[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

A CATALYTIC DECOMPOSITION OF CERTAIN PHENOL SILVER SALTS. VI. THE SYNTHESIS OF 4-HYDROXY-3,5-DIBROMO-2',6'-DIIODO-4'-CHLORODIPHENYL ETHER AND THE DECOMPOSITION OF ITS METALLIC SALTS[1]

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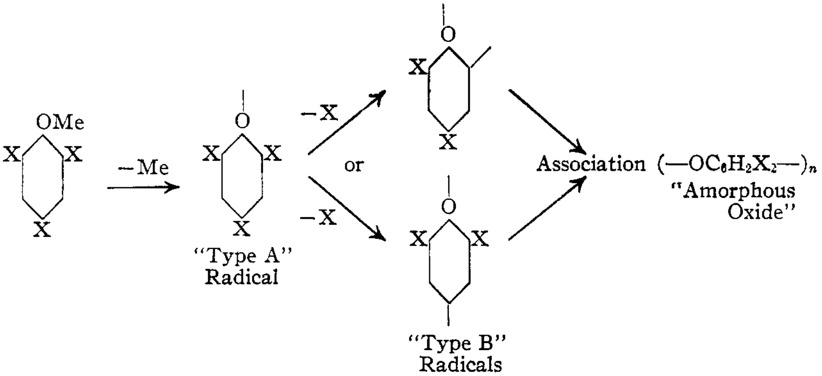
Introduction

Earlier investigations in this Laboratory and elsewhere by Hunter and his students[3] have been concerned with the decomposition of the metallic salts of the symmetrically trihalogenated phenols and related compounds. These decompositions have been observed to take place under the influence of certain catalysts, such as the halogens and alkyl halides, and also may be induced by heating the dry salts of the trihalogenated phenols, suspended in an inert medium such as benzene.

As a result of these studies, it has been suggested that the decomposition of these metallic salts under the influence of heat or catalysts proceeds through the following steps



It has been shown that the amorphous oxides are formed by the union of Type B radicals, involving the formation of new oxygen-to-carbon bonds, *i. e.*, that the association results in linkages of the diphenyl ether type. No evidence has been found for the formation of new carbon-to-

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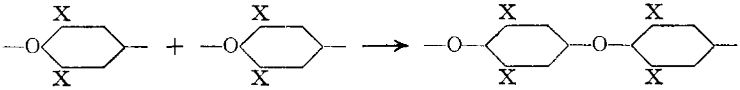
[1] This paper was prepared from a portion of the Thesis of M. A. Dahlen presented to the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1928. The manuscript was written by the junior author after the death of Dr. Hunter in 1931.—L. I. SMITH.

[2] Du Pont Fellow in Chemistry, University of Minnesota, 1927–1928.

[3] (a) Torrey and Hunter, THIS JOURNAL, **33**, 204 (1911); (b) Hunter and others, *ibid.*, **38**, 1761, 2474 (1916); (c) **39**, 2640 (1917); (d) **43**, 131, 135, 151 (1921); (e) Lauer, Thesis, University of Minnesota, 1924; (f) Whitney, THIS JOURNAL, **54**, 1167 (1932); (g) Rathmann, Thesis, University of Minnesota, 1927.

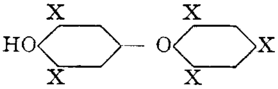
carbon and oxygen-to-oxygen bonds; indeed, tests for peroxides, which would result from the latter type of union, have given negative results in every case.

Therefore, the first stage of this association process may be expressed as follows, assuming that it involves the union of two Type B radicals resulting from the loss of halogen from the para positions of the corresponding Type A radicals

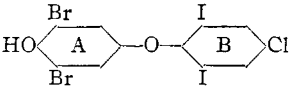


Since the union of radicals of Type A and Type B leads to the formation of products containing linkages of the diphenyl ether type, it was hoped that the preparation and study of a halogenated phenol related to the symmetrically trihalogenated phenols, but already containing a diphenyl ether linkage similar to that present in the oxidation products and amorphous oxides, would cast further light on the nature of the decomposition and oxidation processes previously studied.

A halogenated phenol of the structure (A) was selected as most closely related to the amorphous oxides and trihalophenoxyquinones obtained in the previous work. In order that the subsequent experiments on the



A



I

decomposition of the metallic salts of the phenol should provide a maximum of information concerning the lability and reactivity of the various halogen atoms, the product actually synthesized was (I). By "labeling" the various non-equivalent positions in the molecule with different halogens, the interpretation of the results of subsequent decomposition experiments was rendered extremely easy.

Decomposition of the Metallic Salts of the New Phenol.—A preliminary consideration of the possibilities involved in the decomposition of the metallic salts of the new phenol suggested that one of the following results might be expected.

(1) The salts might not decompose under the conditions which cause amorphous oxide formation from the salts of the trihalogenated phenols.

(2) The salts might decompose in a manner analogous with the decomposition of salts of the trihalogenated phenols, and the loss of halogen from the Type A radical first obtained would be confined to Ring "A." The products of such a decomposition would be an amorphous oxide and the metal bromide.

(3) A decomposition would result in which the loss of halogen from the Type A radical would be confined to Ring "B." The products of such

a decomposition would be an amorphous oxide and the metal iodide, chloride, or a mixture of the iodide and chloride.

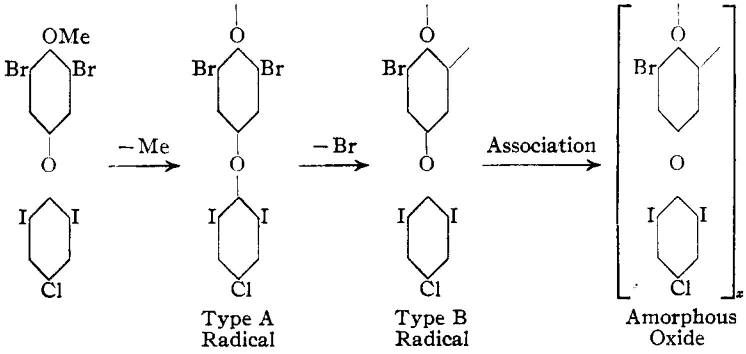
(4) A decomposition would result which would involve all the halogens present in the molecule. The products of such a decomposition would be an amorphous oxide and the mixture of the metal chloride, bromide and iodide.

The potassium salt of the new phenol was decomposed in water solution by the addition of a trace of bromine, following the procedure used in the earlier work on the metal salts of the trihalogenated phenols. The colorless solution of the phenol salt momentarily turned blue-green, then became colorless and a copious precipitate of the white amorphous oxide appeared. The behavior was entirely analogous to the action of the potassium salt of a trihalogenated phenol under the same conditions.

The solution was tested qualitatively for the halogens, but the bromide ion alone was present. The amorphous oxide was analyzed for total halogen and also for the various halogens, and the results were found to correspond closely with the empirical formula $(C_{12}H_4O_2ClBrI_2)_x$. These results indicated that the decomposition had proceeded according to "2" above.

The silver salt of the new phenol was decomposed in benzene suspension by the action of ethyl iodide, iodine and heat, respectively. In each case an amorphous oxide was obtained corresponding with the above empirical formula. The silver halide produced by the decomposition under the influence of heat alone was examined carefully and found to be silver bromide. No trace of iodide or chloride could be found.

The above experiments demonstrated that the decompositions of the salts of the new phenol had taken place in the following manner, assuming that the mechanism previously proposed may be applied to these analogous decompositions



Type A Radical

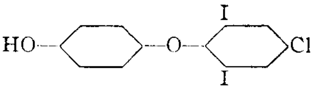
Type B Radical

Amorphous Oxide

Discussion of the Results

The fact that metallic salts of the new halogenated phenol decomposed in a manner analogous to the decomposition of salts of the symmetrically trihalogenated phenols was not especially surprising, even though the decomposition reaction was confined to the benzene nucleus containing only two halogen atoms; for recent work by Rathmann in this Laboratory[3g] has disclosed that the salts of dihalogenated ortho and para cresols may be decomposed in a similar manner. However, the fact that halogen atoms were removed only from the hydroxyl-bearing nucleus seems to be most important, especially since in the molecule studied the other benzene nucleus was substituted by three halogen atoms oriented as in the trihalogenated phenols previously studied. On the basis of previous work, it might be expected that the halogen atoms in Ring "B" would be as reactive or labile as those in Ring "A." The fact that all halogen loss occurs from Ring A must be interpreted as meaning that the influences responsible for decompositions of this type are confined to the ring bearing a free hydroxyl group. The conversion of a trihalogenated phenol to an ether apparently results in diminution or complete disappearance of these influences.

In order to check this point, an attempt was made to decompose the salts of the phenol II, which was prepared as an intermediate in the synthesis of I. It was found that the salts of II did not decompose under the conditions which result in rapid amorphous oxide formation in the case of I and of the ordinary trihalogenated phenols. Similar experiments on the salts of 4-hydroxy-2′,6′-diiodo-4′-bromodiphenyl ether also gave negative results. These experiments seemed to prove that the hydroxyl group must be present in the halogenated nucleus in order that this type of decomposition may occur.



(II)

A second important result of this study was the disclosure of additional evidence for the existence of radicals of Type A and Type B. First of all, the momentary appearance of a blue-green color, followed by decoloration and precipitation of the amorphous oxide during the decomposition of the phenol salts, coincides with the behavior of the ordinary trihalogenated phenol derivatives. The colored intermediate products have been assumed, in previous work, to be the free radicals The present work adds strength to the previous theory, since similar observations have now been made on substances quite different in chemical constitution.

More important, however, is the fact that the results of the present study make it appear less likely than ever that the metallic salt decompositions are intermolecular reactions involving the "splitting-off" of metal halide between molecules, forming the diphenyl ether type linkages. If such a mechanism actually were correct, then it would appear most probable that halogen atoms in Ring B of I would be involved. A correlation of the work of Hunter and Joyce[4] on the decomposition of salts of

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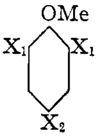
[4] Hunter and Joyce, THIS JOURNAL, **39**, 2640 (1917).

the type indicated, where X_1 and X_2 are different halogens, with the results of the new decompositions, would indicate that a reaction mechanism involving intermolecular reaction is almost mathematically impossible in the case of certain trihalogenated phenols of the above type. This is especially true in the case where X_1 represents Cl and X_2 is Br. If intermolecular condensation is not possible as an explanation of the decompositions, the mechanism involving the Type A and Type B radicals receives added confirmation.



Experimental Part

4-Methoxy-2′,6′-diiodo-4′-nitrodiphenyl Ether.—The above substance was prepared according to the synthesis described by Harington and Barger.[5]

This method was found to give excellent results when pure starting materials were used. However, the reaction failed entirely when impure ethyl methyl ketone was used as a solvent, and gave poor results unless the other starting materials were of high purity. The best experiments in this work gave condensation yields of 70% of the theoretical, as compared with the 67% yield reported by the above authors.

4-Methoxy-2′,6′-diiodo-4′-aminodiphenyl Ether Hydrochloride.—The method of Harington and Barger was used for the reduction of the above nitro compound to this amine. The yield was usually about 65% of the theoretical.

4-Methoxy-2′,6′-diiodo-4′-chlorodiphenyl Ether.—Twenty-five grams of the hydrochloride of 4-methoxy-2′,6′-diiodo-4′-aminodiphenyl ether was ground very finely in an agate mortar. It was then suspended in 150 cc. of glacial acetic acid to which had been added 10 cc. of water. The suspension was agitated with a high-speed stirrer and cooled externally to 15°. Eight cubic centimeters of *tert.*-amyl nitrite was now added slowly, the temperature being held at 15°. The mixture was then stirred at this temperature for one-half hour, to allow the diazotization to go to completion.[6]

Fifty grams of cuprous chloride was dissolved in 250 cc. of concd. hydrochloric acid and 150 cc. of water was added to the solution. It was then heated to about 60° on the steam-bath, and the diazo solution prepared as above added slowly with vigorous stirring. Much nitrogen was evolved, and the product settled out as a black oil. The mass was heated on the steam-bath for about one hour to complete the replacement and was then cooled to room temperature. The product solidified to a black crystalline mass and was filtered. It was dissolved in benzene, dried overnight over calcium chloride, and the benzene removed by distillation at atmospheric pressure. The product was then distilled in a vacuum. The fraction boiling at 200–218° under 4 mm. pressure was collected. It distilled as a yellow oil which quickly solidified. The yield at this point was 15.4 g. or about 64% of the theoretical. The product was recrystallized from a mixture of 67 parts absolute alcohol and 33 parts benzene until it showed a constant melting point.

Anal. (Carius) Calcd. for $C_{13}H_9O_2ClI_2$: Cl, 2I, 59.47. Found: X, 59.41, 59.21.

The product crystallizes from alcohol in long white plates melting at 101–102°.

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[5] Harington and Barger, *Biochem. J.*, **21**, 175 (1927).

[6] Harington and Barger used the above method of diazotization in the conversion of this base to the corresponding nitrile. It was found in the present work that the use of *tert.*-amyl nitrite gave better results than the mixture of amyl nitrites prepared from commercial amyl alcohol. It was also found that the addition of a small quantity of water facilitated the diazotization process.

4-Methoxy-2′,6′-diiodo-4′-bromodiphenyl ether.—This material was prepared by a process similar to the above. The product crystallizes from alcohol in bunches of white plates, melting at 123–123.5°, and boiling at 209–219° under 2 mm. pressure.

Anal. (Carius). Calcd. for $C_{13}H_9O_2BrI_2$: Br, 2I, 62.87. Found: X, 62.78, 62.62.

4-Methoxy-2′,4′,6′-triiododiphenyl Ether.—This material, similarly prepared, showed the following properties.

Anal. (Carius). Calcd. for $C_{13}H_9O_2I_3$: I, 65.89. Found: I, 65.92, 65.72.

The substance crystallizes from a benzene–alcohol mixture in white needles melting at 132–132.5°, and boiling at 220–230° under 1–2 mm. pressure.

4-Hydroxy-2′,6′-diiodo-4′-chlorodiphenyl Ether.—Five grams of the corresponding methoxy compound was dissolved in 35 cc. of boiling glacial acetic acid, 0.1 g. of red phosphorus added, and then 44 cc. of pure 57% hydriodic acid was poured in through the reflux condenser. The mixture was held at the boiling point until all of the methoxy compound, which separated as an oil upon the addition of hydriodic acid, redissolved. The mixture was then cooled and poured into an equal volume of water, precipitating the phenol as a white solid.

The crude product obtained as above was dissolved in warm dilute sodium hydroxide solution, filtered, and the phenol reprecipitated by the addition of hydrochloric acid. The product was filtered, washed with water, and then crystallized from 50% alcohol. The yield at this point was about 82% of the theoretical. Repeated crystallization from alcohol gave a product melting sharply at 154.5°. The hydroxy compound crystallizes in the form of very small white needles. The sodium and potassium salts of the phenol are only slightly soluble in cold water, but dissolve readily at the boiling point.

Anal. (Carius). Calcd. for $C_{12}H_7O_2ClI_2$: Cl, 2I, 61.24. Found: X, 60.57, 60.55.

4-Hydroxy-2′,6′-diiodo-4′-bromo-diphenyl Ether.—This phenol was prepared from the corresponding methoxy compound by a process similar to the above. It crystallizes from alcohol in white needles melting at 162–163°. The sodium and potassium salts are quite insoluble in cold water but dissolve readily at the boiling point.

Anal. (Carius). Calcd. for $C_{12}H_7O_2BrI_2$: Br, 2I, 64.57. Found: X, 64.54, 64.47.

4-Hydroxy-3,5-dibromo-2′,6′-diiodo-4′-chlorodiphenyl Ether.—2.7 grams of 4-hydroxy-2′,6′-diiodo-4′-chlorodiphenyl ether was dissolved in 20 cc. of glacial acetic acid in an acetylating flask, and the solution was heated to about 75°; 1.88 g. (3% excess) of bromine was dissolved in 20 cc. of glacial acetic acid and added to the solution of the phenol through the reflux condenser. The solution was heated to boiling for ten minutes, cooled and poured into about 200 cc. of water. The phenol was filtered, washed with water, and crystallized from a mixture of chloroform and alcohol. It was then crystallized repeatedly from absolute alcohol containing a little benzene until a product melting at 194.5° was obtained. The yield on bromination was practically the theoretical, but much material was lost in the purification process.

Anal. (Carius). Calcd. for $C_{12}H_5O_2ClBr_2I_2$: Cl, 2Br, 2I, 71.26. Found: X, 70.92.

The phenol crystallizes from absolute alcohol in white micro needles. It is very slightly soluble in alcohol, moderately soluble in benzene and very soluble in chloroform. The sodium and potassium salts are quite insoluble in cold water but dissolve readily on heating.

Silver Salt of **4-Hydroxy-3,5-dibromo-2′,6′-diiodo-4′-chlorodiphenyl Ether.**—One gram of the phenol was dissolved in 30 cc. of hot, very dilute sodium hydroxide. The solution was filtered and cooled, the sodium salt separating from the filtrate in white plates. The sodium salt was filtered, washed with a little cold water, and then suspended in 20 cc. of distilled water. The suspension was heated to bring the salt into solution, then cooled rapidly in order to obtain the product in the form of very fine crystals. Two-tenths gram of pure silver nitrate was dissolved in distilled water and added to the suspension of the sodium salt. The silver salt immediately formed as a gelatinous white solid. It was filtered, washed with water and dried overnight in a vacuum desiccator.

Catalytic Decomposition of the Potassium Salt of 4-Hydroxy-3,5-dibromo-2′,6′-diiodo-4′-chlorodiphenyl Ether. A. By Bromine.—Three grams of the phenol was dissolved by heating with 25 cc. of a very dilute solution of potassium hydroxide. A cubic centimeter of bromine water was then added. The solution immediately turned bluish-green, and an amorphous oxide quickly appeared as an almost white gelatinous precipitate. The solution was boiled for one-half hour to insure complete decomposition. It was then filtered, and the oxide was collected and dried. The filtrate was reserved for qualitative tests for halogen (see below).

The oxide was purified by dissolving in 20 cc. of warm benzene, filtering, and re-precipitating by the addition of 40 cc. of low-boiling ligroin. The process was repeated four times and the product was then white and practically pure; melting point, 245–257° with decomposition. The yield of crude amorphous oxide was 2.2 g., corresponding to 85% of the theoretical. About 2 g. of purified material was obtained from this crude product.

Anal. (Carius) Calcd. for $(C_{12}H_4O_2ClBrI_2)_x$: Cl, Br, 2I, 67.21. Found: X, 66.38, 66.17. *Analysis* of silver salts by electrolysis: 0.2967 g. of mixed silver salts gave 0.1592 g. Ag. Calcd. for AgCl, AgBr, 2AgI: 0.1599.

Tests for Halogen in Filtrate from Amorphous Oxide Precipitation.—The filtrate from the above decomposition of the potassium salt was acidified with nitric acid and filtered. A little pure sodium bisulfite was added to reduce all halogen to halide ion, and the solution boiled to remove excess bisulfite. It was then extracted with benzene to remove organic matter.

The solution was now tested for each of the halide ions by the usual qualitative procedure. The test for bromide ion was positive; all other halides were absent.

B. By Iodine.—Another sample of the phenol was treated in the same manner, except that a drop of a solution of iodine in potassium iodide was substituted for bromine water. Apparently the same decomposition took place and the same amorphous oxide was produced. Analyses of the amorphous oxide corresponded with the results given above. The filtrate from this decomposition was also tested for halide ions, and was found to contain bromide and iodide ions. The iodide ion undoubtedly was introduced by the decomposition catalyst.

Catalytic Decomposition of the Silver Salt of 4-Hydroxy-3,5-dibromo-2′,6′-diiodo-4′-chlorodiphenyl Ether. A. By Ethyl Iodide.—A small sample of the dry salt was suspended in 5 cc. of dry benzene. A drop of ethyl iodide was added. The solution turned bluish-green in color almost immediately. This color persisted for about ten minutes, then disappeared, and the solution remained a light yellow. The solid remaining was filtered and qualitative tests showed it to be silver bromide mixed with a little unchanged silver salt. The addition of an equal volume of ligroin to the filtrate precipitated an amorphous oxide. Analysis of this material showed it to be identical with the product obtained from the decomposition of the potassium salt.

B. By Iodine.—The above experiment was repeated, using a small crystal of iodine instead of ethyl iodide as the catalyst. The same decomposition occurred, yielding the same products.

C. By Heat.—A small sample of the silver salt was suspended in 5 cc. of benzene and the solution heated to about 70°. The mass turned blue-green momentarily, then faded to a pale yellow. A precipitate of silver bromide was obtained, and from the filtrate the same amorphous oxide was isolated.

Attempted Catalytic Decomposition of the Potassium and Silver Salts of 4-Hydroxy-2′,6′-diiodo-4′-chlorodiphenyl Ether.—The potassium and silver salts of 4-hydroxy-2′, 6′-diiodo-4′-chlorodiphenyl ether were prepared by the usual methods. They were subjected to the action of the above catalysts under similar conditions, but in no case did a decomposition to amorphous oxide occur.

Summary

1. 4-Hydroxy-3,5-dibromo-2′,6′-diiodo-4′-chlorodiphenyl ether, a new halogenated phenol related to the symmetrically trihalogenated phenols, has been prepared.

2. The catalytic decomposition of metallic salts of the new phenol has been studied. The decomposition occurs in a manner entirely analogous to that of the trihalogenated phenols previously studied. It was observed that only the halogen in the hydroxyl-bearing nucleus is removed in such decomposition.

3. Additional confirmation of the mechanism previously suggested for the catalytic decomposition of metal salts of halogenated phenols has been obtained.

4. Additional evidence for the existence of Type A and Type B radicals has been disclosed.

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RESEARCHES ON HYDANTOINS. L.[1] THE SYNTHESIS OF HYDANTOINS POSSESSING THE PROPERTIES OF HYPNOTICS

By Robert M. Herbst[2] and Treat B. Johnson

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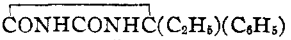
That the hydantoin nucleus exhibits hypnotic properties has been known for several years. This pharmacological behavior is most pronounced in the drug "*nirvanol*" (phenylethylhydantoin) I, which is the hydantoin analog of the pyrimidine "*luminal*" or phenylethylbarbituric acid II. The latter cyclic ureide and several of its representatives have been used effectively as sedatives and hypnotics in simple insomnia, hysteria, neurasthenia, thyroid disease, chorea, epilepsy and certain mental disturbances.


$\mathrm{CONHCONHC(C_2H_5)(C_6H_5)}$

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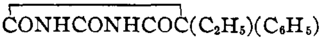
$\mathrm{CONHCONHCOC(C_2H_5)(C_6H_5)}$

II

Although nirvanol I has fallen into disrepute in recent years as an hypnotic because of the fever and skin eruptions induced by its continued ad-

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[1] Constructed from a dissertation presented by Robert M. Herbst to the Faculty of the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1930.

[2] Eli Lilly Company Graduate Scholar, 1928–1929.