THE PREPARATION AND BENZYLATION OF ORTHO-BROMOPHENOL

THESIS FOR THE DEGREE OF M. S.

Murel M. Ballard

1932

THESIS

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THE PREPARATION AND BENZYLATION
OF
O-BROMOPHENOL

by

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THESIS

SUBMITTED TO THE FACULTY OF MICHIGAN STATE
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PREPARATIONS OF O-BROMOPHENOL.

Many instances of the preparation of o-bromophenol appear in the literature. The following is a brief resume of the methods that have been reported.

The earliest recorded work on the preparation of o-bromophenol is that of Hubner and Brenken in 1873, (Ber. 6, 171). They report having obtained the compound, along with p-bromophenol, by the direct bromination of phenol dissolved in glacial acetic acid.

The results of Hubner and Brenken, however, were denied by Gordon, (Proc. 1891, 64), who repeated their work and were led to the conclusion that "the product of this method is almost entirely p-bromophenol".

This method was further investigated by Meldola and Streatfield, (J. Chem. Soc. London 73, 681. 1893), who verified the results of Hubner and Brenken.

In 1884, Lellmann and Grothmann, (Ber. 17, 2726), prepared the compound from 2-bromo, 3-oxy benzoic acid. They heated the acid for five to six hours at 180°C., Carbon dioxide splitting off from the carboxyl group and yielding o-bromophenol. They reported satisfactory yields by the use of this method.

Fittig and Mager, (Ber. 8, 362), and also Korner, (Gazz. Chim. Ital. 4, 388), reported the preparation from O-bromoaniline by diazotization and subsequent decomposition of the diazonium salt with water.

In 1893, E. Merck, (Ber. 27, R957), prepared o-bromophenol by the direct bromination of phenol at high temperature.

He reported an almost quantitative yield. This method will be discussed in more detail later.

In 1898, Meldola and Streatfield made the compound from o-aminophenol, by replacing the amino group with bromine by diazotization according to the Sandmeyer reaction, (J. Chem. Soc. London 73, 685).

In 1909, Obermiller, (Ber. 42, 4361), obtained o-bromophenol along with other products, by bromination of sulfonic and carboxylic acids of phenol with a mixture of sodium bromide and sodium hypobromite. He believed this to be a suitable brominating agent since it liberated bromine slowly allowing slow bromination of the phenol, the tendency being to maintain a constant supply of the active bromine.

In 1910, Holleman, (K. Akad. Wettenschappen 18, 476-8), obtained pure o-bromophenol by the distillation of the dry picrate. This method was also used by Rinkers in 1911, (Rec. Trav. Chim. 30, 48-100).

In 1912, Dinwiddie and Kastle, (C. A. 6, 482), brominated phenol by adding an excess of bromine to phenol dissolved in various solvents such as chloroform, carbon tetrachloride and carbon disulfide. They obtained mixtures of mono- and dibromophenols.

In 1922, H. Baines, (J. Chem. Soc. 121, 2810-2813; C.A. 17, 995), carried out the direct bromination of phenol in carbon tetrachloride and studied the effect of adding water to the reaction mixture. He found that the dry reagents gave ortho, para, or 2,4-dibromophenol, whereas the addition of water seemed to favor the formation of the tribromoderivative. The theory involved in this method will be discussed to some extent later.

In 1925, Takagi and Kutani, (J. Pharm. Soc. Japan 517, 247-252; C. A. 20, 2669), prepared o-chloro- and o-bromophenol by adding the halogen slowly, at room temperature, to a solution of phenoldisulfonic acid. They report very good yields in the case of the chlorine derivative. Apparently the yield was considerable lower when bromine was used. This method will be given in more detail later.

In 1927, Skraup and Beifuss, (Bul. Soc. Chim. 48, 809), investigated the direct bromination of phenol dissolved in pyridine. They reported 54-64% yields of the ortho compound by this method.

The most recent report of the investigation of the bromination of phenol is that of M. V. Likhosherstov in 1929, (J. Russ. Phys. Chem. Soc. 61, 1019-1023; C. A. 24, 836). The method is a unique one and uses as the brominating agent, a mixture of potassium bromide and dichlorourea. Monobromo-derivatives were obtained in almost quantitative yields by using molar quantities of phenol and potassium bromide to half molar quantities of dichlorourea. This is possible, since one equivalent of dichlorourea reacts with two equivalents of potassium bromide, liberating two equivalents of bromine. The product of this process is a mixture of ortho- and para-bromophenol which are separated by fractional distillation.

CONDENSATIONS OF PHENOLIC COMPOUNDS.

Since E. Paterno, (Gazz. Chim. Ital. 1, 166. 1872), first prepared benzyl phenol, there have been innumerable investigations concerning this and similar types of condensations of phenols and related compounds. While it would be impractical to give a complete resumeof these investigations, the following is designed to present a brief outline of the development of proceedures and theories that appear to have a distinct bearing on the problem covered in this thesis.

Paterno brought about the condensation of phenol and benzyl chloride through the agency of zinc chloride. From the product of this reaction he isolated a compound existing as white needles and melting at 84°, which he assumed to be benzyl phenol. He also prepared various derivatives of this compound with a view to establishing its constitution.

In 1874, Paterno and M. Fileti, (Gazz. Chim. Ital. 3, 121-129; 251-254), reported the preparation of other derivatives of benzyl phenol as further attempts at identification.

In 1875, these same workers prepared the same benzyl phenol in a slightly different way, using benzyl alcohol instead of benzyl chloride, and bringing about condensation by the elimination of water. They used a mixture of sulfuric acid and acetic acid as a dehydrating agent. In addition to the compound previously obtained, there resulted from this method an oil which they assumed to be an isomeric benzyl phenol.

In 1879, Paterno and Mazzarre, (Gazz. Chim. Ital. 8, 303-305), brought about the con ation using zinc turnings.

In 1880, Perkins and Hodgkinson, (J. Chem. Soc. 724), prepared benzyl phenol by the condensation of benzyl chloride and phenyl acetate in alkaline solution. Their compound melted at 80°-81°, and was believed to be the para compound.

In 1882, Rennie, (J. Chem. Soc. 41, 220), carried out a series of investigations in which he identified the crystalline compound melting at 84° as the para isomer and the oil as the ortho isomer.

In the same year, Leibmann, (Ber. 15, 152), accomplished the same condensation in the presence of zinc chloride.

In 1883, Mazzarro, (Gazz. Chim. Ital. 12, 505-511), brought about the condensation by the use of magnesium chloride.

In the several years following these investigations, there were reported many cases of condensations which are so remotely related to the present problem as not to require discussion.

Probably the most satisfactory and most widely used method of condensation of phenolic compounds with alkyl halides owes its development to the work of Claisen. Because of its importance, it is given here somewhat in detail.

The following is a summary of his method as reported in 1923, (L. Angew. Chem. 36, 478-479). The phenol, dissolved in a non-dissociating medium such as toluene, was first converted to the sodium salt by heating with metallic sodium. After this reaction was completed, an alkyl or substituted alkyl halide was introduced and the heating continued. The product of this reaction was found to contain not only alkylated phenol but also alkyl phenyl ether in varying amounts. Claisen separated these by first treating the mixture with alcoholic potash solution which dissolved the alkylated phenols. The alkyl phenyl ether was then extracted with petroleum ether. The residue from this was then treated with hydrochloric acid which again liberated the phenols present. These were then extracted with ethyl ether.

Claisen also carried out other important condensations, (Ann. 442, 210-245). The work of Claisen will be discussed in more detail later.

In 1927, Busch and Knoll, (Ber. 60B, 2343-2357), reported work on the alkyl condensation of substituted phenols in which they indicate that the presence of electro-negative groups on the nucleus of the phenol favors the formation of alkyl phenyl ether, while the presence of electro-positive groups favors the formation of the alkylated phenol.

Another type of condensation which is of great importance, especially since it has been employed to a considerable extent in this laboratory, is that brought about by the catalytic action of aluminum chloride. Since, however, the work outlined in this thesis has not been particularly concerned with the aluminum chloride condensation, it will not be discussed in great detail. Following is a brief account of its development.

Kuhlman first employed the method, (Ann. 33-34, 97-204. 1840), in the preparation of ethers from alcohols.

In 1877, Friedel and Craft, to whom has been given most of the credit for the development of the method, reported a great deal of work, (Bul. Soc. Chem. 27, 48; Compt. Rend. 84, 1392-1395), particularly on the application of this process to the condensation of aliphatic compounds.

In 1881, Merz and Weith, (Ber. 17, 187), applied the method to aromatic condensations.

In 1916, Huston and Friedeman, (J. Amer. Chem. Soc. 38, 2527), used aluminum chloride to bring about the condensation of benzene and benzyl alcohol to diphenylmethane.

In 1918, the same men, (J. Amer. Chem. Soc. 40, 785-793), carried out condensations using secondary alcohols.

In 1924, Huston, (J. Amer Chem. Soc. 46, 2775-2779), reported the condensation of phenol and benzyl alcohol to p-benzyl phenol through the use of aluminum chloride.

During the last few years a great deal of work has been done in this laboratory on the aluminum chloride condensation as well as the Claisen condensation of benzyl chloride and its halogen derivatives with phenol and related phenolic compounds. Since it would be useless to attempt a complete summary of this work, it is thought most advisable to limit the scope of this paper to data directly bearing on the problem at hand.

DISCUSSION.

THE BROMINATION OF PHENOL.

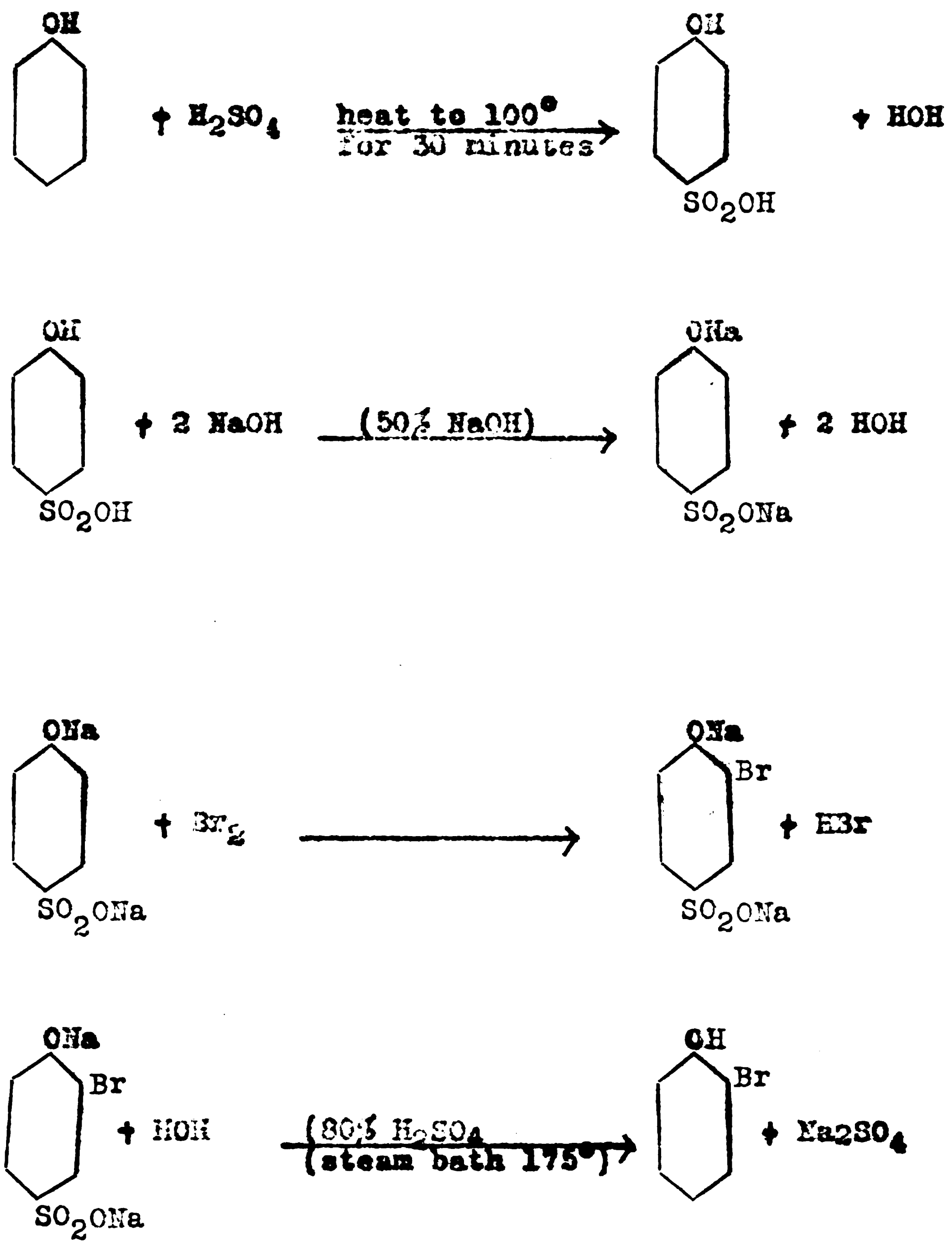
Considerable time was spent in the development of the method for preparing o-bromophenol, not because methods of preparation were lacking, but because none of the methods already available gave satisfactory results for preparation on a small scale in a student laboratory. It was desired to provide a simple, dependable, fairly efficient method for preparing o-bromophenol from easily obtainable materials.

With the exception of the method of Merck and that of Takagi and Kutani, the methods of preparation already in use involve the use of expensive materials and are therefore unsatisfactory. The method of Merck and that of Takagi and Kutani will be discussed in some detail later.

The method with which this paper is chiefly concerned was first carried out by R. Dosser in 1931 in this laboratory. It was adapted from the preparation of 2,6-dibromophenol, (F. H. Maxfield, 1930), which, in turn was adapted from the preparation of 2,6-dichlorophenol, (M. Tanaka and K. Kutani, C. A. 21, 2255).

It is a well known principle of Organic Chemistry that the hydroxyl group on a benzene nucleus tends to direct the substitution of bromine to the ortho and para positions. The mechanism of the reaction involved in this preparation is based on the blocking of the para position by a sodium sulfonate group, ($-SO_2ONa$), thus leaving only the ortho position to be filled.

The preparation as originally carried out by Dosser in this laboratory is represented by the following scheme:



Very good yields were reported for this method. On repitition of the work, however, an innumerable number of trials failed to duplicate the results of Mr Dosser, the yield of the ortho compound being, in fact, very low. The process invariably resulted in the formation of higher bromo derivatives along with a tarry residue. To explain this discrepancy it was assumed that some important

condition of the process as previously carried out had not been noticed or recorded.

The negative results led to a series of modifications of the process and the development of a method which has given satisfactory results that may be readily duplicated.

Attention is called to the fact that in phenol there are three positions, (2, 4, and 6), in which bromine may be quite readily substituted. In the above process, only one, the para or 4 position, is blocked leaving the two ortho positions open. Theoretically it may be possible to stop the reaction at such a point that only one of these open positions is filled with bromine, but this would necessarily be difficult and independable. This is believed to account for the formation of the higher bromine derivatives. It seems more reasonable to assume, as did Takagi and Kutani, (page 3), that if two positions, the para and one ortho, were blocked, the chances for obtaining the o-bromophenol would be considerably increased. Thus it seemed more advisable to first form the 2,4-disulfonic rather than the 4-monosulfonic acid.

It is further believed that the thirty minutes heating as used in the above process is not sufficient for the sulfonation of the phenol. This idea is supported by Tanaka and Kutani, who originally worked on the problem. They heated the reaction mixture for three hours to complete the sulfonation.

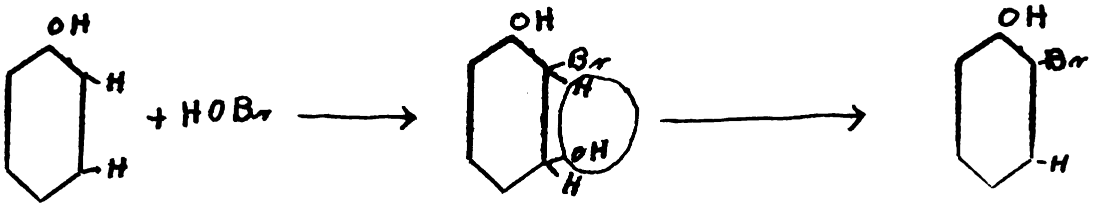
The literature seems to indicate a number of conflicting opinions in regard to halogenation. Takagi and Kutani claim to have obtained satisfactory results by brominating the phenoldisulfonic acid directly. According to Datta and Bhoumik, (J. Amer. Chem. Soc. 43, 303. 1921), chlorine, bromine and in some cases iodine, has been demonstrated to replace the sulfonic acid group, (-SO_2OH), with the production of aromatic halogen derivatives. They found that frequently halogens not only replaced the sulfonic acid groups, but that usually more halogens entered the ring with the formation of higher halogen derivatives. This they believed to be a good general method for the preparation of halogen derivatives of phenolic compounds since they found that replacement of sulfonic acid groups by bromine takes place readily at ordinary temperatures in the case of compounds having one or more hydroxyl groups attached to the nucleus.

If the interpretations of Datta and Bhoumik are correct, it seems that Takagi and Kutani have defeated their own purpose in attempting to block the 2 and 4 positions of phenol with sulfonic acid groups.

The statement of Datta and Bhoumik that "when bromine is used in small quantities, only a partial detachment of the sulfonic group occurs and a bromosulfonic acid is produced" and that "replacement of the sulfonic group by halogens takes place more easily in the case of mono- than with di- or trisulfonic acid derivatives", leaves some possibility of the truth of the assumptions of Takagi and Kutani.

The writer agrees in part with both of these views but not in entirety with either. It is believed that the evidence indicated in the experimental part of this paper will present more or less definite views in regard to this disagreement.

Datta and Bhoumik also state that "instead of free bromine, it has been found that a mixture of alkali bromide and bromate", provides a better brominating agent. This is in agreement with Obermiller, (page 2), who used a mixture of sodium bromide and sodium hypobromite. The theory involved in this proceedure was satisfactorily explained by H. Baines, (page 2), who studied the effect of the addition of water to the bromination mixture. His explanation assumes that the slow reaction between dry phenol and dry bromine is one of direct substitution only, while in the presence of water it is one of addition. The bromine reacts with the water present forming HOBr, which, he believed, reacts in the following way:



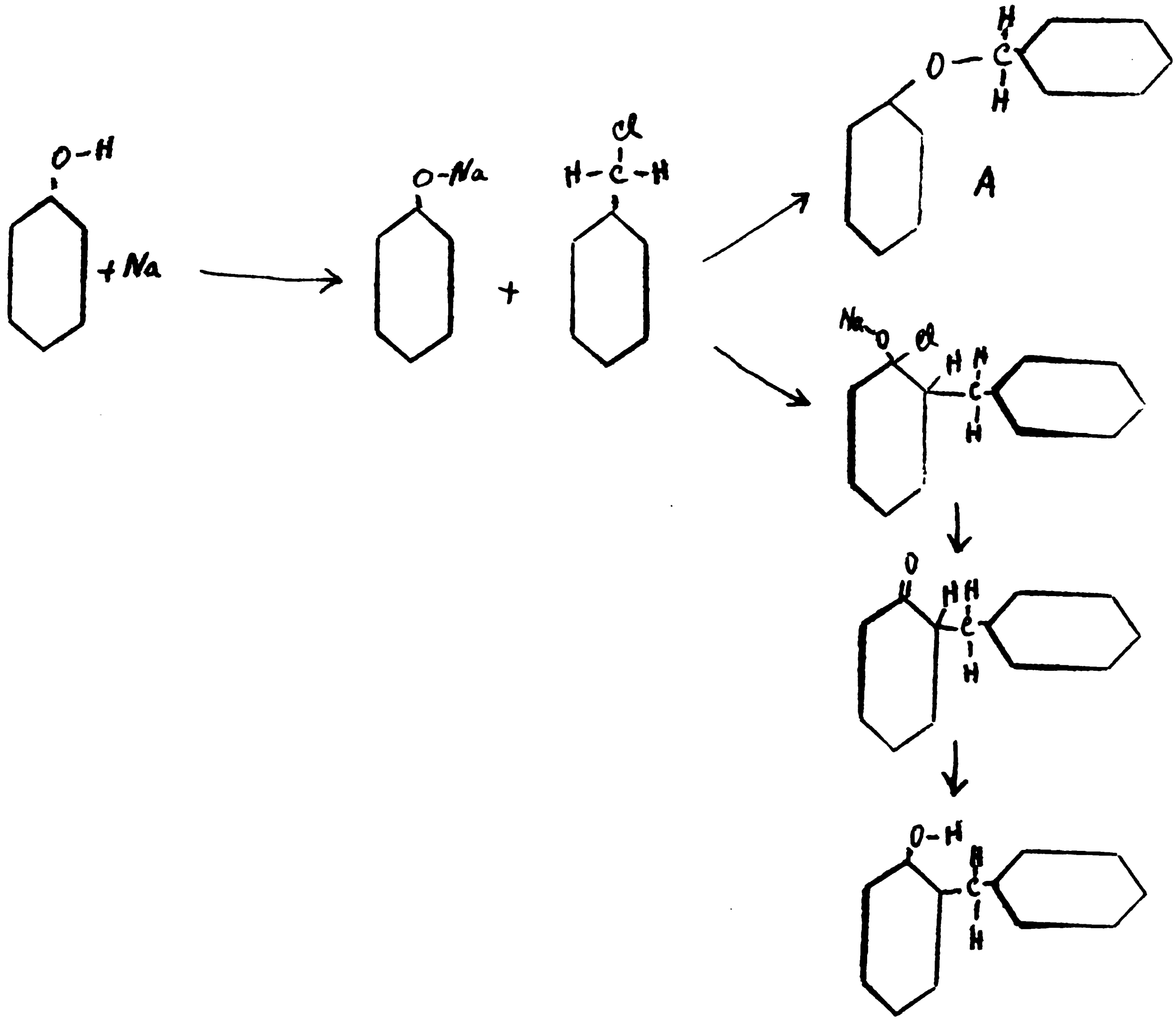
Addition of a molecule of HOBr is followed by the splitting off of a molecule of water leaving the brominated product. This view was confirmed by the direct action of HOBr on phenol and further supported by the fact that bromination is retarded by conditions that tend to hinder the formation of HOBr.

In the method used by Dosser, the temperature of the reaction mixture during hydrolysis of the sulfonic acid to o-bromophenol, was maintained at 175°. According to

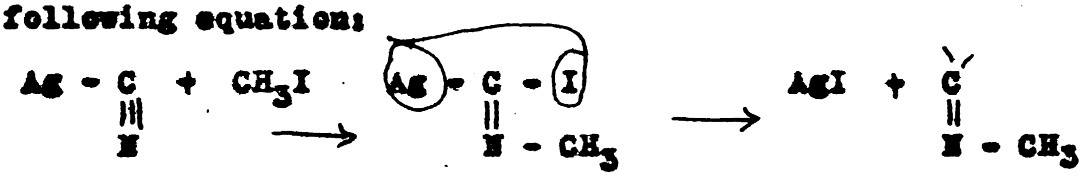
Tanaka and Kutani, (J. Pharm. Soc. Japan 541, 196, 1927), who first used this proceedure, the yield is much better if the temperature of the reaction at this point is raised to 200°- 210°. The effect of this change will be discussed in the experimental part of this paper.

THEORIES INVOLVED IN THE CLAISEN CONDENSATION.

The condensation of phenol and benzyl chloride according to the method of Claisen may berepresented by the following scheme:



Obviously, the simplest course of the reaction would result in the formation of A, phenyl benzyl ether. This product was expected by Claisen and was found to be practically the only product when the reaction was carried out in a dissociating medium such as methyl alcohol. When the reaction was carried out in non-dissociating medium, however, it was found that along with the ether was obtained a considerable amount of o-benzyl phenol. The above scheme accounts for this by assuming that the benzyl chloride adds on to the phenol in the manner shown, sodium chloride then splits off, leaving a compound of quinonic structure which enolizes, forming the ortho substituted phenol. Claisen based this theory of the mechanism of this reaction on the theory proposed by Micheal, (J. Pr. 37, 486; 46, 189), regarding the reaction between silver cyanide and methyl iodide, which he believed proceeded according to the following equation:



$$Ag-\underset{\underset{\displaystyle N}{|||}}{C} + CH_3I \longrightarrow Ag-\underset{\underset{\displaystyle N-CH_3}{\|}}{C}-I \longrightarrow AgI + \underset{\underset{\displaystyle N-CH_3}{\|}}{C}$$

Claisen maintained that unsaturated groups substitute in the ring more readily than saturated groups and also that the tendency toward ring alkylation increased with the substitution of alkyl groups on the ring.

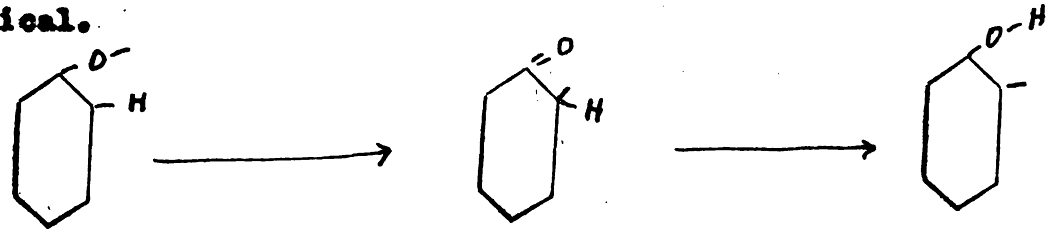
Claisen did not indicate the formation of a p-benzyl derivative in his preparation, however, some recent workers have reported evidences of para substitution. It is difficult to explain para substitution on the basis of the above theory.

In 1926, K. vonAuwers, (Chem. Zentr. 1, 2347-2348), attempted to explain the ring alkylation noted in connection with the Claisen reaction. He suggested the following three possibilities.

1. The formation of addition products and the subsequent splitting off of salt as indicated by Claisen.

2. Oxygen alkylation, followed by rearrangement of the molecule.

3. The separation of the metal and halogen as a metallic halide, leaving a free alkyl radical and a free enol radical.



The two radicals then combine to form the alkylated phenol.

The first hypothesis is the one most generally accepted. It is rather difficult to postulate rearrangement in one medium and not in another, which would make the second theory seem doubtful. The third theory is fairly reasonable but seems less probable than the theory as first advanced by Claisen.

The present problem involves the benzylation of o-bromophenol according to the method of Claisen. From the findings of Busch and Knoll, (page 6), it was suspected that the presence of bromine attached to the nucleus would favor the formation of the phenyl benzyl ether.

STATEMENT OF THE PROBLEM

The problem outlined in this thesis may be considered as consisting of the following four parts:

1. The development of a satisfactory method of preparation of o-bromophenol from easily obtainable materials.
2. The benzylation of the o-bromophenol according to the method of Claisen.
3. The preparation of various derivatives from the benzylated o-bromophenol.
4. The analysis of the derivatives prepared for the purpose of identification.

EXPERIMENTAL DATA

THE PREPARATION OF O-BROMOPHENOL

The preparation of o-bromophenol according to the method of Dosser was first carried out using one fourth molar quantities of reagents. 24 grams of phenol and 30 grams, (a slight excess over theoretical), of sulfuric acid were heated on the steam bath for thirty minutes to form p-phenolsulfonic acid. The mixture was then cooled and made alkaline with 50% sodium hydroxide solution, cooling. To the cooled mixture was then added slowly, 40.5 grams of bromine while shaking. After bromination, the mixture was transferred to a flask arranged for steam distillation. The mixture was then steam distilled to remove any tribromophenol that had been formed in the reaction. During the steam distillation, the flask containing the reaction mixture was heated in an oil bath at a temperature of 125°-150°.

When all the tribromophenol had been removed, the mixture was cooled and acidified with concentrated sulfuric acid. Enough acid was added to make the solution about 80% acid. Steam distillation was again carried out while heating the reaction mixture at 160°-175°. As the sulfonic acid hydrolyzed, the brominated phenol was liberated and passed over with the steam.

When no more oil distilled over the distillation was stopped. The oil in the distillate was then extracted with ethyl ether, the ether evaporated off and the residue distilled. The following fractions were obtained:

180° - 194° - - - - 10 grams.

194° - 200° - - - - 2 grams.

200° - 215° - - - - 5 grams.
215° - 235° - - - - 8 grams.
235° - 255° - - - - 10 grams.

Pure o-bromophenol boils at 195° at atmospheric pressure. The fraction boiling at 194°-200° was assumed to be mostly the desired compound. Throughout the subsequent experiments this same fraction was saved and weighed, thus furnishing a means of comparing the yields as obtained in the various trials. As may be seen from the above figures, there was practically no yield of the o-bromophenol. The rather large fraction from 180°-194° was undoubtedly unchanged phenol. The large higher boiling fractions were likely higher bromine derivatives.

The preparation was repeated many times using the same amounts of materials and following the directions as closely as possible. It has not been considered neccessary to tabulate the results from all of these trials, but simply to state that, in general, they were in close agreement with those obtained in the first run, and in no case was there enough of the desired compound to be called a yield. It rather represented merely the passing from one fraction to the next.

After consistent failures to obtain o-bromophenol by this precedure, it became evident that the method was at fault. Undoubtedly, some important condition for carrying out the reaction had not been observed nor recorded when the method was first carried out.

As a result of this conclusion, the method was carefully studied with a view to locate possible difficulties. The correction of these difficulties required a long series of trials of modifications of the method. During the development of the various modifications, the same general proceedure was followed, attempting to study and draw the proper conclusions concerning each of the modifications carried out.

The first difficulty observed was concerned with the sodium salt of the phenolsulfonic acid. To do this, 50% sodium hydroxide solution had been used. This made a solution so concentrated that during bromination the reaction mixture solidified and thus prevented thorough mixing. It seemed reasonable that this should have some effect on the results.

The proceedure was then carried out in the same way as before but using 40% sodium hydroxide solution. Since the reaction mixture still solidified during bromination, this run was not duplicated. The final distillation of the product seemed to show no change.

35% sodium hydroxide was used next. Again, since the mixture solidified during bromination, this was not duplicated. Again, the final results showed little change.

30% sodium hydroxide solution was next used. This time the mixture did not solidify during bromination and the material was mixed thoroughly. On distillation of the final product, the following fractions were obtained:

180° - 194° - - - - 11 grams.

194° - 200° - - - - 5 grams.

200° - 215° - - - - 6 grams.
215° - 235° - - - - 7 grams.
235° - 255° - - - - 12 grams.

A duplicate trial gave the following results which check fairly well:

180° - 194° - - - - 10 grams.
194° - 200° - - - - 6 grams.
200° - 215° - - - - 6 grams.
215° - 235° - - - - 6 grams.
235° - 255° - - - - 11 grams.

As may be seen, the results of this change show an increase in the fraction representing o-bromophenol.

The preparation was carried out using 20% and 10% solutions of sodium hydroxide, respectively, with the following results in the final distillation:

20%NaOH

180° - 194° - - - - 10 grams.
194° - 200° - - - - 4 grams.
200° - 215° - - - - 5 grams.
215°- 235° - - - - 8 grams.
235° - 255° - - - - 12 grams.

10% NaOH

180° - 194° - - - - 10 grams.
194° - 200° - - - - 1 gram .
200° - 215° - - - - 4 grams.
215° - 235° - - - - 8 grams.
235° - 255° - - - - 14 grams.

When using the 10% solution the yield dropped so low that it was not considered necessary to run a duplicate on it. A duplicate was run with the 20% solution with results practically identical with those shown above.

The results shown from changing the concentration of the sodium hydroxide justify rather definite conclusions. Apparently an increase in the amount of water present during the reaction tends to cut down the yield of o-bromophenol, increasing the amount of higher bromine derivatives. This is in accord with the views of H Baines, (page 2).. The advantage, however, in being able to thoroughly mix the reagents during bromination, accounts for the higher yield of o-bromophenol when using the 30% sodium hydroxide.

On the basis of the above conclusions, 30% sodium hydroxide solution was used in all subsequent runs. From this point on, a mechanical stirrer was used during the addition of the sodium hydroxide and bromine.

As was stated in the discussion, (page 10), it seemed logical to expect a greater yield of o-bromophenol if two rather than only one of the three open positions of phenol were blocked. The amount of sulfuric acid used in the preparation up to this point was only slightly more than the theoretical amount required for a monosulfonic acid. With the idea in mind of blocking two of the positions, the para and one ortho, by forming 2,4-phenoldisulfonic acid, a series of trials of the preparation were carried out, increasing the quantity of sulfuric acid by varying amounts.

The preparation was carried out using 24 grams of phenol together with 60 grams, 90 grams and 120 grams of sulfuric acid respectively. In other respects the conditions of the preceedure were kept the same as before, using, of course, 30% sodium hydroxide for the formation of the sulfonate. Duplicates were run on each of these trials. The following represents the results from final distillation of products:

60 grams of H_2SO_4	#1.	#2.
180° - 194° - - -	8 grams	8 grams.
194° - 200° - - -	8 grams	7 grams.
200° - 215° - - -	6 grams	5 grams.
215° - 235° - - -	5 grams	5 grams.
235° - 255° - - -	7 grams	8 grams.
90 grams of H_2SO_4		
180° - 194° - - -	7 grams	7 grams.
194° - 200° - - -	9 grams	9 grams.
200° - 215° - - -	5 grams	3 grams.
215° - 235° - - -	3 grams	3 grams.
235° - 255° - - -	7 grams	8 grams.
120 grams of H_2SO_4		
180° - 194° - - -	7 grams	7 grams.
194° - 200° - - -	7 grams	6 grams.
200° - 215° - - -	5 grams	5 grams.
215° - 235° - - -	5 grams	6 grams.
235° - 255° - - -	8 grams	3 grams.

From the above figures it may be seen that an increase in the yield of o-bromophenol resulted from increasing the amount of sulfuric acid used, up to a certain point, (90 grams of H_2SO_4 to 24 grams of phenol), which doubtless represented the blocking of two positions. More than that amount of sulfuric acid probably resulted in the formation of a trisulfonic acid and the blocking of all three positions, which would not permit any bromination. This is indicated by the fall in yield observed when 120 grams of sulfuric acid were used. The large excess of sulfuric acid, (three and one half moles of H_2SO_4 to one mole of phenol), which seemed to give the best results was somewhat surprising. It is assumed that this much excess is necessary in order to maintain the proper equilibrium between the sulfuric acid and phenol and the phenoldisulfonic acid. In the trials which followed, phenol and sulfuric acid were used in the ratio of 24 grams of phenol to 90 grams of H_2SO_4.

The next modification had to do with the time required for formation of the sulfonic acid. As was stated in the discussion, Tanaka and Kutani heated for three hours at 100°. It appeared that thirty minutes heating was insufficient and left a rather large amount of unchanged phenol.

In order to determine the optimum length of time for producing the sulfonic acid, a series of trials were carried out using the same amounts of materials as in the preceeding runs but heating for varying lengths of time. Four duplicate trials were run, heating for one, two, three and four hours respectively, on the steam bath. The following is a tabulation of the results of distillation of the final product in each case:

One hour heating	#1.	#2.
180° - 194° - - - -	7 grams	7 grams.
194° - 200° - - - -	9 grams	10 grams.
200° - 215° - - - -	5 grams	4 grams.
215° - 235° - - - -	4 grams	4 grams.
235° - 255° - - - -	7 grams	8 grams.
Two hours heating		
180° - 194° - - - -	6 grams	6 grams.
194° - 200° - - - -	11 grams	11 grams.
200° - 215° - - - -	4 grams	3 grams.
215° - 235° - - - -	4 grams	4 grams.
235° - 255° - - - -	6 grams	6 grams.
Three hours heating		
180° - 194° - - - -	6 grams	6 grams.
194° - 200° - - - -	13 grams	12 grams.
200° - 215° - - - -	3 grams	4 grams.
215° - 235° - - - -	3 grams	4 grams.
235° - 255° - - - -	6 grams	6 grams.
Four hours heating		
180° - 194° - - - -	5 grams	6 grams.
194° - 200° - - - -	13 grams	13 grams.
200° - 215° - - - -	3 grams	3 grams.
215° - 235° - - - -	6 grams	6 grams.

Observation of the above figures indicates an increase in the yield of the desired product as the time of heating is increased up to three hours. Heating for a longer period of time did not seem to affect the yield. On the assumption that the disulfonic acid gives the best yield of o-bromophenol, it appears that about three hours heating at 100° is most effective in converting the phenol and sulfuric acid to the phenoldisulfonic acid. In the following trials, three hour periods were used for the formation of the sulfonic acid.

In each preparation up to this point there had been obtained, in the first steam distillation, considerable quantities of tribromophenol. It was believed that if something could be done to prevent the formation of tribromophenol, the yield of the ortho compound might be correspondingly increased. The following reasoning was applied to the problem.

During bromination by substitution, one mole of bromine produces, along with the brominated product, one mole of hydrobromic acid. The hydrobromic acid liberated during the bromination of phenol should be expected to react with the sulfonates present in the reaction mixture, converting the sodium sulfonate group to the sulfonic acid group. According to Datta and Bhoumik, (page 11), the sulfonic acid group is readily replaced by halogens, while it is believed that the sodium sulfonate group is not so replaced. If, then, the already brominated phenol has one or both of its sodium sulfonate groups converted to sulfonic acid groups, and these are readily replaced by bromine, it is easy to account for the formation of higher bromine derivatives. In other words, if the monobromo compound is desired, and if the sulfonic acid group is easily replaced by bromine while the sodium sulfonate group is not, then the simple neutralization of the reaction mixture before bromination is insufficient. In order to maintain the blocking effect of the sodium sulfonate group, there must be added to the phenoldisulfonic acid enough sodium hydroxide to convert all the sulfonic acid groups to sulfonate groups, all the excess sulfuric acid to sodium sulfate, all the phenolic groups to phenolate groups and all the hydrogen bromide liberated during the reaction to sodium bromide. This excess alkali should not interfere in any way with the bromination since alkaline hypobromite solution is recognized to be a good brominating agent.

The amount of sodium hydroxide to be added to the reaction mixture was calculated in the following way. On the basis of molar quantities, one mole of phenol, when sulfonated with three and one half moles of sulfuric acid, (the amount previously determined by experiment to be most satisfactory), should yield one mole of phenoldisulfonic acid and leave an excess of one and one half moles of sulfuric acid. Also, during bromination, one mole of hydrogen bromide is liberated. Three moles of sodium hydroxide are required to replace the three ionizable hydrogens of the phenoldisulfonic acid, three to neutralize the excess sulfuric acid, and one to neutralize the hydrogen bromide. This makes a total of seven moles of sodium hydroxide per mole of phenol, or, one and three fourths moles for a one fourth molar run.

On the basis of this reasoning, the preparation was carried out using the same quantities of phenol and sulfuric acid and forming the sulfonic acid as before. This mixture was then made alkaline with 75 grams of sodium hydroxide, (a slight excess over one and three fourths moles, to allow for incomplete formation of the disulfonic acid), dissolved in 175 cc. of water. Bromination was carried out as before. When the mixture was steamdistilled to remove tribromophenol, it was noted that *not any* appeared, whereas it had appeared in varying amounts during previous runs. Final distillation of the product gave the following fractions:

180° - 194° - - - - 4 grams.
194° - 200° - - - - 15 grams.
200° - 215° - - - - 2 grams.
215° - 235° - - - - 2 grams.
235° - 255° - - - - 6 grams.

These results were very satisfactory and appeared to bear out the reasoning. The writer considers this as possibly the most significant point in regard to the various modifications of the procedure. It not only strengthened the belief in the blocking power of the sodium sulfonate group, but raised considerable doubt as to the advisability of brominating the sulfonic acid directly, (Takagi and Kutani), or of replacing sulfonic acid groups with an alkaline brominating agent, (Datta and Bhoumik).

A very interesting phenomenon in connection with this procedure was the evidence of a color reaction during the addition of the sodium hydroxide. As the excess alkali was added, there developed a pink color in the solution which disappeared abruptly, almost simultaneous with the addition of the last few cc. of the calculated amount of base. No attempt was made to explain this, and though it seemed to have no further significance, it furnished an almost infallible means of determining the right excess of base without calculation.

A number of trials were made of this proceedure in order to verify the results obtained in the first run. Though it seems unnecessary to record here all the figures obtained, it may be stated while in one or two cases the yield of o-bromophenol was a little low, in general, it was in close agreement with that shown above.

The next modification of the proceedure had to do with the temperature of the reaction mixture during the hydrolysis of the sulfonic acid to bromophenol. The change was made after a review of the work of Tanaki and Kutani, (page 13), who carried out the process at 175° but stated that the yield could be increased if the temperature of the reaction mixture was raised to 200°-210°. On the basis of this information, a trial was run, using the method previously described only carrying out the hydrolysis of the sulfonic acid at 200°-210°. The following tabulation of the results of this trial show an increase in the total brominated product and a corresponding slight increase in the fraction taken as o-bromophenol:

180° - 194° - - - - 5 grams.

194° - 200° - - - - 16 grams.

200° - 215° - - - - 5 grams.
215° - 235° - - - - 4 grams.
235° - 255° - - - - 8 grams.

Several repetitions of this proceedure verified the above results. Apparently this modification did not increase the relative amount of o-bromophenol in the reaction mixture but brought about the increase in the final yield by allowing a more perfect hydrolysis of the brominated phenolsulfonic acid. This modification was carried out in all subsequent proceedures.

Throughout the work thus far described the thought was held that anything that might be done to make more efficient the conversion of phenol to phenoldisulfonic acid would correspondingly increase the yield of o-bromophenol. With this in mind it was believed that stirring during the heating of the sulfuric acid and phenol might result in more complete sulfonation, or at least cut down the time necessary for the maximum reaction.

To study the effect of this proceedure, a series of duplicate runs of the preparation were carried out, stirring while heating the reaction mixture on a boiling water bath for one, two, three and four hour periods respectively. In other respects the method was carried out as previously found to be most satisfactory. Following is a tabulation of the results of final distillation of the various products:

One hour heating #1. #2.
180° - 194° - - - - 8 grams 8 grams.
194° - 200° - - - - 10 grams 10 grams.

200° - 215° - - - - 3 grams 4 grams.
215° - 235° - - - - 6 grams 4 grams.
235° - 255° - - - - 11 grams 12 grams.

Two hours heating.

180° - 194° - - - - 4 grams 4 grams.
194° - 200° - - - - 15 grams 16 grams.
200° - 215° - - - - 4 grams 3 grams.
215° - 235° - - - - 5 grams 4 grams.
235° - 255° - - - - 6 grams 6 grams.

Three hours heating

180° - 194° - - - - 3 grams 4 grams.
194° - 200° - - - - 19 grams 19grams.
200° - 215° - - - - 3 grams 3 grams.
215° - 235° - - - - 3 grams 4 grams.
235° - 255° - - - - 5 grams 6 grams.

Four hours heating

180° - 194° - - - - 4 grams 4 grams.
194° - 200° - - - - 19 grams 18 grams.
200° - 215° - - - - 2 grams 2 grams.
215° - 235° - - - - 4 grams 5 grams.
235° - 255° - - - - 5 grams 6 grams.

The above figures satisfactorily bear out the reasoning. It was shown that stirring and heating for two hours produced practically the same yield as heating alone for three hours. It was also shown, however, that stirring and heating for three hours resulted in an increase in yield. The same proceedure carried out for a period longer than three hours seemed to be of no advantage.

Up to this point no mention has been made concerning the temperature during bromination. It seemed possible that this might have some bearing on the results of the preparation. Ordinarily the bromination was carried out on the cooled mixture but no attempt was made to maintain a definite temperature. During this proceedure the temperature usually rose to about 45°-50°. To determine the effect of temperature on the bromination a series of duplicate trials were run. By stirring with the flask containing the reaction mixture immersed in a water bath, the temperatures in three different cases were maintained at 20°-25°, 40°-45° and 60°-65° respectively. The following results were obtained on distillation of the final product:

20°-25°	#1.	#2.
180° - 194°	5 grams	5 grams.
194° - 200°	16 grams	17 grams.
200° - 215°	3 grams	3 grams.
215° - 235°	3 grams	4 grams.
235° - 255°	6 grams	6 grams.

40°-45°		
180° - 194°	3 grams	3 grams.
194° - 200°	18 grams	19 grams.
200° - 215°	2 grams	3 grams.
215° - 235°	4 grams	4 grams.

235° - 255° - - - -	6 grams	6 grams.

60°-65°

180° - 194° - - - -	4 grams	4 grams.
194° - 200° - - - -	15 grams	14 grams.
200° - 215° - - - -	3 grams	4 grams.
215° - 235° - - - -	5 grams	4 grams.
235° - 255° - - - -	7 grams	8 grams.

As may be seen from the figures the temperature was not very critical, however, there appeared to be a slight decrease in the yield at the higher and at the lower temperatures. It was difficult to explain this. Possibly at the lower temperature bromination proceeds more slowly and was not given time to reach completion. At the higher temperature, possibly the tendency of the bromine to vaporize and pass off without reacting is greater than the increased tendency toward reaction. These are admitted to be not very satisfactory explanations. At any rate, since it was indicated that the temperature for bromination was not extremely critical, and since the temperature usually taken by the bromination mixture seemed to give maximum yields of the desired product, no change was made concerning this part of the proceedure.

Only one other slight change was made. This was made, however, for the purpose of saving materials rather than for increasing the yield. It was found that if, after the first steam distillation, the open flask containing the reaction mixture was heated for a while on the oil bath and the mixture evaporated nearly to dryness, less sulfuric acid was required to make the mixture 80% acid, the right concentration for hydrolysis of the sulfonic acid, the next step in the proceedure.

Successive runs of the proceedure were then made, incorporating all of the various modifications and using half molar quantities, (double the amounts previously used). It is not believed necessary to record here all the figures obtained from these runs. The following tabulation is typical;

180° - 194° - - - - 7 grams.
194° - 200° - - - 38 grams.
200° - 215° - - - - 7 grams.
215° - 235° - - - - 8 grams.
235° - 255° - - - 15 grams.

The yield of 38 grams of o-bromophenol represents a yield of 44.4% which appears to be very satisfactory. The rather high fraction boiling at 235°- 255° is believed to be mostly 2,6-dibromophenol.

Following are the complete directions for the preparation of o-bromophenol incorporation all of the modifications previously mentioned. The materials are taken on the basis of molar quantities.

THE MODIFIED METHOD FOR PREPARING O-BROMOPHENOL.

One mole, (94 grams), of phenol and three and one half moles, (350 grams), of concentrated sulfuric acid in a two liter, three-necked flask are heated on a boiling water bath for three hours, stirring constantly with a mechanical stirrer. At the end of this time the reaction mixture is cooled by replacing the boiling water bath with a cold water bath. The mixture is then made alkaline by adding a solution of seven moles, (280 grams), of sodium hydroxide dissolved in 700 cc. of water. This must be done very slowly on account of the heat evolved by neutralization of the acid.

The alkaline solution is then cooled to room temperature and brominated by adding slowly one mole, (160 grams), of bromine, still stirring constantly. During this operation the temperature of the reaction mixture is allowed to rise to 40°-50°. Stirring is continued for about half an hour after all the bromine has been added. The mixture should still be alkaline.

The reaction mixture is then transferred to a three liter flask set for steam distillation. During the steam distillation the reaction mixture is heated on an oil bath to about 150°. This removes any tribromophenol which should not appear as more than a trace.

As soon as no more tribromophenol is noticed in the distillate, the steam distillation is stopped and the reaction mixture, still on the oil bath is evaporated to a thick pasty gray mass. This is allowed to cool and then acidified with about 800 cc. of concentrated sulfuric acid. This must be done slowly on account of the rapid evolution of hydrogen bromide.

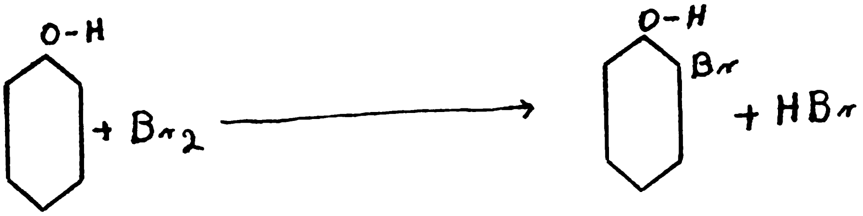
The mixture is again steam distilled, this time from an oil bath heated to 200°-210°. The sulfonic acid is hydrolyzed by this proceedure and the brominated phenols distill over as a heavy colorless or pale yellow oil.

When no more oil appears in the distillate, steam distillation is stopped. The brominated phenols are then extracted with ethyl ether, the ether evaporated off and the residue distilled under ordinary pressure. The fraction boiling from 194° to 200° represents practically pure o-bromophenol. The yield should be 70-75 grams. O-bromophenol is a colorless oil with a very characteristic odor. It is rather unstable and decomposes on standing, becoming a brown or red liquid.

THE METHOD OF E. MERCK.

The preparation of o-bromophenol according to the method of E. Merck was carried out for the purpose of forming a suitable basis of comparison of the method just described. This method was referred to in the historical part of this paper and consists of the direct bromination of phenol at high temperature.

Reaction:



The reaction was carried out in a one liter three necked flask fitted with a mechanical stirrer, reflux condenser, and a glass tube of rather large bore for introducing the bromine vapors. One mole of phenol, (94 grams), was placed in the flask and heated on an oil bath to 160°-180°. One mole of bromine, (160 grams), were placed in a small flask connected with the glass tube from the reaction flask. The bromine was vaporized by warming on a water bath, the vapors passing over and bubbling up through the heated phenol. During this operation the mixture was stirred vigorously. Hydrogen bromide was liberated as bromination proceeded and passed out through the reflux condenser, the preparation being carried out in the hood. Stirring was continued for half an hour after all the bromine had been introduced.

The brominated phenol was then cooled, washed with 50% sodium hydroxide solution, with water and then distilled. The following is a tabulation of the results of this distillation.

180° - 194° - - - - 15 grams.
194°- 200° - - - - 41 grams.
200° - 215° - - - - 17 grams.
215° - 235° - - - - 43 grams.
235° - 255° - - - - 35 grams.

The yield of o-bromophenol, 41 grams boiling at 194°-200° represented a yield of 23.2%. According to the literature the yield should have been much higher.

This method of preparation involves one difficulty which makes it undesirable without special equipment. The hot hydrogen bromide liberated in the reaction attacked cork and rubber connections so vigorously that it was impossible to keep the system from leaking. This also resulted in the formation of a considerable amount of tar.

THE METHOD OF TAKAGI AND KUTANI.

This method was also run for comparison with the previously described method and also to check the theory of blocking with sulfonic acid groups. This has already been referred to a number of times. According to the report of this method: "800 grams of melted phenol is placed in a five liter flask, 2800 grams of sulfuric acid is added and heated at 90°-100° for three hours. The disulfonic acid derivative is formed. The mixture is cooled to room temperature, diluted with 750 cc. of water, and the theoretical amount of bromine added, stirring. The brominated phenol is obtained by steam distillation, extraction of the distillate, then distillation of the final product".

This method was carried out in duplicate using one half mole of phenol, (47 grams). To the phenol was added 175 grams of sulfuric acid and the mixture heated on a boiling water bath for three hours, stirring. It is interesting that the method up to this point is practically identical with that found previously to be most effective. This is assumed to result in the formation of phenoldisulfonic acid.

The mixture was then cooled and one half mole, (80 grams), of bromine added slowly. When bromination was complete, the mixture was steam distilled. The following results were obtained:

	#1.	#2.
180° - 194° - - - -	19 grams	20 grams.
194° - 200° - - - -	17 grams	15 grams.
200° - 215° - - - -	4 grams	3 grams.

215° - 235° - - - -	2 grams	3 grams.
235° - 255° - - - -	11 grams	11 grams.

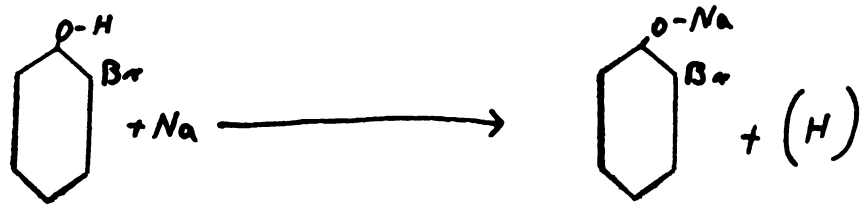
A rather large residue was left in each case. These were rather poor yields of o-bromophenol. The highest, (17 grams), was calculated to be only 19.7% of the theoretical.

Besides indicating the superiority of the previously described method for preparing o-bromophenol, these results had an important significance. The beliefs of Datta and Bhoumik of the replacement of the sulfonic acid group by a halogen was strengthened while the sodium sulfonate group was indicated to be a more effective blocking agent than the sulfonic acid group.

THE BENZYLATION OF O-BROMOPHENOL.

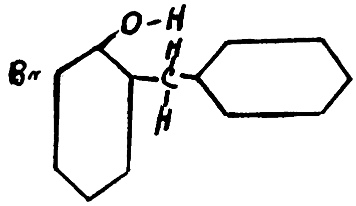
The second part of the problem was the condensation of o-bromophenol with benzyl chloride according to the method of Claisen. This method has already been briefly referred to and is given in detail in Annalen der Chemie 442, 224.

The first Claisen reaction run was on half molar basis and was carried out in the following way. 300 cc. of toluene were placed in a ~~three~~ one liter three necked flask fitted with a mercury sealed mechanical stirrer and a reflux condenser. To this was then added one half mole, (11.5 grams), of clean sodium. The flask was then heated on an oil bath until the sodium melted, stirred vigorously and allowed to cool. On cooling, the sodium solidified in very fine globules which presented great reacting surface. While the reaction mixture was still at about 70°-80°, one half mole, (86 grams), of o-bromophenol was slowly added. This resulted in the formation of the sodium phenolate:

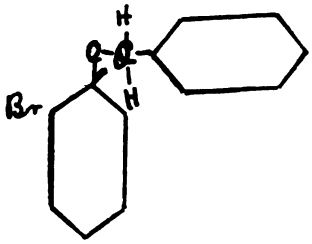


When the o-bromophenol had all been added the mixture was heated to 140°-150° and allowed to reflux for about two hours. As the reaction proceeded, the dark colored sodium disappeared and the sodium phenolate appeared as a thick, white, pasty mass.

After the o-bromophenol had been completely converted to the corresponding phenolate, the mixture was again allowed to cool somewhat and one half mole, (63 grams), of benzyl chloride was added. The mixture was again heated and allowed to reflux at 150°-155° for eight hours. It was then let stand over night. During this time it was assumed that the ordinary Claisen reaction took place as previously discussed, the benzyl group substituting on the ring to form 2-bromo,6-benzyl phenol:



and on the oxygen of the phenol to form 2-bromophenyl-benzyl ether;



On the following day the reaction mixture was placed in a separatory funnel and washed thoroughly to remove the sodium chloride that had been formed during the reaction. It was then transferred to a distilling flask and the toluene distilled off. The residue was heated to 125° to remove all traces of toluene.

The residue was then treated with an excess, (300 cc.), of Claisen's alcoholic potash solution. This converted the phenolic substances present to alkali salts which were insoluble in petrolic ether, which was then used to extract the benzyl ether. The mixture was extracted three times with 200 cc. portions of petrolic ether.

The residue from this extraction, containing the alkali salts of the phenolic substances, was acidified with HCl, cooling, which liberated the phenols. These were then extracted three times, using 200 cc. portions of ethyl ether.

The petroleum ether extract, which was suspected to contain the substituted phenylbenzyl ether, was transferred to a Claisen flask and the petroleum ether evaporated off. All traces of petroleum ether and water were removed by heating up to 125° under 15 mm. pressure. The residue was then distilled at 2 mm. pressure, yielding the following fractions:

Up to 135° - - - - 3 grams.
135° - 140° - - - - 3 grams.
140° - 145° - - - -20 grams.
145° - 150° - - - - 9 grams.
150° - 155° - - - - 2 grams.
155° - 200° - - - - 2 grams.

Since it was believed that the large fractions between 140° and 150° represented the desired product, these two fractions were combined and refractionated at 2 mm. pressure with the following results:

Up to 140° - - - - 3 grams.
140° - 142° - - - - 3 grams.
142° - 144° - - - - 21 grams.
144° - 146° - - - - 2 grams.
146° - 160° - - - - 2 grams.

The fraction boiling at 142°-144° was assumed to be the 2-bromophenyl-benzyl ether. Analysis for halogen content, (page 53), confirmed this.

The ethyl ether extract, which was suspected to contain the 2-bromo,6-benzyl phenol, was then transferred to a Claisen flask and the ether evaporated off. As before, all the ether and water were removed by heating to 125° at 15 mm. pressure. The residue was then distilled at 2 mm. pressure with the following results:

Up to 135° - - - - 5 grams.
135° - 150° - - - - 8 grams.
150° - 155° - - - - 19 grams.
155° - 165° - - - - 5 grams.
165° - 200° - - - - 3 grams.

The large fraction boiling at 150°-155° seemed to indicate the desired product and was therefore refractionated with the following results:

Up to 150° - - - - 2 grams.
150° - 153° - - - - 14 grams.
153° - up - - - - 1 gram .

The fraction boiling at 150°-153° was assumed to be the 2-bromo,6-benzyl phenol. This was also confirmed by analysis for halogen content, (page 53).

The yields in the above reaction were calculated to be 15.9% of the ether and 10.6% of the phenol.

Two more Claisen condensations were run using the same proceedure with molar quantities of the reagents. This was for the purpose of obtaining enough of the phenol for analysis and the preparation of derivatives.

Refractionation, as described in connection with the first run, gave, for these two molar runs, the following results:

2-bromophenyl-benzyl ether. 2 mm.

	#1.	#2.
Up to 140° - - - -	3 grams	4 grams.
140° - 142° - - - -	8 grams	8 grams.
142° - 144° - - - -	40 grams	38 grams.
144° - 146° - - - -	2 grams	2 grams.
146° - up - - - -	2 grams	2 grams.

2-bromo,6-benzyl phenol. 2 mm.

Up to 150° - - - -	3 grams	3 grams.
150° - 153° - - - -	35 grams	33 grams.
153° - up - - - -	5 grams	5 grams.

The yields of the ether in these two runs were, respectively, 15.2% and 14.4%.

The yields of the phenol were 13.3% and 12.6%.

In order to further identify the compound assumed to be 2-bromophenyl-benzyl ether, a Claisen condensation was run in methyl alcohol. As was pointed out in the previous discussion, the condensation carried out in a dissociating medium such as methyl alcohol, yields only the oxygen alkylated compound. One fourth molar quantities of reagents were used. The first part of the proceedure was identical with that used in the previous runs. After the reaction mixture had been heated and the reaction had gone to completion, the alcohol was evaporated off, water added to dissolve the salt that had been formed in the process, and the 2-bromophenyl-benzyl ether was extracted three times with 100 cc. portions of petroleum ether. It was not necessary to use Claisen's alcoholic potash in this case since this proceedure does not yield benzylated phenols. The petroleum ether extract was then transferred to a Claisen flask, the petroleum ether evaporated off, and traces of the solvent and water removed as before by heating to 125° at 15 mm. pressure. The residue was then distilled at 2 mm. pressure giving the following fractions:

Up to 135° - - - - 2 grams.
135° - 140° - - - - 2 grams.
140° - 145° - - - - 11 grams.
145° - 150° - - - - 8 grams.
150° - 155° - - - - 2 grams.
155° - 200° - - - - 3 grams.

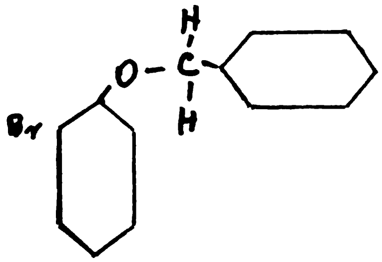
As before, the fractions boiling at 140°-150° were combined and refractionated at 2 mm. pressure with the following results:

Up to 140° - - - - 2 grams.
140° - 142° - - - - 1 gram .
142° - 144° - - - - 13 grams.

144° - 146° - - - - 1 gram.

146° - up - - - - - - - -

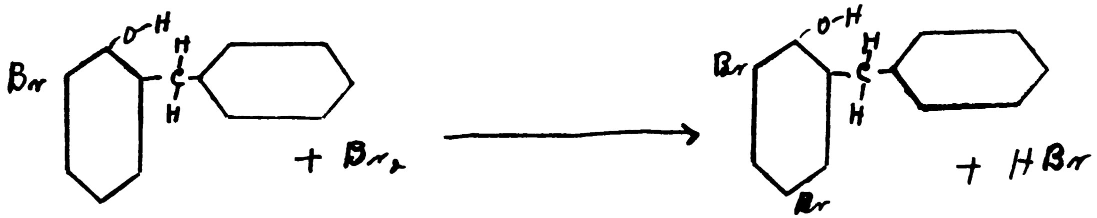
The large fraction is again assumed to represent the 2-bromophenyl-benzyl ether. Its boiling point, 142°-144° at 2 mm. pressure checks with that as found from the ether condensations. This is believed to definitely establish the identity of the compound in question as 2-bromophenyl-benzyl ether.



VARIOUS DERIVATIVES OF 2-BROMO,6-BENZYL PHENOL.

The purpose of this part of the problem was not only to prepare various new compounds but to use them as a further means of identifying the 2-bromo,6-benzyl phenol.

The first derivative prepared was 2,4-dibromo,6-benzyl phenol. This was done by the direct bromination of the benzylated phenol according to the following equation:

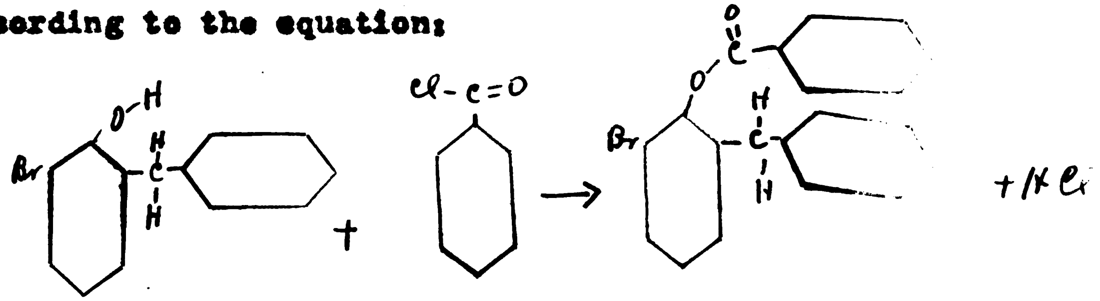


A considerable amount of this derivative was made in order that it might be used in the preparation of other derivatives.

13.1 grams, (.05 moles), of 2-bromo,6-benzyl phenol was dissolved in chloroform and to it was added 8.8 grams, (.05 moles plus a 10% excess), of bromine also dissolved in chloroform. The reaction mixture was cooled with ice. When bromination was complete, evidenced by the disappearance of the bromine color, the chloroform was evaporated off, leaving a white solid. This compound, after being recrystallized from petroleum ether five times, gave a constant melting point of 90.5°, identical with the melting point as determined for 2,4-dibromo,6-benzyl phenol by F. H. Maxfield, (Master's thesis, 1930). Thus, the identity of this and the monobromobenzyl phenol from which it was prepared were established.

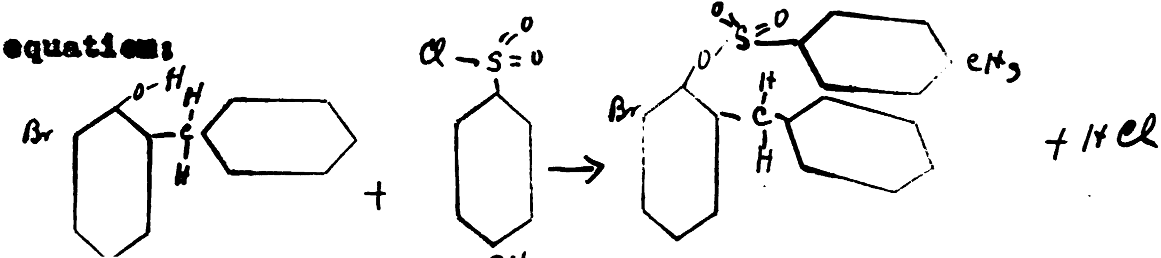
Next were prepared the benzoyl and toluenesulfonyl esters of the mono and dibromobenzyl phenols. This was done by the method described by Porter, Stewart and Branch. The phenol was dissolved in pyridine and to it was added a 10% excess of the acyl chloride. After standing over night an equal volume of water was added to this reaction mixture to react with the excess acyl chloride. The mixture was then acidified with sulfuric acid to form a water soluble salt of the pyridine and the ester was extracted with ethyl ether. Evaporation of the ether solution then gave the free ester.

The first ester prepared was the benzoyl ester of 2-bromo,6-benzyl phenol. 8 grams of the phenol were dissolved in 20 grams of pyridine and to this was added 4.6 grams, (a calculated 10% excess), of benzoyl chloride. The proceedure was followed as described and the ester formed according to the equation:



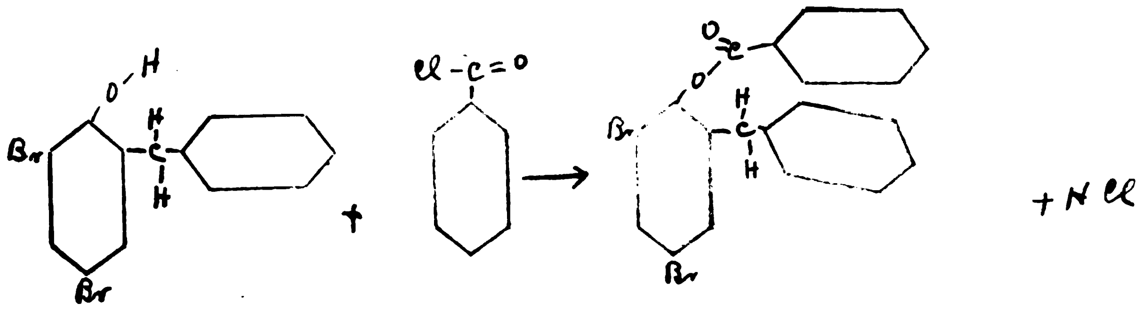
Evaporation of the ether extract gave a white solid which after being recrystallized from ethyl alcohol five times, showed a constant melting point of 89.5°-90°.

The p-toluenesulfonyl ester of 2-bromo,6-benzyl phenol was prepared in the same way from 8 grams of the phenol and 6.6 grams of p-toluenesulfonyl chloride, according to the equation:



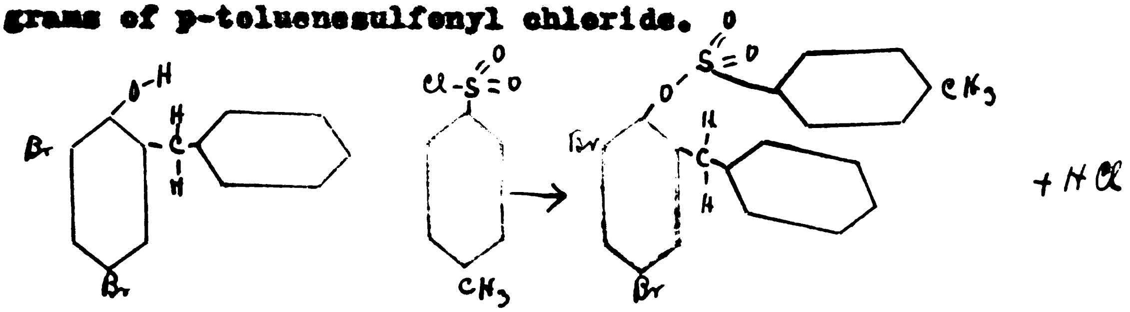
Recrystallization of this compound five times from ethyl alcohol gave a white crystalline compound having a constant melting point of 85°-85.5°.

The benzoyl ester of 2,4-dibromo,6-benzyl phenol was prepared in the same way using 4 grams of the phenol and 2 grams benzoyl chloride, according to the following equation:



Five recrystallizations of this compound from ethyl alcohol gave a white crystalline compound with a constant melting point of 102°.

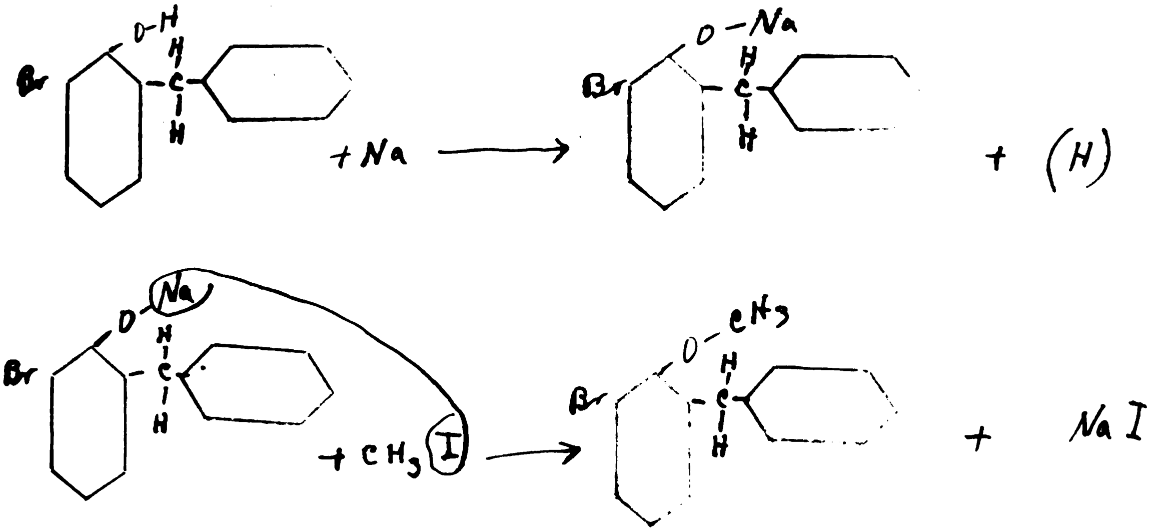
The p-toluenesulfonyl ester of 2,4-dibromo,6-benzyl phenol was prepared from 4 grams of the phenol and 2.9 grams of p-toluenesulfonyl chloride.



This compound, when purified by successive recrystallizations from alcohol gave a white crystalline compound having a constant melting point of 119°.

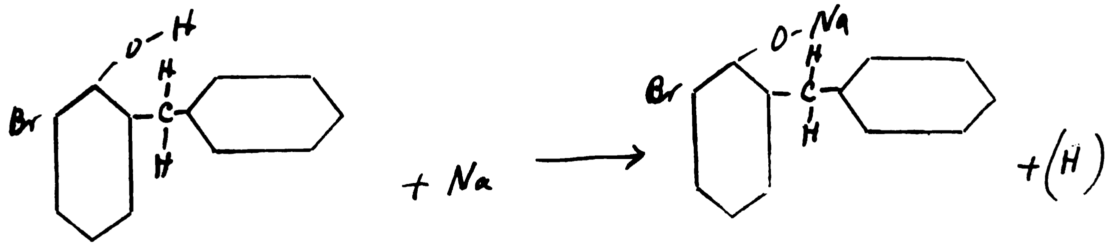
The methyl and ethyl ethers of 2-bromo,6-benzyl phenol were next prepared in the following way: The phenol was dissolved in the corresponding alcohol and the theoretical amount of sodium added to form the sodium phenolate. When this reaction was complete the theoretical amount of the alkyl iodide was added, the mixture refluxed for five hours and allowed to stand overnight. The alcohol was then evaporated off and the residue washed with water to remove the sodium iodide formed in the reaction. The ether was extracted with ethyl ether and was obtained by evaporating off the solvent.

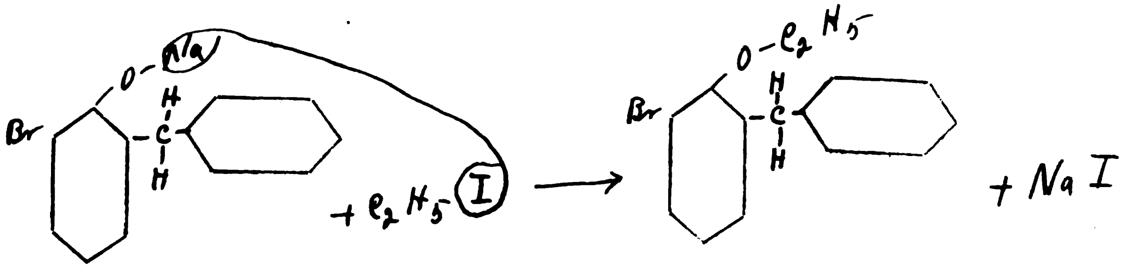
By this method the methyl ether was prepared, using 20 grams of 2-bromo,6-benzyl phenol, 1.75 grams of sodium, 10.8 grams of methyl iodide and 25 cc. of methyl alcohol. The reactions are represented by the following equations:



This ether was then purified by fractional distillation at reduced pressure. It was found to boil at 139°-141° at 2 mm. pressure.

The ethyl ether was prepared in the same way, using 20 grams of the 2-bromo,6-benzyl phenol, 1.75 grams of sodium, 11.5 grams of ethyl iodide and 25 cc. of ethyl alcohol. The following reactions were involved:



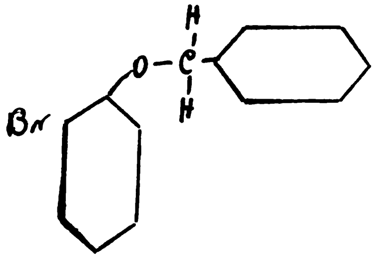


This ether was also purified by fractional distillation at reduced pressure. It was found to boil at 141°-143° at 2 mm. pressure.

ANALYSIS OF THE VARIOUS PREPARATIONS.

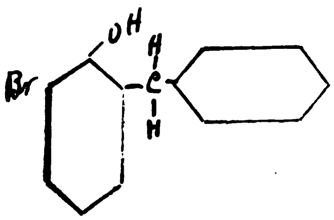
The final part of this problem consisted of the analysis of each of the various compounds prepared from o-bromophenol for the purpose of determining their constitution and thus verifying their identity. The analysis was made for halogen content. This was done by the Parr Bomb method as described by J. Lemp and H. Broderson, (J. Amer. Chem. Soc. 39, 2069. 1917). Duplicate samples were run on all but two of the compounds, the benzoyl and toluenesulfonyl esters of 2,4-dibromo,6-benzyl phenol. There was only a small amount of these two compounds on hand and since in each case the first analysis gave results that checked very satisfactorily with the theoretical values, it was not considered necessary to run duplicates. Following is a tabulation of the results of the various analyses:

2-bromophenyl benzyl ether.



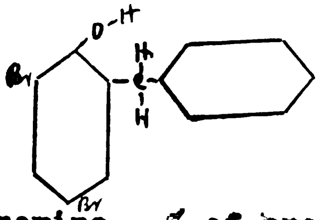
	wt. of sample	wt. of bromine determined	% of bromine by analysis	% of bromine calculated
#1.	.2021	.06085	30.11%	30.38%
#2.	.2110	.06381	30.24%	

2-bromo,6-benzyl phenol.



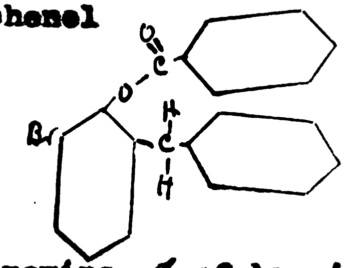
	wt. of sample	wt of bromine determined	% of bromine by analysis	% of bromine calculated
#1.	.2013	.06079	30.20%	30.38%
#2.	.1962	.05934	30.26%	

2,4-dibromo,6-benzyl phenol.



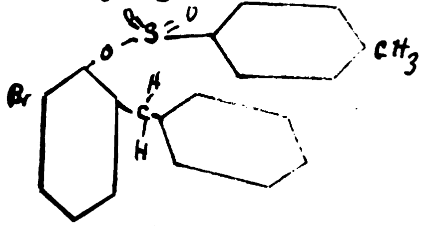
	wt. of sample	wt of bromine determined	% of bromine by analysis	% of bromine calculated
#1.	.2082	.09687	46.54%	46.75%
#2.	.2131	.09933	46.62%	

Benzoyl ester of 2-bromo,6-benzyl phenol



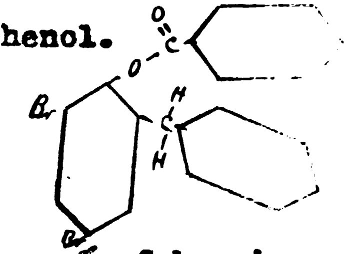
	wt. of sample	wt. of bromine determined	% of bromine by analysis	% of bromine calculated
#1.	.1986	.04169	21.49%	21.77%
#2.	.2041	.04402	21.57%	

p-Toluenesulfonyl ester of 2-bromo,6-benzyl phenol



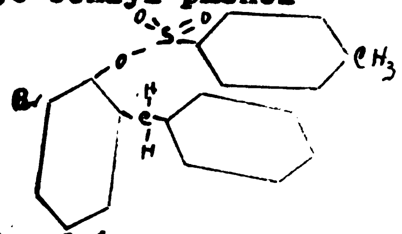
	wt. of sample	wt. of bromine determined	% of bromine by analysis	% of bromine calculated
#1.	.2092	.03991	19.09%	19.16%
#2.	.2085	.03988	19.13%	

Benzoyl ester of 2,4-dibromo,6-benzyl phenol.



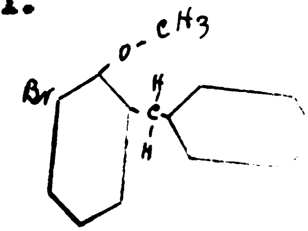
	wt. of sample	wt. of bromine determined	% of bromine by analysis	% of bromine calculated
#1.	.2043	.07279	35.64%	35.84%

p-Toluenesulfonyl ester of 2,4-dibromo,6-benzyl phenol



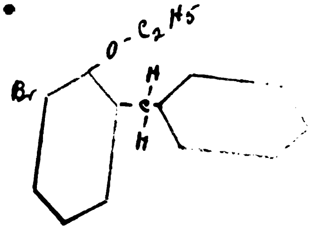
	wt. of sample	wt. of bromine determined	% of bromine by analysis	% of bromine calculated
#1.	.2042	.06556	32.11%	32.22%

Methyl ether of 2-bromo,6-benzyl phenol.



	wt. of sample	wt. of bromine determined	% of bromine by analysis	% of bromine calculated
#1.	.1951	.05541	28.40%	28.85%
#2.	.2013	.05729	28.46	

Ethyl ether of 2-bromo,6-benzyl phenol.



	wt. of sample	wt of bromine determined	% of bromine by analysis	% of bromine calculated
#1.	.1903	.05197	27.31%	27.46%
#2.	.1997	.05448	27.28%	

In each case, the structure that had been assigned to the compound, was verified by analysis.

SUMMARY.

The results of the work outlined in this thesis may be summarized in the following way:

A satisfactory method was developed for the preparation of o-bromophenol.

By comparison with other simple methods of preparation this method was shown to be superior.

The views of Datta and Bhoumik, that the sulfonic acid group may be readily replaced by halogens, was supported.

The sodium sulfonate group was shown to be suitable for blocking the substitution of halogens.

The oxygen and carbon benzylation products of o-bromophenol were prepared and identified in various ways.

The following new compounds were prepared:

The benzoyl ester of 2-bromo,6-benzyl phenol.

The p-toluenesulfonyl ester of 2-bromo,6-benzyl phenol.

The benzoyl ester of 2,4-dibromo,6-benzyl phenol.

The p-toluenesulfonyl ester of 2,4-dibromo,6-benzyl phenol.

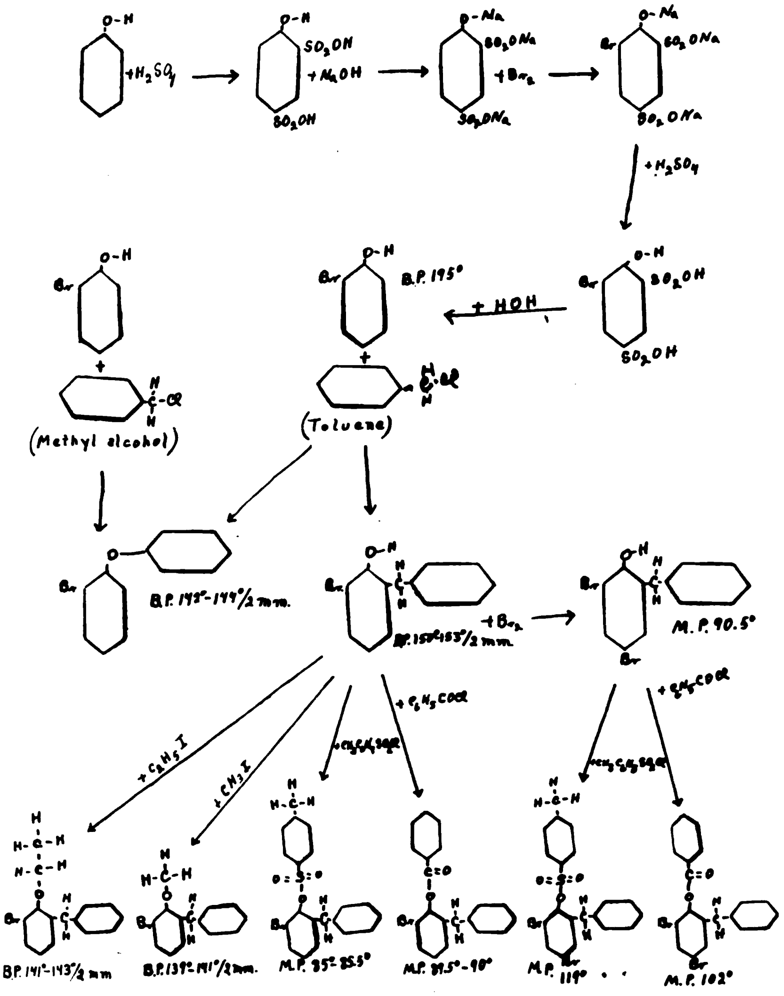
The methyl ether of 2-bromo,6-benzyl phenol.

The ethyl ether of 2-bromo,6-benzyl phenol.

2,4-dibromo,6-benzyl phenol was previously prepared and identified by F. H. Maxfield.

2-bromophenyl-benzyl ether and 2,bromo,6-benzyl phenol were prepared by R. Dosser but were not identified by analysis at that time.

DIAGRAM OF REACTIONS.



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