueous methyl alcohol melted at 127.5°.

Anal. Calcd. for $C_8H_5O_2Br_3$: Br, 64.3. Found: Br, 64.5.

Decomposition of 2,4,6-Tribromo-3-hydroxyacetophenone (VII) with Alkali.—Two grams of 2,4,6-tribromo-3-hydroxyacetophenone was placed in a small Erlenmeyer flask, and to it was added 8 cc. of a 50% potassium hydroxide solution. The mixture was heated on a steam-bath for three days. A small sample was then removed and reprecipitated from dilute acid, but the starting material was obtained. The mixture was then refluxed over a small flame for two days, and a small sample removed and reprecipitated as above. From this material was obtained only a colorless solid which was insoluble in ether, alcohol and acetic acid, but which crystallized from benzene. The melting point of this material was above 400°.

***m*-Cyano-2,4,6-tribromoacetophenone (IX).**—Seven grams of *m*-amino-2,4,6-tribromoacetophenone was diazotized with 6.0 cc. of concentrated hydrochloric acid and 1.5 g. of sodium nitrite dissolved in 30 cc. of water. The solution was added in portions with stirring to a solution of 5.6 g. of copper sulfate in 18 cc. of water, to which had been added 12.0 g. of potassium cyanide in 18 cc. of water. A dark brown material separated, was filtered, removed by ether extraction and crystallized from a small amount of ethyl acetate. The melting point was 115°; yield, 3 g., or 44% of the theoretical.

Anal. Calcd. for $C_9H_4OBr_3N$: Br, 62.8. Found: Br, 62.7.

Summary

The following di-ortho-bromo derivatives of acetophenone have been prepared: 2,4,6-tribromo-3-aminoacetophenone (II), 2,4,6-tribromo-3-hydroxyacetophenone (VII), 2,4,6-tribromo-3-cyanoacetophenone (IX), 2,4,6-tribromophenacyl chloride (VIII) and 2,4,6-tribromoacetophenone (III).

All of these ketones have been treated with solutions of sodium hypochlorite and sodium hypobromite but only two of the corresponding trihalomethyl ketones have been obtained.

2,4,6-Tribromophenacyl chloride has been shown to yield α,α,α-trichloro-2,4,6-tribromoacetophenone (V) when treated with solutions of sodium hypochlorite. 2,4,6-Tribromoacetophenone yields the same trichloromethyl derivative when treated with pyridine–sodium hypochlorite solutions. Both 2,4,6-tribromoacetophenone and 2,4,6-tribromophenacyl chloride upon long treatment with sodium hypobromite solutions have been found to yield α,α,α-2,4,6-hexabromoacetophenone (IV). Hot concentrated sodium hydroxide solutions caused a very slow decomposition of the trichloromethyl and the tribromomethyl ketones but the normal cleavage product could be isolated only in the first case. Long treatment of 2,4,6-tribromoacetophenone with pyridine–sodium hypohalite solutions caused complete conversion to 2,4,6-tribromobenzoic acid (X).

The results which have been obtained indicate that the two ortho-bromine atoms in these methyl aryl ketones effect a retardation of the haloform reaction which makes it very difficult to effect either the halogena-

tion or the cleavage. Some evidence has been obtained which indicates that the apparent rates of these reactions may be dependent on solubility factors.

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DIHYDRO-1,4-PYRANS. III. THE SYNTHESIS OF THE 1,2-DIBENZOYLCYCLOBUTANES

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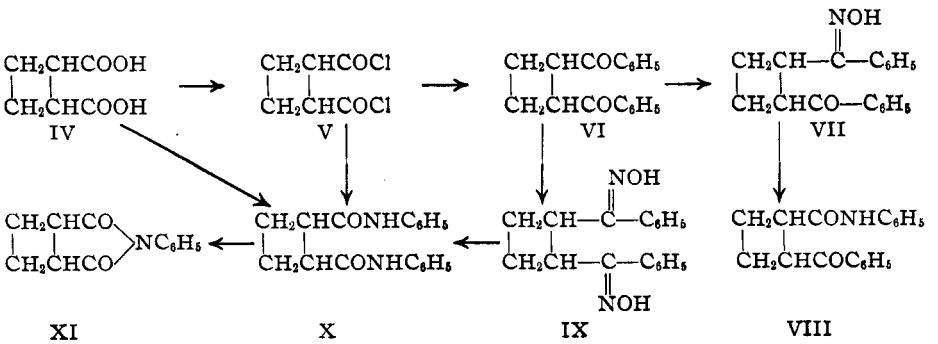
In assigning the structures of the dihydro-1,4-pyrans the alternative formulas considered were 1,2-dibenzoylcyclobutane derivatives.[1] Since these are not known it was determined to synthesize a compound of this type for comparison with the dihydro-1,4-pyrans.

Of the cyclobutane compounds which would offer a direct comparison with the pyrans, 1,2-dibenzoylcyclobutane promised to be easiest to prepare. This compound has now been synthesized and has been found to exist in *cis* and *trans* modifications. This report describes the preparation of these diketones and gives a proof of their structure.

The starting material was the *trans*-1,2-cyclobutanedicarboxylic acid (IV). The *trans* modification of this acid was chosen because it was to be expected that its chloride would be less likely to react in the unsymmetrical form to yield a lactone derivative in the Friedel and Crafts condensation. It was prepared by the methods of Perkin[2] and Fuson and Kao.[3] On treatment with thionyl chloride it gave the corresponding acid chloride (V). This compound when treated with benzene in the presence of aluminum chloride gave two isomeric compounds whose properties corresponded with those predicted for the 1,2-dibenzoylcyclobutane (VI).



[1] Kao and Fuson, THIS JOURNAL, **54**, 313 (1932).

[2] Perkin, *J. Chem. Soc.*, **65**, 585 (1894).

[3] Fuson and Kao, THIS JOURNAL, **51**, 1536 (1929).