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## An Investigation of Some Iodine Derivatives of Ortho and Para Halogenated Phenols

Robert M. Abernathey  
*Fort Hays Kansas State College*

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AN INVESTIGATION OF SOME IODINE DERIVATIVES  
OF ORTHO AND PARA HALOGENATED PHENOLS

being

A thesis presented to the Graduate Faculty  
of the Fort Hays Kansas State College in  
partial fulfillment of the requirements for  
the Degree of Master of Science

by

Robert M. Abernathy, B. S.

Fort Hays Kansas State College

Date May 6, 1951

Approved Harold S. Choquill  
Major Professor

Ralph G. Coder  
Chairman Graduate Council

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Author

7.30.51

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## INTRODUCTION

Phenol has long been recognized as an effective germicide, having been introduced into medicine and surgery as a disinfectant by Joseph Lister in 1865. A dilution of 1:100 will kill most bacteria in five to ten minutes. It is used as a standard reference for comparison of all disinfectants; a measure of the germicidal efficiency of an unknown disinfectant is obtained by a comparison of concentrations of solutions of phenol and of the unknown which will kill a given organism in the same time. This ratio is called the phenol coefficient of the unknown disinfectant. (16)

Phenol itself is not now widely used as a disinfectant because it is irritating to the skin and it has a strong odor. However, some of the phenol derivatives are much more satisfactory. Halogenated phenols have been found to be very effective germicides. The following phenol coefficients, measured against *Staphylococcus aureus*, show interesting effects:

Derivative	Phenol Coefficient
2-chlorophenol	3.8
2,4-dichlorophenol	13.0
2,4,6-trichlorophenol	25.0
2,4-dibromophenol	22.0

It is evident that when halogens are substituted into phenol the increase in bactericidal power is more than additive. The effect on phenol coefficient of the substitution of a halogen appears to depend upon whether or not halogens are already present, and how many. It is also affected by the atomic weight of the substituting

halogen, the heavier ones causing a greater increase in phenol coefficient. This is illustrated by the fact that 2,4-dichlorophenol has a phenol coefficient of 13.0, while the corresponding dibromo derivative has a coefficient of 22.0. (17)

While the chloro and bromo phenols have been extensively investigated, comparatively little is known of the iodophenols. Iodine itself, in a three per cent alcoholic solution, has a phenol coefficient of 5.8. This together with the fact that iodine is the heaviest of the halogens, suggests that the halogenated phenols, when substituted further with iodine, should yield products which might be very effective germicides.

The purpose of this investigation was to prepare and investigate the composition and properties of some iodine derivatives of halogen substituted phenols. Because of the limited time available, and because of the difficulty in obtaining materials, this investigation was limited to the ortho and para halogenated phenols. In addition, the reactions and properties of ortho and para substituted compounds are usually more similar to each other than to those of the meta isomers. Compounds which were iodinated were: o-chlorophenol, p-chlorophenol, o-bromophenol, p-bromophenol, and o-iodophenol. The remaining compounds of the series, p-iodophenol, o-fluorophenol and p-fluorophenol were not available for use. Several unsuccessful attempts were made to prepare p-iodophenol from the diazonium salt obtained from p-aminophenol. Melting points of the products, and, as far as possible, the composition and isomeric arrangements, were



determined. The determination of phenol coefficients was left for an investigator who has had experience in bacteriology.

### THEORY

When applied to organic chemistry, the term iodination may refer to any process by which iodine is introduced into an organic molecule. This may be done by addition at a double bond, either by  $I_2$  or by HI, or by substitution of an atom of iodine for an atom of hydrogen or for some replaceable group. Because of the high stability of the aromatic nucleus, the reactions of benzene usually involve replacement of one or more of the hydrogen atoms by substituents. (2) Iodination of a benzene derivative such as a phenol would therefore be expected to be accomplished by a process of substitution rather than by addition.

In the case of benzene, chlorine or bromine substitution is aided by the presence of a suitable catalyst. Anhydrous aluminum chloride is a very active catalyst in chlorination. Often metallic iron or aluminum is added and the catalyst becomes the corresponding metallic halide. Iodine does not react in the presence of such a catalyst, or carrier, as they are sometimes called, as do chlorine and bromine. Iodine in the absence of an oxidizing agent has little or no action on benzene. In the preparation of iodine compounds, substitution does not take place unless the reaction is rendered exothermic. This can be accomplished by adding an oxidizing agent, as for example iodic acid or nitric acid, to the mixture of iodine

and aromatic hydrocarbon. In the case of some very reactive compounds, the addition of alkali is all that is necessary. (12)

Numerous methods of iodination of phenolic compounds have been successfully used, and several conflicting theories of the mechanisms involved have been offered. Li has done extensive work at the University of California in the iodination of tyrosine, a para-substituted phenol. He reacted tyrosine with iodine directly in a basic solution, and concluded that the reaction was mainly between ionized tyrosine and hypiodite ion. He further concluded that the rate-determining step in the reaction was the formation of the monoiodo derivative which reacts much more rapidly to form the diiodo derivative. (11)

Fialkov and Gengrinovich report that active iodinating action is exhibited by an alcoholic mixture of iodine and silver nitrate. They reported quantitative yields of triiodophenol when the mixture was 65 per cent alcohol with the molar ratio of silver nitrate to iodine being 1.5:1. (7)

Iodine monochloride has been used in numerous iodinations. Block and Powell at Columbia reported an 85% yield of diiodotyrosine by warming tyrosine in acetic acid with iodine monochloride. (1)

Dains and co-workers at the University of Kansas carried out iodination by refluxing phenetole with iodine on an oil bath and periodically adding nitric acid as an oxidizer. The main product was o-iodophenetole. (5) A point of interest is that with this method,

all the iodine enters the organic molecule. In other methods using molecular iodine, one atom enters the ring and the other forms hydriodic acid with the hydrogen atom being replaced.

Hunter and Budrow at the University of Minnesota iodinated phenol under anhydrous conditions by melting oxide-free metallic sodium under xylene and adding an anhydrous xylene solution of phenol and resublimed iodine. The reaction was instantaneous until about 85 per cent of the iodine had been added, then slowed somewhat. Since there was no opportunity for the formation of hypiodite ion, this result proves that the iodinating agent is not in every case the hypiodite ion, as earlier suggested.

In the iodination of hydroxy diphenyl ethers, Choguill added a solution of iodine in potassium iodide to the compound in a concentrated solution of ammonium hydroxide. The iodinating agent was assumed to be the highly active nitrogen triiodide formed by the action of ammonium hydroxide on iodine. (4)

Gill used this method in iodinating p-alkyl phenols. After carrying out iodinations in different concentrations of ammonia to determine the most favorable conditions, he used a 7.1 per cent ammonia solution. (8)

In substitution in aromatic compounds, certain rules aid in predicting the position or positions at which substitution will take place. If a second substituent, Y, is to be introduced into a benzene derivative,  $C_6H_5X$ , the position taken by Y depends upon the electronic character of the group X already present on the ring.

Whether the disubstitution products are ortho or para or meta is closely associated with the speed of reaction. Cases of rapid substitution lead to the formation of ortho and para compounds, while meta substituted compounds are usually obtained in cases where substitution is slow. If the group X tends to increase the electron density of the ring, substitution is rapid and occurs in the ortho and/or para position. If the group decreases the electron density, substitution takes place slowly if at all, and the product is chiefly the meta isomer. Some of the most common substituting groups have been classified according to their orienting power in the following manner:

Class I. Ortho-para orienting groups (electron donors)

A. Very strong:  $-\text{N}(\text{CH}_3)_2$ ;  $-\text{NH}_2$ ;  $-\text{OH}$

B. Intermediate:  $-\text{NHCOCH}_3$ ;  $-\text{OCOCH}_3$ ;  $-\text{OCH}_3$

C. Comparatively weak:  $-\text{Cl}$ ;  $-\text{Br}$ ;  $-\text{I}$ ;  $-\text{CH}_3$

Class II. Meta Orienting groups (electron acceptors)

$\text{NO}_2 > \text{SO}_3\text{H} > \text{CN} > \text{COOH} > \text{CHO}$

Any group in division A of class I has greater directing power than any group in division B, which, in turn, exceeds any group in division C. The effects of these groups may be summarized in these four rules:

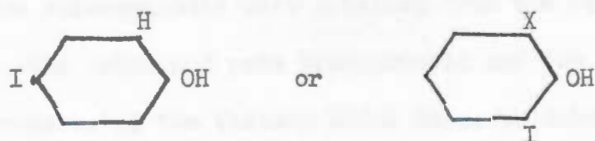
1. The group already present on the benzene ring determines the position taken by the next entering group.

2. Class I groups (electron donors) direct a new group to the ortho or para position, and the rate of substitution is faster than it is in benzene.

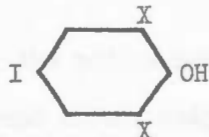
3. Class II groups (electron acceptors) direct a new group to the meta position, and the rate of substitution is slower than it is in benzene.

4. Class I groups always take precedence over class II groups in benzene derivatives which contain a representative of each class. (3)

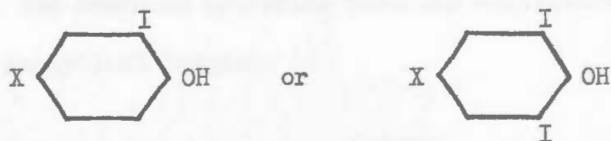
According to these rules, the orienting group in a halogenated phenol is the -OH group, since it is a much stronger directing agent than any halogen. The iodinated products of ortho halogenated phenols would then be of the type



if a single substitution occurs, or of the type



if disubstitution occurs. Iodinated products of para halogenated phenols should be of the type



depending upon whether mono or disubstitution has taken place.

## MATERIALS

## Phenols

The phenols which were iodinated were not of a high degree of purity and were used without further purification, since it would be necessary to purify the products in any case. The ortho and para chlorophenols were obtained from the Paragon Testing Laboratory. The ortho and para bromophenols and the ortho iodophenol were products of the Eastman Kodak Research Laboratory and were obtained from Eimer and Amend.

## Sodium Hydroxide

The sodium hydroxide solutions used were prepared from Eimer and Amend A.C.S. reagent grade electrolytic pellets in a concentration of about six normal.

## Ammonium Hydroxide

The ammonium hydroxide used was Mallinckrodt's 26% Ammonia Water Analytical Reagent.

## Iodine

The iodine solution was prepared from Merck reagent grade re-sublimed iodine and Merck reagent grade granular potassium iodide. The iodine was ground under water with a minimum amount of potassium iodide to effect solution. It was diluted to a concentration of two

hundred grams of iodine per liter of solution.

#### Hydrochloric and Nitric Acids

The hydrochloric and nitric acid solutions were prepared from Eimer and Amend A.C.S. reagent grade acids by dilution to a concentration of about six normal.

#### Sodium Bisulfite

The sodium bisulfite solutions were prepared from Eimer and Amend A.C.S. reagent grade sodium metabisulfite.

#### Ethanol

The ethanol was industrial ethyl alcohol produced by U. S. Industrial Chemicals, Inc.

#### Sodium Peroxide

The sodium peroxide was Eimer and Amend A.C.S. calorific sodium dioxide. It was finely divided to facilitate mixing.

#### Silver Nitrate

The silver nitrate solution was prepared from Mallinckrodt C.P. crystalline silver nitrate in a concentration of about 0.1 and standardized by comparison with a thiocyanate solution which was standardized against a weighed sample of silver nitrate.

## EXPERIMENTAL

The method of iodination used was very similar to that used by Gill (8) and Higgins, (9) which was found to be quite satisfactory. The materials for this method were readily available. However, their procedure was modified after the discovery that the use of a more concentrated ammonia solution gave a better yield with less by-product and the reaction took place at a more rapid rate.

Five grams of the halogenated phenol were dissolved in a minimum amount of dilute sodium hydroxide solution. Fifty milliliters of concentrated ammonium hydroxide were added, followed by small portions of a solution of iodine in potassium iodide until the desired amount of iodine had been added. The mixture was stirred constantly with a mechanical stirrer while the iodine was being added. The mixture was acidified and the excess iodine was destroyed by the addition of sodium bisulfite. The product was then filtered and recrystallized, in most cases from an ethanol-water mixture, and the melting point determined. Some of the products required additional recrystallizations in order to obtain a sufficient degree of purity.

## ANALYSIS

The analysis of the products to determine the amount of combined iodine was the greatest problem in this investigation. The usual method of peroxide bomb fusion followed by determination by



the Volhard method is unsatisfactory in the presence of two halogens. When two halogens are present in an unknown ratio, the determination gives only the weight of the compound which will precipitate one equivalent weight of silver. For example, chlorophenol has a silver equivalent of 128.56, monoiodochlorophenol has a silver equivalent of 127.24, and diiodochlorophenol has a silver equivalent of 126.79. The Volhard method is not adequate to differentiate between any of these compounds.

The first attempt to determine the number of iodine atoms added was by a molecular weight determination by depression of the freezing point of benzene in a Beckmann freezing point apparatus. (6) The iodinated product of o-chlorophenol gave a value of 425, which does not correspond to either of the expected values of 256 for the monoiodo product or 380 for the diiodo product. It was later learned from literature that the molecular weights of phenolic compounds cannot be satisfactorily determined by the depression of the freezing point of benzene, due to association. The degree of association of phenol in benzene increases with increase in concentration. As the concentration approaches ten per cent, the apparent molecular weight by the freezing point method becomes nearly 200, or 215 per cent of the true value. (18) Since the degree of association of the iodochlorophenols is not known, the freezing point method is of little value in this investigation. The value of 425 obtained for the molecular weight of the iodinated chlorophenol seems to indicate that the product is monoiodochlorophenol, which would have a molecular weight of 256.

Another attempt to determine molecular weight was made using the macroprocedure for acetylation described by Ogg and co-workers. (13) a definite amount of acetic anhydride-pyridine acetylating reagent was pipetted into a flask containing a weighed sample of the phenol, and the flask was heated on a steam bath for an hour. A small amount of water was added, then the excess acetic acid was titrated with a standard alcoholic solution of sodium hydroxide. A blank titration of the reagent was made to determine the amount of acetic acid used up in esterification. The compound failed to acetylate, as indicated by the fact that more alkali was required in the flasks containing the samples than for the blanks. This suggested the possibility that the substitution of halogens had increased the acidity of the phenol sufficiently that it could be titrated to give the equivalent weight as an acid. This effort also failed.

Reasonably satisfactory results were finally obtained in the halogen analysis by precipitation titration. The course of a precipitation titration is readily followed by electrometric methods, provided an electrode that will be at equilibrium with one of the ions involved in the reaction is used. An example is the precipitation of silver chloride by titration of silver ion with chloride ion. The cell is:



The silver electrode dips into the titration solution. As the concentration of silver ion is changed, the EMF changes according to

the equation relating EMF and concentration

$$E = E_{\text{Ag}}^{\circ} - E_{\text{Calomel}}^{\circ} - 0.0591 \log [\text{Ag}^{\oplus}] .$$

At the stoichiometric end point there is an abrupt change in the silver-ion concentration and a corresponding change in the voltage of the cell. (15)

The samples were prepared by ignition in a Parr bomb according to the directions furnished by the manufacturer. (14) A 0.200 g. sample of the halogenated phenol was mixed with 1.000 g. of sucrose in an ignition bomb. Fifteen grams of sodium peroxide were added by use of the measure provided with the bomb. The charge was thoroughly mixed and the bomb assembled. Two ml. of water were placed in the recess in the bomb head and the charge was ignited by heating over a Bunsen burner at full heat. As soon as the water on the head began to boil, the bomb was quenched in a trough of cold water. The fusion mass was dissolved in about 100 ml. of hot distilled water in a 600 ml. beaker. The solution was neutralized and made slightly acid with dilute nitric acid, and sufficient sodium bisulfite solution was added to reduce to iodides the iodates formed in the combustion. The solution was then warmed for several minutes to remove the excess sulfur dioxide and was then cooled and titrated with a standard solution of silver nitrate.

A Macbeth Model 1051 Titration-pH Meter with a silver indicator electrode and a calomel reference electrode, as suggested by Willard, Merritt, and Dean (20), were used in the titrations.

Settings for the instrument which gave good sensitivity without going past the scale during the titration were determined by trial. Satisfactory results were obtained by setting the sensitivity control at 65 or 70 and setting the needle at 300 on the millivolt scale at the beginning of the titration by the use of the bucking potential. Potential readings were taken at 0.5 ml. intervals in the vicinity of rapid changes and a 1 ml. or larger intervals at other times. Potential-volume curves were plotted, from which the volumes of silver nitrate necessary to precipitate the halogens were estimated.

## Iodination of o-Chlorophenol

Five grams of o-chlorophenol were dissolved in a minimum amount of sodium hydroxide and 50 ml. of ammonium hydroxide was added. The mechanical stirrer was started, and a solution of iodine in potassium iodide was added until the color of iodine persisted. Sodium bisulfite was added to reduce the excess iodine and the mixture was acidified with dilute hydrochloric acid. The precipitate was filtered and recrystallized twice from an ethanol-water mixture. The product was fine, pale pink needles with a melting point of  $98^{\circ}$  C.

In the analysis, approximately 10.6 ml. of silver nitrate solution were required to precipitate the iodide from the sample, and 15.3 - 10.6 or 4.7 ml. were required for the chloride. This indicates that the iodine and chlorine are present in 10.6:4.7 or 2.26:1 ratio and that the product is diiodo chlorophenol.

TABLE I

DATA FROM PRECIPITATION TITRATION OF IODINATED o-CHLOROPHENOL

---

---

<u>ML. AgNO<sub>3</sub></u>	<u>M. V. Scale Reading</u>
0	300
1	298
2	310
4	350
5	335
6	340
7	335
8	320
9	300
10	270
10.5	235
11	75
11.5	35
12	20
13	-5
14	-20
14.5	-25
15	-40
15.5	-90
16	-110
17	-135
18	-145
20	-145

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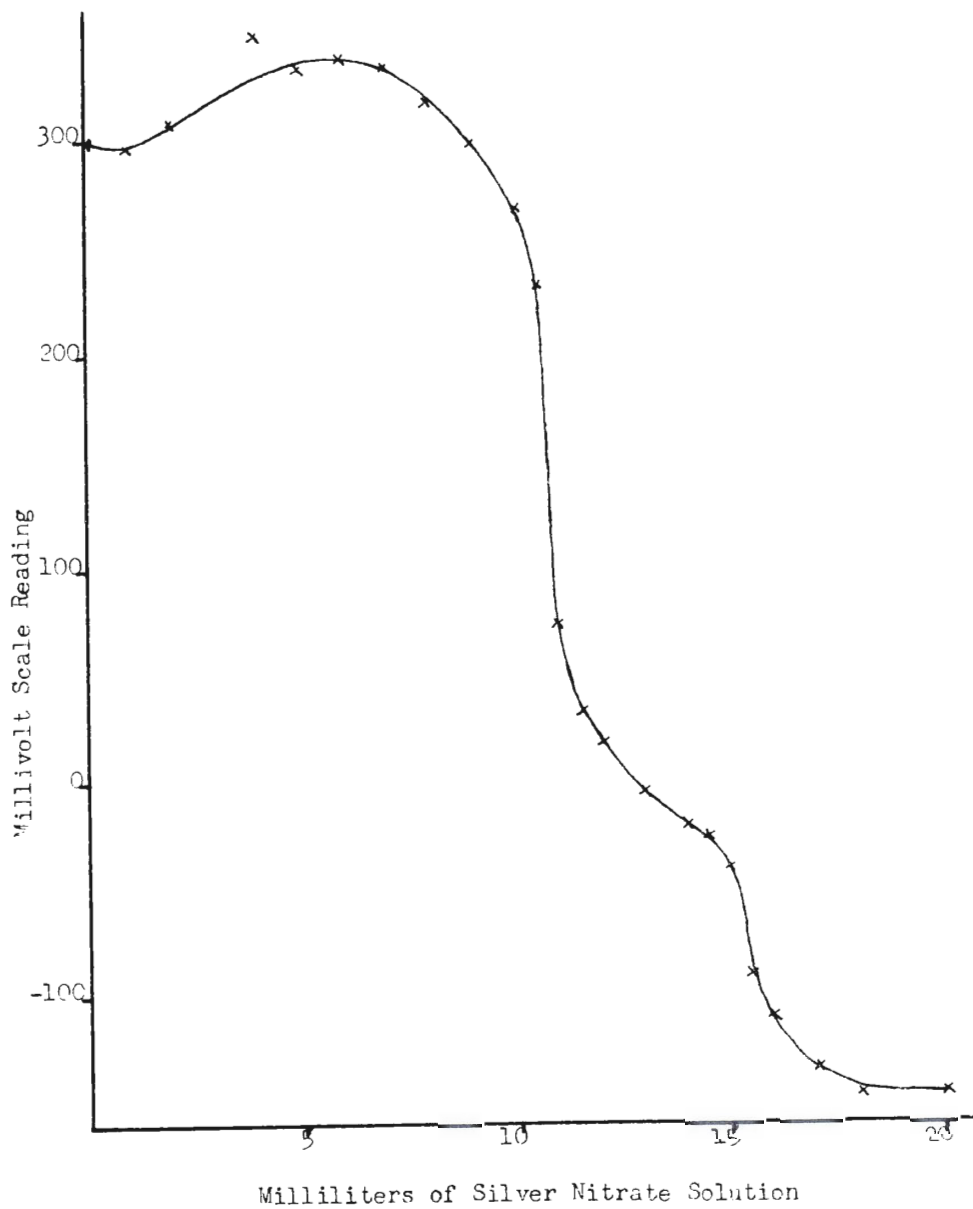


Figure 1.

PRECIPITATION TITRATION CURVE OF IODINATED *o*-CHLOROPHENOL

## Iodination of p-Chlorophenol

Five grams of p-chlorophenol were dissolved in a minimum amount of sodium hydroxide, and 50 ml. of concentrated ammonium hydroxide were added. Iodine solution was added slowly with stirring until the iodine color persisted, then the excess iodine was removed with sodium bisulfite. The mixture was acidified and the precipitate removed by filtering. The precipitate was dissolved in dilute sodium hydroxide and reprecipitated with dilute hydrochloric acid. It was then recrystallized from an ethanol-water mixture to give fine pale yellow crystals which melted at  $110^{\circ}$  C. Varma and Yashoda reported preparing 2,6-diiodo-4-chlorophenol from p-chlorophenol by a similar procedure. The product melted at  $107^{\circ}$ - $108^{\circ}$  C. (19)

In the analysis approximately 10.2 ml. of silver nitrate were required to precipitate the iodide from the sample, and 15.2 - 10.2, or 5.0 ml were required for the chloride. This indicates that the iodine and chlorine are present in 10.2:5 or 2.04:1 ratio and that the product is diiodochlorophenol.



TABLE II

DATA FROM PRECIPITATION TITRATION OF IODINATED p-CHLOROPHENOL

---

---

<u>ml. AgNO<sub>3</sub></u>	<u>M. V. Scale Reading</u>
0	300
1	300
2	297
3	295
4	292
5	290
6	285
7	280
8	270
9	275
9.5	200
10	165
10.5	-10
11	-20
12	-15
13	-20
14	-35
14.5	-40
15	-55
15.5	-100
16	-125
17	-130
18	-145
25	-175

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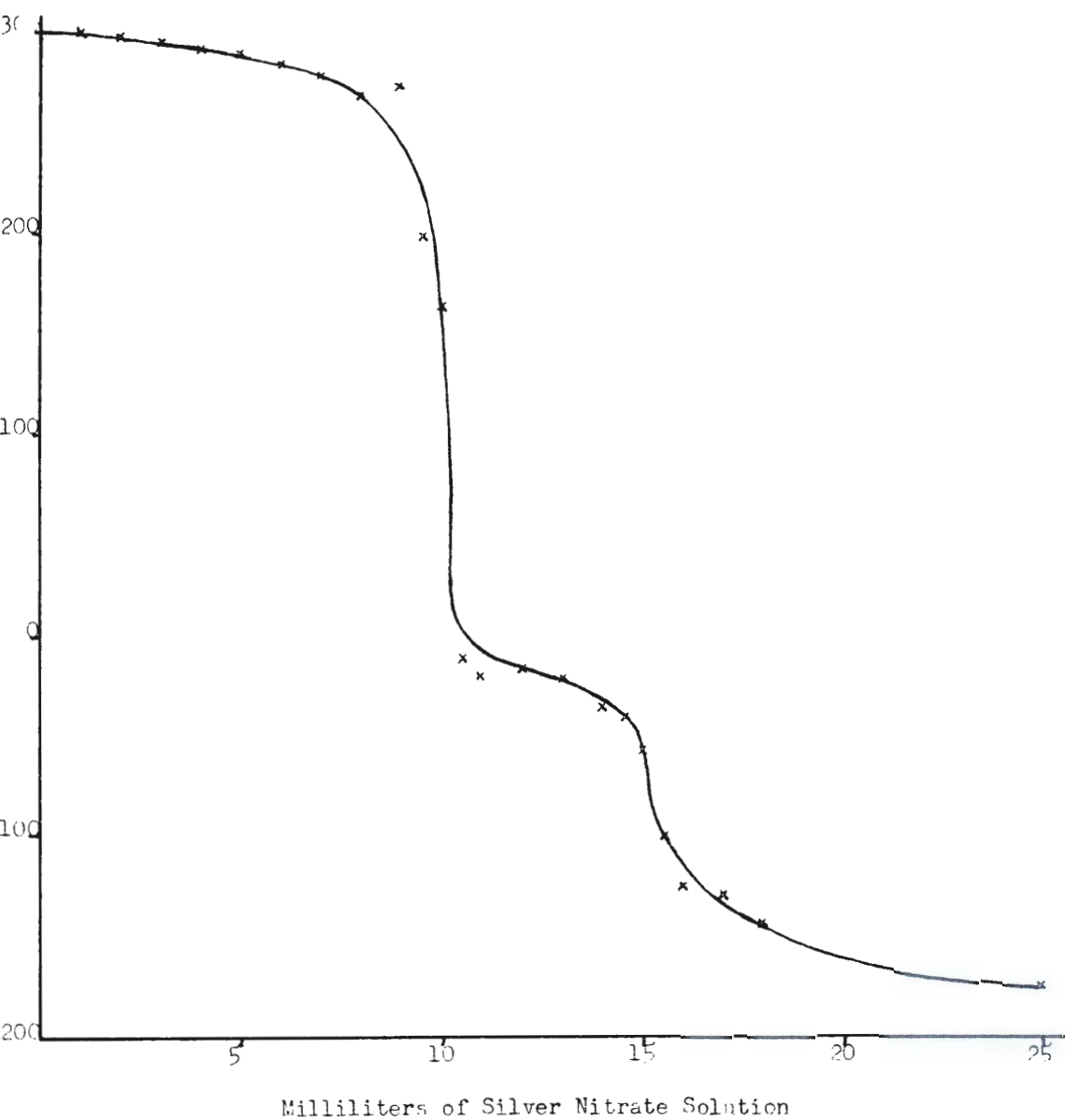


Figure 2.

PRECIPITATION TITRATION CURVE OF IODINATED p-CHLOROPHENOL

## Iodination of o-Bromophenol

Five grams of o-bromophenol were dissolved in a minimum amount of sodium hydroxide and 50 ml. of ammonium hydroxide was added. The mechanical stirrer was started, and a solution of iodine in potassium iodide was added slowly with stirring until the color of iodine persisted, then sodium bisulfite was added to reduce the excess iodine and the mixture was acidified with dilute hydrochloric acid. The precipitate was filtered and recrystallized from an ethanol-water mixture. The product was fine pale pink needles which melted at 125° C.

In the analysis, approximately 9.2 ml. of silver nitrate solution were required to precipitate the iodide from the sample, and 13.7 - 9.2, or 4.6 ml. were required for the bromide. This indicates that the iodine and bromine are present in 9.2:4.6 or 2.00:1 ratio, and that the product is diiodobromophenol.

TABLE III

DATA FROM PRECIPITATION TITRATION OF IODINATED o-BROFOPHENOL

<u>ml. AgNO<sub>3</sub></u>	<u>P. V. Scale reading</u>
0	300
1	300
2	295
3	292
4	288
5	205
6	275
7	270
8	255
8.5	240
9	215
9.5	95
10	50
10.5	85
11	60
12	70
12.5	65
13	45
13.5	-10
14	-95
14.5	-130
15	-155
15.5	-165
16	-175
17	-185
18	-193
20	-205

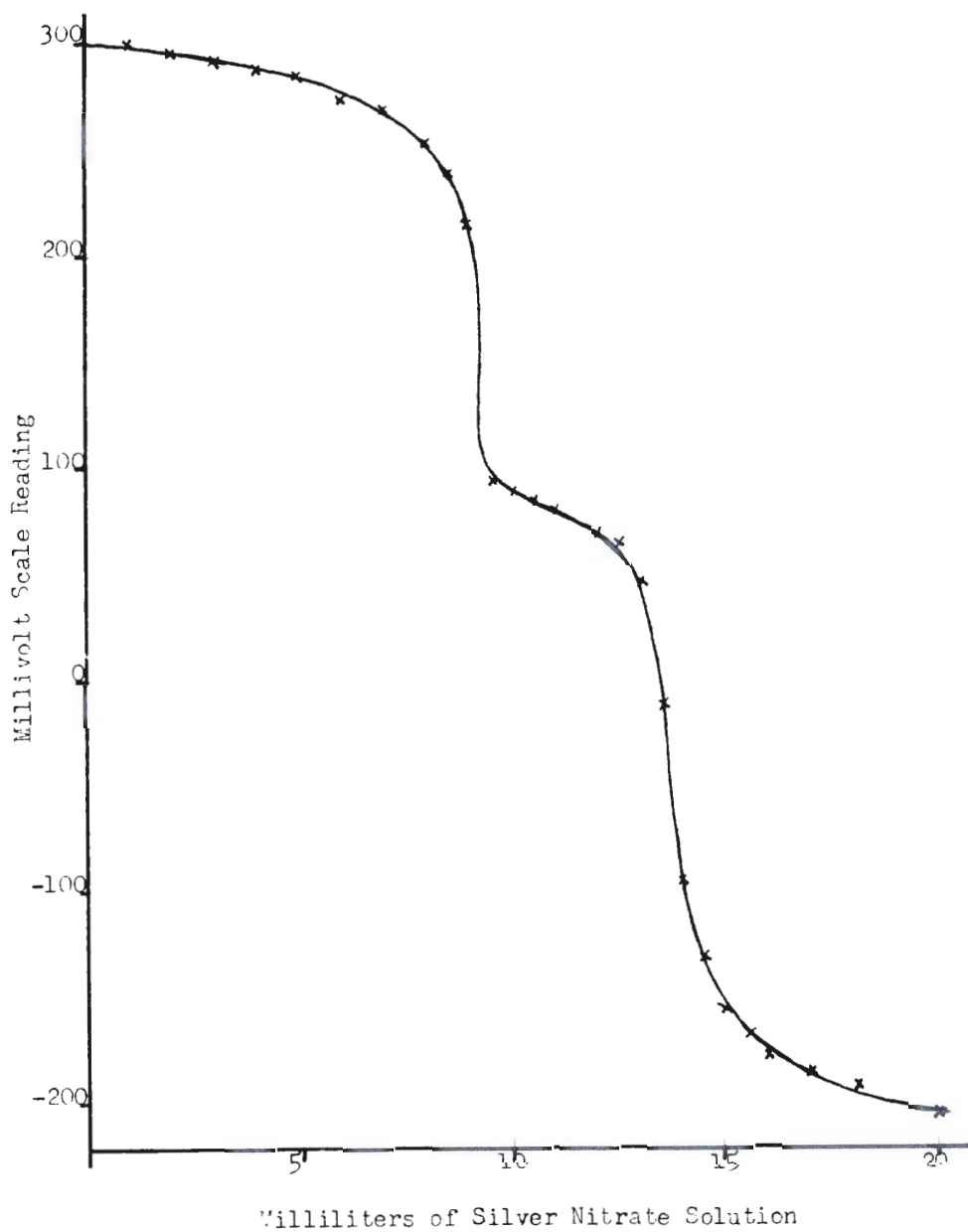


Figure 3.

PRECIPITATION TITRATION CURVE OF IODINATED o-BROMOPHENOL

## Iodination of p-Bromophenol

Five grams of p-bromophenol were dissolved in a minimum of sodium hydroxide, and 50 ml. of ammonium hydroxide were added. An excess of iodine solution was added with stirring and the mixture allowed to stand overnight. The excess iodine was removed with sodium bisulfite, the mixture acidified, and the product filtered. It was then dissolved in warm dilute sodium hydroxide and reprecipitated with dilute hydrochloric acid. The precipitate was dissolved in warm ethanol, water was added until the solution began to appear cloudy, and it was set aside to crystallize. The product was pink-white needles which melted at  $128^{\circ}$  C.

In the analysis, approximately 9.2 ml. of silver nitrate solution were required to precipitate the iodide from the sample, and 13.9 - 9.2, or 4.7 ml. were required for the bromide. This indicates that the iodine and bromine are present in 9.2:4.7 or 1.96:1 ratio and that the product is diiodobromophenol.

TABLE IV

DATA FROM PRECIPITATION TITRATION OF IODINATED p-BROMOPHENOL

---

---

<u>ml. AgNO<sub>3</sub></u>	<u>M. V. Scale Reading</u>
0	300
0.5	300
2	295
3	290
4	285
5	280
5.5	275
6	275
7	260
7.5	250
8	245
8.5	230
9	195
9.5	85
10	75
10.5	70
11	65
12	55
13	30
13.5	10
14	-60
14.5	-100
15	-115
15.5	-130
16	-140
17	-150
20	-160

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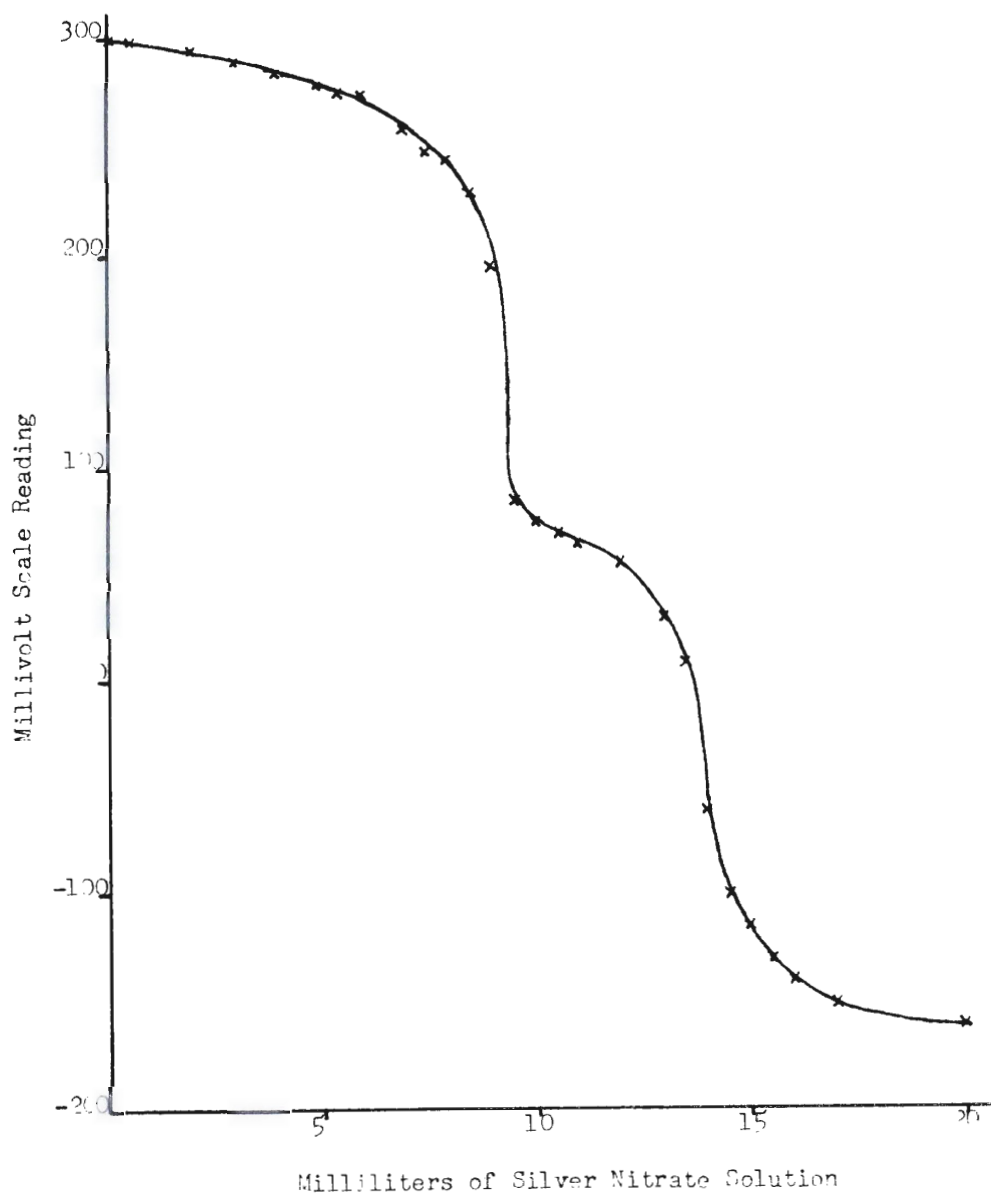


Figure 4.

PRECIPITATION TITRATION CURVE OF IODINATED p-BROMOPHENOL



## Iodination of o-Iodophenol

Five grams of o-iodophenol were dissolved in a minimum amount of sodium hydroxide and 150 ml. of dilute ammonium hydroxide were added. An excess of iodine solution was added with stirring and the mixture set aside for two hours. The mixture was then acidified with dilute hydrochloric acid and sodium bisulfite was added to remove the excess iodine. The product was removed by filtering and dissolved in warm ethanol. Water was added until the solution became cloudy, when it was set aside to crystallize. Recrystallization gave pale pink needles which melted at 157° C. A mixed melting point was 156-157° C., which showed the product to be the same as that obtained from phenol when iodinated by a similar procedure.

2,4,6-Triiodophenol melts at 156-158° C., indicating that iodine has entered the iodophenol molecule in the 4 and 6 positions.

## SUMMARY

Only five of the ortho and para halogenated phenols were available for use: o-chlorophenol, p-chlorophenol, o-bromophenol, p-bromophenol, and o-iodophenol. Iodinated products of these phenols were prepared in a fair degree of purity in several gram quantities. The composition of these compounds has been fairly well established. In all cases, indications were that two iodine atoms were substituted into the halogenated phenols. This agreed with predictions. According to the substitution rules, these trisubstituted phenols could be expected to have the halogens in the 2, 4, and 6 positions. This apparently was the case with the iodinated o-iodophenol; however, the arrangements of the other products were not determined. Further work on these compounds is needed to verify the composition and establish the structural arrangement of each.

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