SOME BROMO DERIVATIVES OF BENZYLPHENOLS

THESIS FOR THE DEGREE OF M. S.

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Some Bromo Derivatives
of
the Benzylphenols

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By

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Thesis

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Contents

Some Bromo Derivatives of the Benzylphenols

1. The work of E. Paterno (1872).

A review of the literature has shown that E. Paterno (Gazz. Chim. Ital. 2, 1--6 (1872)) was apparently the first to prepare benzyl phenol. He heated gently a mixture of benzyl chloride and phenol in the presence of zinc dust. It was noted that a reaction started and hydrochloric acid was given off, and the liquid entered into ebullition. Later, a brown liquid or oil was separated from the unchanged zinc, and distilled.

The uncombined benzyl chloride and phenol were distilled off below 260°. The remaining mass was distilled at 6 mm. The main fraction distilling at 180- 190° solidified to a mass of small needles, which retained some of the original oil. The crystals were pressed between filter paper and the oily part discarded, while the needles were recrystallized from alcohol. This benzylated phenol crystallized in white silky needles M.P. 84 which were soluble in alcohol, ether, benzene, and chloroform. The pure phenol boiled at 175--180° (4-5 mm.).

It was soluble in alkaline solutions, but was reprecipitated by acids. It was not soluble in ammonia. When it was treated with nitric acid it would form substitution products. When treated with sulphuric acid it produced a sulphonic acid with the phenol, the barium salt of which was soluble in water.

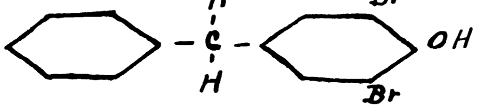
They also found that benzylated anisole treated with hydriodic acid, and boiled for eight hours at 170° gave methyl iodide, and the same benzyl phenol as just described.

Two years later in 1874, E. Paterno and M. Fileti (Gazz. Chim. Ital. **3**, 121-129, 251-254) gave a further description of possible derivatives of the same benzyl phenol. The action of bromine on benzylated phenol in acetic acid solution gave rise to an unstable oily compound. But they also described a compound prepared by adding excess bromine to a solution of benzyl phenol in carbon disulphide which melts at 175°. This remained an amorphorous substance, soluble in chloroform and carbon disulphide, but insoluble in alcohol and ether. They say it, "appears" to be a "di-bromide". However later workers have questioned this compound.

2. The work of Zincke and Walter (1904).

In 1904 Zincke and Walter (Ann. 334, 367-385) published some work on bromine substitution in phenols, especially in the case of para- benzyl phenol. They prepared the benzyl phenol by condensing benzyl chloride and phenol with zinc dust, as E. Paterno had done before. (Gazz. Chim. Ital. 2, 1-6 (1872)). This 4-hydroxydiphenylmethane formed silky needles and melted at 84°. Its benzoyl derivative formed needles and melted at 87°.

The 3 : 5 -dibromo-4-hydroxydiphenylmethane was prepared by the gradual addition of the calculated amount of bromine to a cold solution of 4-hydroxydiphenylmethane in chloroform, which existed in two crystalline modifications; one formed colorless needles and melted at 44°, the other formed rhombic crystals and melted at 57°. The former variety is unstable and passed readily into the latter on being left at the ordinary temperature. The acetyl derivative formed monoclinic prisms and melted at 53°.



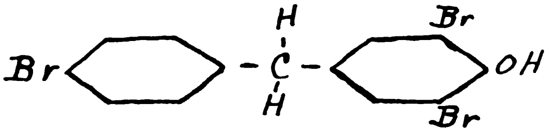
3 : 5-dibromo-4-hydroxydiphenylmethane

It may be noted here that Zincke's di-brom- derivative did not have the same properties as Paterno's di-brom-compound.

The acetyl derivative of 3 : 5-dibromo-4-hydroxydiphenylmethane formed mono-clinic prisms, melted at 53°. They base the proof of the structure upon the following facts; when the di-bromo benzyl phenol was treated with sodium nitrite, a bromine atom was readily replaced with a NO_2 as is the case when ordinary brom-phenols are treated with sodium nitrite.

Zincke and Walter in the same paper described a tri-brom compound. This 3 : 5 : 4' -tribromo-4-hydroxydiphenylmethane was prepared by agitating 4-hydroxydiphenylmethane with a calculated excess of bromine until all had dissolved. After the removal of the bromine from the petroleum ether, they crystallized the product, which formed slender needles melting at 88°. When its solution in glacial acetic acid was treated with sodium nitrite, one atom of bromine was replaced by one nitro- group. Its acetyl derivative melted at 105°.

They assigned the following formula;



3 : 5 : 4' -tribromo-4-hydroxydiphenylmethane

In the same paper they describe a penta- brom derivative but give no absolute proof of its formula.

They also found that by the reduction of benzylidenedibromquinone by the use of hydriodic acid a di-brom-4-hydroxydiphenylmethane was formed.

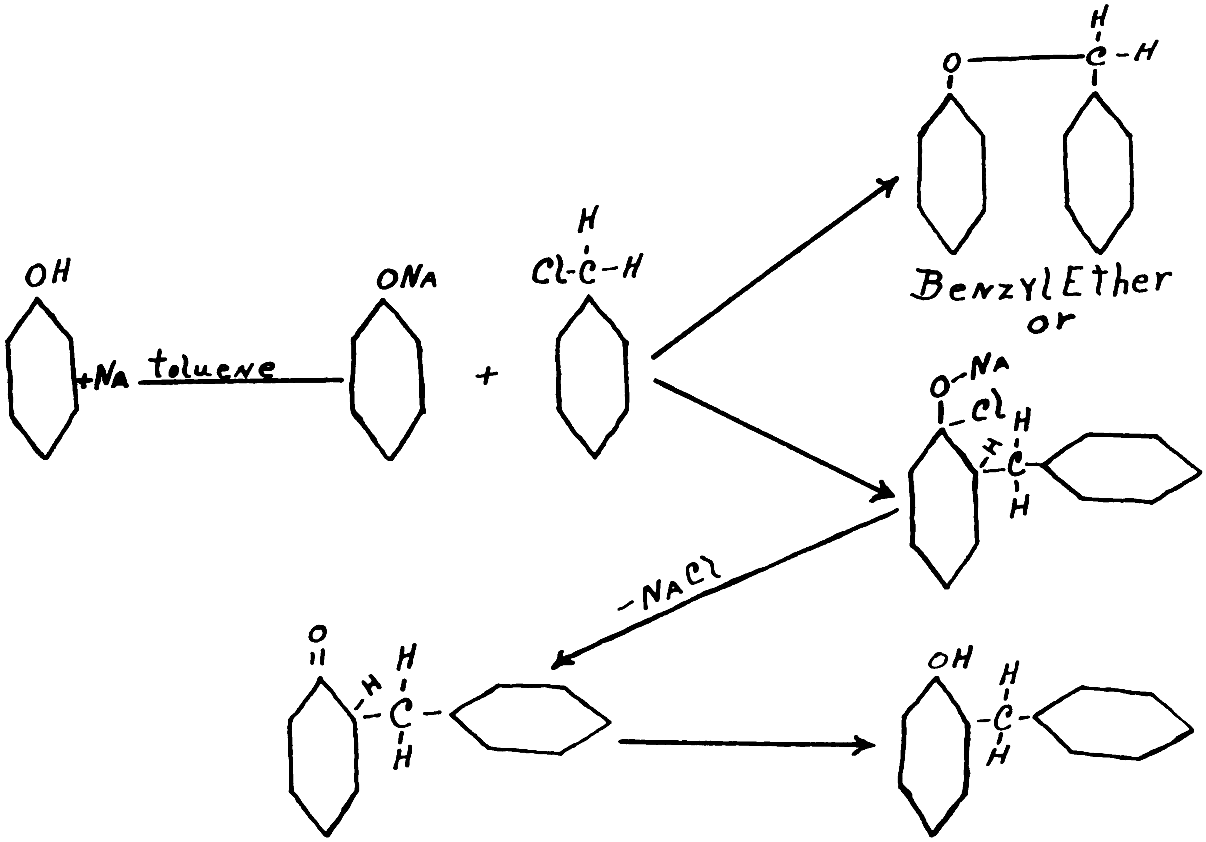
It may be noted here that this tri-brom compound of Zincke and Walter's will be further discussed in the description of the experimental work.

3. The work of Claisen and his followers.

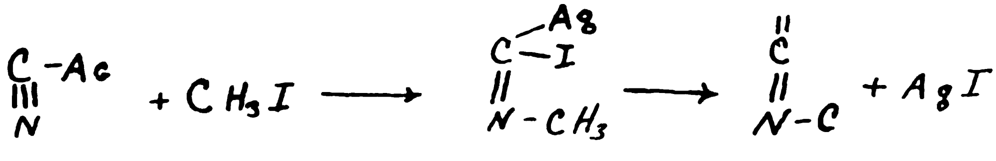
In 1923 L. Claisen published work on the carbon alkylation of phenols in the ring. (Z. Angew. Chem. 36, 478-479) He found that both oxygen and carbon alkylation of phenols took place, when the reaction between alkyl halides and the sodium derivatives of monohydric phenols of the benzene and napthalene series took place. This was due to the medium in which the reaction was carried out which is the important factor. When a dissociating medium was used such as methyl or ethyl alcohol or acetone as a rule we have more oxygen alkylation; while in a non-dissociating medium such as benzene and toluene more of the carbon alkylation is produced.

He further noted that the unsaturated alkyls, (e.g; allyl, homoallyl, etc.) effect the carbon alkylation to a greater extent than do saturated alkyls. The use of the halide of the unsaturated alkyl permits the carbon alkylation of phenols that could not otherwise be thus alkylated. The tendency toward carbon alkylation is still further increased if alkyl phenols be used. The substituent enters in the ortho- position to the hydroxyl, provided this is unsubstituted.

In 1925 L. Claisen, F. Kremers, F. Roth, and E. Tietz (Ann. 442, 210-245) studied the Claisen's reaction further and gave a number of interesting points. Claisen in his early work most generally used an alkali metal in a suitable medium (e.g; toluene) which was allowed to react with the phenol making a phenolate. When in turn this mixture was treated with alkyl or benzyl halide it reacted to give a mixture as shown in the following diagram (Z. Angew. Chem. 36.); the oxygen alkylation or the ether and the carbon alkylation of the benzyl phenol.



If we should examine the above equations closely we could see why Claisen said, the ether is the product one would expect to be formed, and that the benzyl phenol is the result of ring alkylation. Claisen's theory of the mechanism of the reaction in which the substituting group takes the position ortho to the hydroxyl is based on Michael's theory of the reaction between silver cyanide and methyl iodide. (J. Pr. 37, 486; 46, 189).



We also know by Claisen's reaction there is the elimination of sodium chloride, therefore the only possible chance is for the substituent to enter in the ortho- position to the hydroxyl, provided this is unsubstituted, para- substitution to the hydroxyl where the ortho- position is occupied has not yet been demonstrated with certainty.

We can see how a shift of the bonds produce the ortho-product, but in other condensation methods the~~ir~~re is nothing assured that we will have the para compound, but are likely to produce mixtures of para and ortho compounds as shown by Huston and Houk (1928).

Claisen in this report enumerated the factors which effect the reaction, and listed them as follows:

1. The kind of phenol.
2. The kind of halide,- whether saturated or unsaturated, aliphatic or aromatic.
3. The kind of halogen.
4. The kind of metal in the metal phenolate.
5. The temperature.
6. The medium in which the reaction occurs.

In discussing these factors Claisen stated that the more complex phenols introduced more trouble than a simple phenol. As was shown in his early report (Z. Angew. Chem; 36, 478-9 (1923)) the unsaturated halides are more easily introduced into the nucleus than the saturated. He stated that the looser the bond between the halogen and the alkyl radicle the more smoothly the reaction progressed. The metal used in these reactions was generally sodium thus forming sodium phenolate. The temperature apparently had little effect so long as the mixture was refluxed gently. The effect of the medium in which the reaction occured can be shown by the following example taken from Ann. 442; allyl bromide with sodium phenolate in alcohol gave 90 % of the ether, while in a non-dissociating medium like benzene or toluene it gave only 30 % ether, the remaining 70 % being mostly monoallylphenol with a slight trace of diallylphenol. The carbon derivatives predominated in non-dissociating media, whereas oxygen-compounds are produced in dissociating solvents, Further more, the tendency towards the production of carbon- derivatives increased with increasing mobility of the halogen atom of the halide.

M. Busch in 1925 working on the alkylation of phenols published a very interesting item in Z. Angew. Chem; 38, 1145-1146. He stated, that the tendency of benzyl radicals toward carbon-alkylation of phenols increased with the increasing substitution of the methane carbon. It was possible to obtain ethers with benzyl chloride in non-dissociating media, but diphenylmethyl chloride yielded only the carbon-derivatives.

Busch had found that diphenylbrom methane with phenol, with or without a solvent, in the presence of heat gave para hydroxy triphenylmethane and with sodium phenolate it gave the ortho- hydroxy triphenylmethane isomer.

M. Busch and R. Knoll (Ber; 60 B, 2243-2257 (1927)) have been able actually to isolate some of these long sought for addition products; claiming the reaction between C H OH and RX

(X--chloride) is assumed to proceed according to the scheme;

$$C_6H_5OH + RX \longrightarrow p\text{-}RC_6H_4OH + HX$$

with C_6H_5ONa according to the scheme;

$$C_6H_5ONa + RX \longrightarrow o\text{-}RC_6H_4OH + NaX$$

in dissociating solvents partly according to the last scheme and partly according to the scheme;

$$C_6H_5ONa + RX \longrightarrow C_6H_5OR + NaX.$$

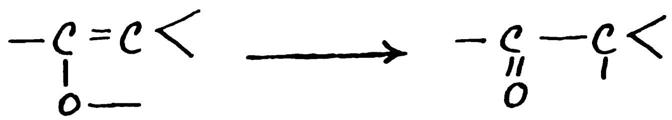
They also reported that the accumulation of alkyl groups, especially those of high molecular weight, on the phenol nucleus materially diminished the ether formation.

K. von Auwers, G. Wegener, and Th. Bahr explained the formation of carbon substituents from salts of keto- enols and alkyl halides by three hypothesis which had been previously advance Chem. Zentr. I, 2347-2348 (1926).

(1) "The initial formation of addition products with subsequent splitting. (Michael).

(2) "The initial formation of normal oxygen derivatives, with rearrangement of these into carbon derivatives.

(3) "The separating of the metal as a metallic halide, formation of free alkyl and enol radicals,



$$-\underset{\displaystyle O-}{\underset{|}{C}}=C< \longrightarrow -\underset{\displaystyle O}{\underset{\|}{C}}-\underset{|}{C}<$$

and with the slight reactivity of the alkyl group partial or complete rearrangement of the enol to keto radical, and finally union of the radicals." (Wislicenus)

Some recent investigations have shown that the course of the alkylization of a keto-enol depends upon its character and upon the alkylization agent. Experiments by L. Claisen (Z. Angew. Chem; 36, 473-479 (1923)) showed that saturated alkyl halides promote the formation of oxygen derivatives and allyl and benzyl halides promote the formation of carbon derivatives. Allyl, benzyl, and similiar radicals furnish preponderantly carbon derivatives and saturated alkyl radicals form oxygen derivatives. At the same time, inactive media were shown to favor the formation of carbon derivatives and dissociating media that of oxygen derivatives. These facts come under the first hypothesis on which Claisen based his theortical consideration.

The second hypothesis is inadequate, for it is not comprehensible why an oxygen ether should be transformed into a carbon derivative in benzene more easily than in ethyl alcohol.

The third hypothesis stated, that the oxygen derivative should be formed with allyl and with benzyl radicals because of their great reactivity, but this is not the case. However, the formation of radicals and the isomerization of enol to keto radicals is necessary to explain the reactions. We can assume that the greater reactivity indicates a large requirement for valence, and vica versa, since allyl and benzyl radicals are distinguished by their slight valence requirements and therefore hold oxygen only loosely, they show a preference for combining with carbon to form a stabile combination. Claisen in Ann. 442 also confirmed these views, when he stated, that unsaturation in the allyl and benzyl radicals result in a comparatively loosely held halogen, and furthermore that reaction mediums such as toluene, and benzene exert a loosening effect on the valence bonds between the alkyl or benzyl radical and the halogen.

J. Van Alphen in 1927 published a article on the migration of the diphanylmethyl and benzyl groups in phenol. (Rev. trav. Chim; 46, 799-812). He found that by heating phenyl benzyl ether, M. P. 39° (Ann. 143, 81 (1867)) with zinc chloride to 160° for one hour; it is converted into 4-hydroxydiphenyl methane, M. P. 84°, and a dyestuff. He also reported the same compound when phenol and benzyl chloride and a small piece of zinc chloride are heated together at 100°.

W. F. Short reported in the J. Chem. Soc. I, 528 (1928) that when benzyl phenyl ether is heated to 225° in the presence of zinc chloride, or to 180° if a stream of hydrogen chloride was passed through the misture, a vigorous reaction occured. The product, on distillation under reduced pressure, yielded phenol, o- hydroxydiphenylmethane M. P. 54°; phenylurethane M. P. 118°; also p- hydroxydiphenylmethane M. P. 84°-84.5°. The para compound was identified by conversion into p- methoxybenzophenol M. P. 61°-62°, and products of high boiling point. Since phenol was produced, it was probable that the reaction followed a course similiar to the Hofmann rearrangement of alkyl-anilines, benzyl chloride being formed as an intermediate.

G. Vavon and N. Zaharia, Compt. rend. 187, 346-348 (1928) stated, in the purification of phenols, it was recommended that petroleum ether be used for the extracting of the oxygen derivative and that an excess of alkali be employed. Phenols may be partially extracted from their alkali solutions by means of ethyl ether. The proportion extracted depends on the structure of the phenol. With the introduction of radicals into phenol, the proportion extracted increases, and is greater for ortho- substituted phenols than for the meta- or para- isomers.

4. The work of Friedel and Crafts.

Friedel and Crafts (Compt. rend. lxxxiv, 1392-1395) in 1876 discovered a new synthetical method of producing hydrocarbons. They noted when amyl chloride was treated with small quantities of anhydrous aluminum chloride there occured a brisk disengagement of hydrochloric acid gas, accompanied by hydrocarbons which are not absorbed by bromine. When this reaction was made to take place in the presence of a hydrocarbon, it was easy to obtain a combination of the radicle of the organic chloride with the hydrocarbon, less the hydrogen replaced. Thus, they were able to condense amyl chloride with an excess of benzene, and having added aluminum chloride by small quantities at a time, they obtained, by fractional distillation of the products, a liquid boiling at 185- 190°, and having the composition and properties of amyl-benzene, $C_6H_5C_5H_{11}$. The other halogen salts of aluminum gave reactions analogous to those of the chloride.

Friedel and Crafts, (J. Chem. Soc; 41, 115-116, (1882)), stated, "we found in general that compounds containing the group OH or OR, i.e; alcohols, phenols, acids, and their ethers undergo decomposition with chloride of aluminum, and the reactions which we have decided are usually impossible in the presence of such bodies."

The mechanism of Friedel and Crafts' reaction has been studied very thorough by J. Boeseken in the following articles: (Rec. Trav. Chim; (1) 19, 19-26 (1900), (2) 20, 102-106 (1901), (3) 22, 301-304 (1903), (4) 22, 315-317 (1903), (5) 23, 98 (1904),

(6) 30, 148-150 (1911)), these views have also been confirmed by G. Perrier (Ber; 33, 815-816 (1900)). Boeseken stated, (Rec. Trav. Chim; 19, 19-26 (1900)) that in the synthesis of aromatic ketones and sulphones by means of Friedel and Crafts' reaction, the condensation takes place in three stages:

(1) $R\text{-}COCl + AlCl_3 \longrightarrow R\text{-}COCl,AlCl_3$

(2) $R\text{-}COCl,AlCl_3 + HR' \longrightarrow R\text{-}COR',AlCl_3 + HCl$

(3) $R\text{-}COR',AlCl_3 + n\ H_2O \longrightarrow R\text{-}COR' + AlCl_3,nH_2O$

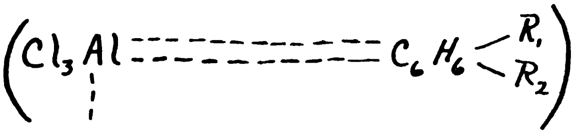
The HR' represented an aromatic hydrocarbon or one of its derivatives.

Analogous additive compounds can be isolated when ferric chloride is used instead of aluminum chloride which has been shown by M. Nencki, (Ber; 30, 1766-1768 (1897)) and (Ber; 32, 2414-2419 (1899)). J. Böeseken (Rev. Trav. Chim; 22, 315-317 (1903) stated that the reaction of ferric chloride was precisely similiar to that of aluminum chloride in the Friedel and Crafts' reaction.

J. Boeseken, (Rev. Trav. Chim; 30, 148-150 (1911)), stated that in the case of a typical Friedel and Crafts' reaction, in every case the initial reaction is the simple addition of the two molecules.

The preceding explains the nature of the Friedel and Crafts' reaction. Three molecules must be present: (a) an unsaturated molecule, (b) a molecule which can be so activated that it can combine with the unsaturated molecule, (c) a catalyst which activates the molecules in (a) and (b). The possibility of the reaction is determined by the loss of free energy. The initial action is due to the encounter of the two molecules with the catalyst; in the case of benzene and other unsaturated cyclic systems the initial additive product, a derivative of dihydrobenzene, etc; cannot be isolated, because by elimination of hydrogen chloride or the like it is converted into a system containing less free energy.

Schaarschmidt (Z. Angew. Chem; 37, 286-288 (1924)) based his theory of the mechanism of Friedel and Crafts' reaction on the fact that the aromatic hydrocarbon was activated by the aluminum chloride or ferric chloride which he claimed appeared possible in producing a simultaneous "loosening" of the bonds of the organic halogen compound. A primary complex was formed, consisting of metallic chloride, hydrocarbon, and addend, in which the metallic chloride was held by auxillary valences and the addend by ordinary valences, thus



$$\left(Cl_3Al \text{-----------} C_6H_6 <^{R_1}_{R_2}\right)$$

The stability of this complex depended upon the division of the inner valences; and according to the author may persue one of two courses, a "molecule course" and the "catalytic course" of the synthesis. The synthesis may be hindered by substituents in the benzene ring which decompose the metallic chloride.

Other authors which confirmed the theory of additive compounds of aluminum chloride, are; Gustavson, (Ber; 11, 2151 (1878)), (Comp. rend; 136, 1065 (1903), 140, 940 (1905)), Schleichen, (J. Pr. Chem; II, 105, 355 (1922)), Kronberg, (J. Pr. Chem; II, 61, 494-496 (1900)), and Menschutkin, (J. Russ. Phys. Chem. Soc; 41, 1053-1089 (1909)).

(5) The theory of the action of aluminum chloride.

Friedel and Crafts' reaction is connected more particularly with the union of aromatic hydrocarbons and their derivatives with a variety of other organic compounds, such as alkyl halides, acid chlorides, etc. (Org. Chem.- Cohen I, 224). Cohen, stated, (Org. Chem.- Cohen I, 347) that the results are best explained by assuming the formation of a compound between one or both of the reacting substances and the aluminum chloride, and by the removal of the latter from the system in combination with the ketone formed.

It may be observed that the union between molecules or parts of a molecule is nearly always determined by unsaturation and by a consequent tendency for the unsaturated atoms to saturate themselves. Thus Cohen, (Org. Chem.- Cohen, I, 196) divided the condensation processes roughly into two groups:

(1) Those in which the combining molecules are induced to unite by being rendered, as it were, artifically unsaturated as the result of withdrawing certain elements.

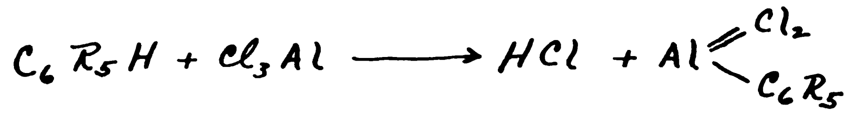
(2) Those which, being already unsaturated, combine either spontaneously or with the help of a reagent or catalyst.

We can see the general theory of the anhydrous aluminum chloride by a number of different authors:

The formation of temporary addition products was showed by; J. Boeseken, (Rec. Trav. Chim; 19, 19-26 (1900); 20, 102-106 (1901); 22, 301-304 (1903); 22, 315-317, (1903); 23, 93- (1904);

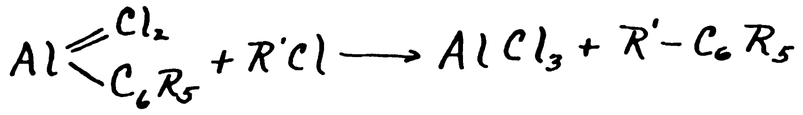
30, 148-150 (1911)), G. Perrier, (Ber; 33, 815-816 (1900)), Gustavson, (Ber; 11, 2151 (1878)), (Comp. rend; 136, 1065 (1903), 140, 940 (1905)), Schleichen, (J. Pr. Chem; II, 105, 355 (1922)), Kronberg, (J. Pr. Chem; II, 61, 494-496 (1900)), and Menschutkin, (J. Russ. Pnys. Chem. Soc; 41, 1053-1089 (1909)).

Sabatier stated (Catalysis in Organic Chemistry, 173), the catalytic activity of anhydrous aluminum chloride in the Friedel and Crafts' reaction can be explained by the production of a temporary combination between the chloride and the organic material. Thus with aromatic hydrocarbons, we would have:



$$C_6R_5H + Cl_3Al \longrightarrow HCl + Al\genfrac{}{}{0pt}{}{/\!\!/\, Cl_2}{\diagdown\, C_6R_5}$$

The latter compound would react immediately on the halogen derivative present and we would have:



$$Al\genfrac{}{}{0pt}{}{/\!\!/\, Cl_2}{\diagdown\, C_6R_5} + R'Cl \longrightarrow AlCl_3 + R'-C_6R_5$$

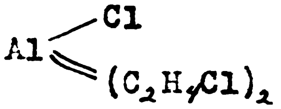
The regenerated aluminum chloride would react again with the hydrocarbon and the same reactions would be repeated.

We can see three important uses of anhydous aluminum chloride, namely:

(1) Catalytic action (J. Böeseken, (Rec. Trav. Chim; 30, 148-150 (1911)), Norris (Ind. Eng. Chem; 16, 184 (1924)).

(2) Dehydrating agent (Merz and Weith (Ber; 14, 187 (1881)).

(3) Intermediate compounds (Gustavson, Perrier, Boeseken, etc.).

Sabatier stated, (Catalysis in Organic Chem; 174) the reality of the formation of addition products of the aluminum chloride with the organic compounds has been established by Gustavson (Ber; II, 2151 (1878)) who has been able to isolate an addition product with benzene, an orange colored oil, $AlCl_3$-3 C_6H_6, decomposable by water, and in the case of the mixture of benzene and ethyl chloride, $AlCl_3$-$(C_2H_4)_2$-3 C_6H_6, which heat dissociates into benzene and  $\mathrm{Al}\begin{array}{l}\diagup \mathrm{Cl}\\ \diagdown\!\!\diagdown (\mathrm{C_2H_4Cl})_2\end{array}$, which is stable and serves as catalyst for the transformation of the mixture. (Compt. rend; 136, 1065 (1903); 140, 940 (1905)).

By these quotations we can see the general theory for the anhydrous aluminum chloride in the Friedel and Crafts' reaction is to form addition products with the organic material and this in turn reacting immediately on the halogen derivative present.

(6) The work of Dr. R. C. Huston.

Huston and Friedmann in 1916 directed their attention to the action of aromatic alcohols on aromatic compounds in the presenee of aluminum chloride. (J. Am. Chem. Soc; 38, 2527-2533 (1916)). When benzyl alcohol in benzene was constantly stirred and slowly treated with anhydrous aluminum chloride their was obtained five products; the chief product being diphenylmethane. They further stated, that the yields are greatly influenced by the amounts of reagents used and by the temperature.

In 1918 Huston and Friedmann (J. Am. Chem. Soc; 40, 785-793 (1918)), further studied the action of aromatic alcohols on aromatic compounds this time including secondary alcohols. They concluded that methyl and ethyl groups interfere to some extent, while the presence of the second phenyl group stimulates the condensation.

Huston (Sci; 52, 206-207 (1920)) applied the theory of the above condensations to the condensing of benzyl alcohol and phenol in the presence of aluminum chloride. He stated a good yield (40-50 %) of p- benzyl phenol was obtained. This p- benzyl phenol had previously been prepared by Paterno (Gazz. Chim. Ital; 2, 1-6 (1872)), (Ber; 5, 288 (1872)) by using zinc dust as a catalyst; Paterno and Mazzura (Ibid; 8, 303 (1887)), Paterno and Fileti (Ibid; 5, 381 (1884)), by the use of a mixture of sulphuric and acetic acid; and Liebman (ber. 15, 152, (1882)) with the use of zinc chloride.

Huston (J. Am. Chem. Soc; 46, 2775-2779 (1924)) noted when phenol in petroleum ether was acted upon by aluminum chloride it gave a viscous mass probably aluminum phenolate, from which the phenol is quantitatively recovered on decomposing with hydrochloric acid. This aluminum phenolate formed may be considered as a intermediate product described earlier. When phenol reacted with benzyl alcohol in petroleum ether the yield was greater than when the petroleum ether was omitted. He further stated, that the yield was not increased by a larger amount of the aluminum chloride.

In 1926 Huston and Sager, (J. Am. Chem. Soc; 48, 1955-1959 (1926)), studied the effect of unsaturation on the activity of alcoholic hydroxyls on benzene in the presence of aluminum chloride. They concluded three points were essential in this study.

(1) Alcohol derivatives of aromatic hydrocarbons, only those in which the hydroxyl is on the carbon atom adjacent to the ring condenses with benzene.

(2) The saturated alcohols up to and including amyl alcohol do not react with benzene.

(3) The unsaturated aliphatic alcohols, as allyl do react with benzene.

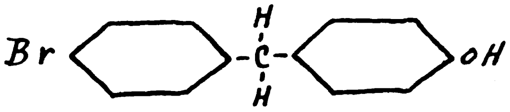
Huston, Lewis, and Grotemut (J. Am. Chem. Soc; 49, 1365-1368 (1927)) studied the action of aromatic alcohols on aromatic compounds in the presence of aluminum chloride. They condensed secondary alcohols with phenol, in the presence of aluminum chloride. These experiments gave additional evidence of the effect of unsaturation of the α- carbon atom on the reactivity of the alcohol hydroxyl group which tended to increase the yield of the product.

The Problem defined.

The work to be studied in this problem are;

(1) To see if ortho- substitution is found in the aluminum chloride condensation of p- brom benzyl chloride and phenol.

(2) To establish the position of the bromine when introduced directly into the compounds;



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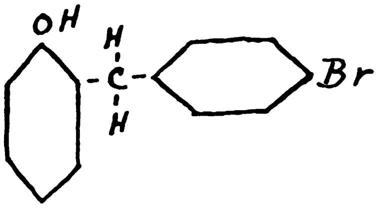


Experimental

We made p- brom toluene by the method described in the Org. Syn. 5, 21 (Bigelow, Marvel, and Broderick). This was then chlorinated by the method used by Jackson and Field (Ber. 11, 904 (1878)). According to the Central-Blatt I, 1136 (1904) it was found to have a M. P. of 41° and B. P. 236°. Errera, (G. 18, 239) in Beilstein II, 62 described p- brom benzyl chloride as glossy white crystals with a M. P. of 38-39°.

The first condensation was with p- brom benzyl chloride and phenol in the presence of anhydrous aluminum chloride. (Huston, J. Am. Chem. Soc; 46, 2775 (1924)). The procedure was similiar to that described in the journal. We took (1 mole) 205.5 gms; of p- brom benzyl chloride (p- $BrC_6H_4CH_2Cl$), (3 moles) 292 gms; phenol (C_6H_5OH), and added slowly while being stirred (½ mole) 63.8 gms; of aluminum chloride ($AlCl_3$). The temperature was kept well below 25°, but it was not necessary to cool as the reaction was very vigorous and the petroleum ether evaporates rapidly so the temperature remained at 12°. Two layers are formed as the anhydrous aluminum chloride was added the top one being mostly all petroleum ether while the lower one was rather viscous and ranged in color from a dark red to a white. A precipitate was formed. The mixture was allowed to stand about twenty-four hours.

The decomposition of this mixture was accomplished by ice and hydrochloric acid (1-1). We should add the acid first so that the oil is well acidified (about 20 cc.) and then pour this into cracked ice. A heavy pink oil settled out. The petroleum ether was then separated and distilled off, the residue was dissolved in ether and was poured back with the original solution. This was sometimes dried over anhydrous potassium carbonate but in two different dondensations, we found it advisable to omit the potassium carbonate.

The first condensation was carried out as described using quarter quantities:

52 gm.	p- $BrC_6H_4CH_2Cl$
72 gm.	C_6H_5OH
15.95 gm.	$AlCl_3$
400 cc.	Petroleum ether

After the reacted substance had stood for twenty- four hours and decomposed. It was then extracted with ether.

The ether was distilled off and the remaining residue fractionally distilled. The following was obtained;

--85°	14 mm.	35.5 gm.
85--125°	10 mm.	31.5 gm.
100--175°	2 mm.	9.0 gm.
175--205°	2 mm.	12.5 gm.
205--260°	2 mm.	8.0 gm.

The fraction boiling between 175-205° at 2 mm. was the fraction in which we expected the phenol condensation product.

It was first thought we had two different compounds, upon recrystallization from gasoline a number of times we obtained a white compound which melted at 59-60°, also a yellow compound which retained its color after several crystallizations from gasoline which melted at 85-86 . The benzoyl ester of these two were made and they melted at the same temperature (118.5-120°), and had the same physical properties. In order to arrive at a more definite conclusion we fractionally distilled both compounds. We obtained from the white crystals (59-60°) a white crystalline solid which was left in the distilling flask which resembled a metal, and also white crystals in the distillate; while their was a heavy yellow oil separated from the yellow compound (85-86°). Both of these compounds distilled over at 164-165°(2 mm.) and when recrystallized had the same melting point 82-83°.

When recrystallized from high test gasoline the crystals were white, small and took a needle-like shape. The yield of this condensation and other similiar onew was 19 % of the theortical. However in the last condensation it was increased a little.

The Parr bomb determination for bromine indicated the formula; $C_{13}H_{11}OBr$

Next we condensed by Claisen's method p- brom benzyl chloride and phenol. Using the following quantities; (1 mole) phenol 94 gms; (1 mole) p- brom benzyl chloride 205.5 gms; (1 mole) sodium 23 gms; and 500 cc. toluene.

The sodium was first put into the toluene and this was then heated. The sodium and toluene was shaken after the sodium was put into a molten mass. This was to break the sodium up into small particles.

The sodium toluene solution was then allowed to cool to room temperature and the phenol then added. The cooling was necessary as the reaction would be too vigorous if allowed to go at some high temperature. A cheesy white mass was formed being sodium phenolate. We allowed this mixture to stand overnight.

At the end of the twelve hour period the p- brom benzyl chloride was added and allowed to reflux at 150° for eight hours in an oil bath. The product was then shaken out with water to dissolve the sodium chloride. The toluene was distilled off, and the mixture treated with 100 cc. of Claisen's alcoholic potash (Ann. 442, 224) solution which dissolves any of the free phenolic hydroxal derivatives leaving a little ether behind. This in turn was separated out with three, fifty cc. portions of petroleum ether. It is not necessary to dry this over anhydrous potassium carbonate as previously stated. This ether portion is saved also for further use and identified as Claisen's ether. This confirms Claisen's early work in which he said their were both oxygen and carbon- derivatives formed.

The alcoholic potash was acidified with 6 N hydrochloric acid and their was formed a heavy red oil. (If this was allowed to stand it solidified). The oil was extracted with ether and the ether distilled off. The remainder was fractionally distilled in a vacum.

In the condensations we used the following portions:

19 gm.	C_6H_5OH
41 gm.	p- $BrC_6H_4CH_2Cl$
4.6 gm.	sodium
100 cc.	toluene

From this we obtained the following;

85--100° 18 mm. 4.5 gm.

125--210°	2 mm.	14.9 gm.
Residue		8.0 gm.

The fraction boiling between 125-210° (2mm.) was the portion in which the phenol desired exists. When the fraction was shown to have a boiling point of 159-160° (2 mm.); and when recrystallized from high test gasoline has a melting point of 72-73°. The phenol was white and separated out of the gasoline in rather large rosette needle crystals.

The yield for this condensation and other similiar ones was 38.1 % of the theortical.

The Parr bomb determination of bromine showed a formula of $C_{13}H_{11}OBr$.

We dissolved a known amount of this 2 hydroxy 4' brom-diphenyl methane in chloroform and added a ten per-cent excess of the theortical amount of bromine required to form a tri- brom phenol. The reaction proceeded very smoothly with a small heat of reaction. The chloroform was allowed to evaporate off and a solid formed in the beaker. This was recrystallized from gasoline and formed a very fine white crystal. When recrystallized again it was found to have a melting point of 80-81°.

The Parr bomb determination of bromine showed the formula $C_{13}H_{9}OBr_{3}$.

In order to prove more definitely the structure of the brominated compound we condensed 2-4 di-brom phenol and p- brom benzyl chloride by Claisen's method. The procedure was similiar to the preparation of 2-hydroxy-4'-brom diphenyl methane.

We used the following in this condensation:

41.0 gm. 2-4 di-brom phenol

23.5 gm. p- brom benzyl chloride

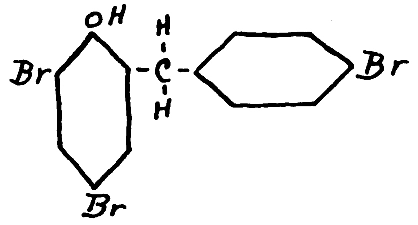
2.3 gm. sodium

30.0 cc. toluene

The reaction yielded ether and phenol as described before. From this condensation their was obtained a 29.71 % yield of the theortical.

This compound had the same physical properties as the brominated compound. The boiling point being 255-256° (2 mm.) and the melting point 80-81°.

A Parr bomb determination showed it to contain the three atoms of bromine as was calculated. Thus we could assigne the same structural formula as that for the brominated 2-hydroxy-4'-brom diphenyl methane.



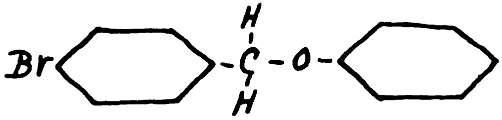
2 hydroxy 3-5-4' tri brom diphenyl methane

This is further evidence that the compound resulting from Claisen's reaction of phenol and p- brom benzyl chloride is 2 hydroxy 4' brom diphenyl methane.

The possible ether formation as mentioned earlier in the work will now be described. The oxygen- derivatives were extracted with petroleum ether which was then distilled off, and then the oxygen- derivatives were distilled in a vacum.

The portion coming from the mono brom- condensation has the following properties. It has a boiling point of 158.3-159° (2 mm.) and melts at 90-91°. The ether formed white flaky crystals when recrystallized from alcohol and water.

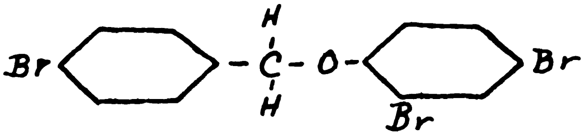
The Parr bomb determination showed it to have one atom of bromine as calculated from;



4 brom- benzyl phenyl ether

The other possible ether formation is that produced from 2-4 di brom phenol and p- brom benzyl chloride. This tri brom ether has a boiling point of 187-188° (2 mm.) and melts at 86-86.5°. It formed small glossy white needles when crystallized from alcohol and water.

The Parr bomb determination showed it to have three atoms of bromine as calculated from;

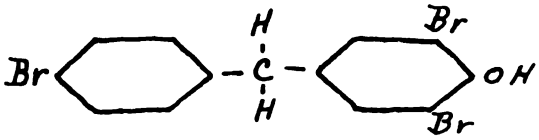


4 brom benzyl 2'-4' dibrom phenyl ether

In order to prove more definitely the position the benzyl group took in the aluminum chloride condensation we carried out the following reactions.

We dissolved the 4 hydroxy 4' brom diphenyl methane in chloroform and brominated with two equivalents of bromine. This tri brom para phenol when seeded with 4 hydroxy 2-6-4' tri brom diphenyl methane, solidified. It formed small white crystals when crystallized from gasoline. It boiled at 205-206° (2 mm.) and melted at 81-82°.

The Parr bomb determination showed it to contain three atoms of bromine as calculated from



4 hydroxy 2-6-4' tri brom diphenyl methane

In order to prove more definitely the position the bromine took in substitution in respect to the hydroxyl; we condensed 2-6 di brom phenol and p- brom benzyl chloride with the use of anhydrous aluminum chloride. (I wish to make note here of the cooperation and kind help of Mr. F.H. Maxfield in the preparation of the 2-6 di brom phenol also this condensation of 2-6 di brom phenol with p- brom benzyl chloride in the presence of aluminum chloride as a catalyst.)

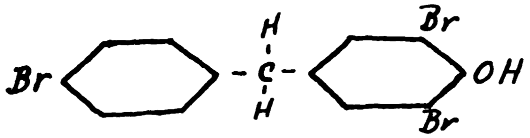
The 2-6 di brom phenol was prepared by adopting the method of preparation of 2-6 di chlor phenol (M. Tanaka and K. Kutani, J. Pharm, Soc; Japan, 541, 196-199 (1927)).

Twenty-four grams of phenol were added to twenty- six grams of sulphuric acid and heated gently 5--10 minutes to change all of the o- sulfonic acid to p- sulfonic acid. This mixture was then made alkaline with 30-40 % sodium hydroxide on standing some crystals of sodium phenol-p-sulfonate may separate out. Eighty-one grams of bromine was added and the contents in the flask was mixed with rotary action. Bromination takes place rapidly but smoothly and in five minutes the mass will resemble a mass of unworked butter. Their was no vigorous evolution of hydrogen bromide probably because of the sodium hydroxide present.

The three neck flask was set for steam distillation, also in a oil bath kept at 100-135°. The tri brom phenol is all distilled out, coming over as flakey material which is apt to clog the condenser. After the tri brom phenol mixture has cooled it is acidified with concentrated sulphuric acid and steam distilled again with the aid of a oil bath at 150-170°. An oil distilled off as the SO_3H is hydrolyzed off the para position. This oil crystallized in needles and may be separated from the water by the use of ether. When purified it boils at 248-253° atmospheric pressure. This experiment yielded 62.74 % of the theortical.

The 2-6 di brom phenol just described was condensed in the usual manner with the p- brom benzyl chloride with the use of anhydrous aluminum chloride. The condensed product was decomposed with ice and hydrochloric acid (1--1) and extracted with ether. When the ether evaporates off it leaves a solid which was crystallized from high test gasoline. It was found to have identical properties as the brominated compound with a boiling point of 205-206° (2 mm.) and melted at 81-82.5°.

The method of preparation of this compound allows only one possible formula:

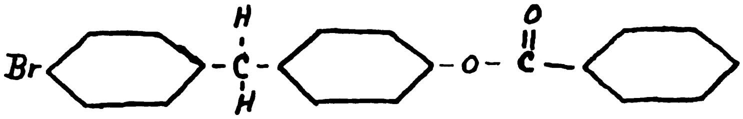


4 hydroxy ~~2~~-~~6~~-4' tri brom diphenyl methane
3-5

The Parr bomb determination varifies the above statement as it shows three bromine atoms are present.

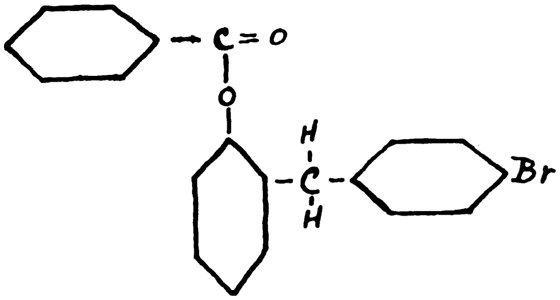
The benzoyl derivatives of the phenols were prepared by dissolving two grams of the phenol in pyridine and adding a ten per cent excess of the calculated amount of benzoyl chloride.

(1)



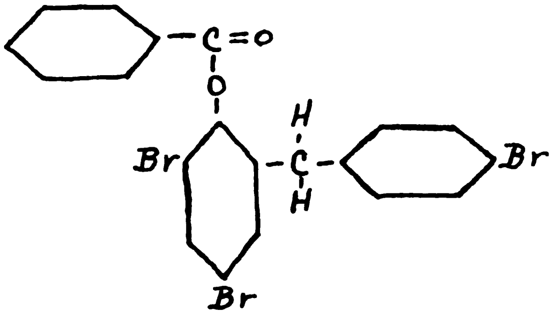
M. P. 118.5--120°

(2)



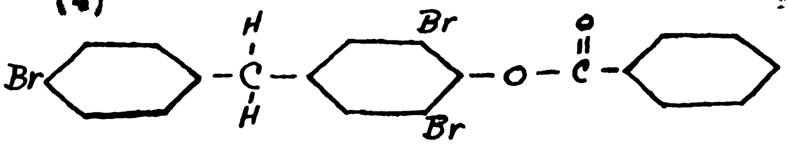
MP. 50-51°

(3)



M. P. 115-116°

(4)

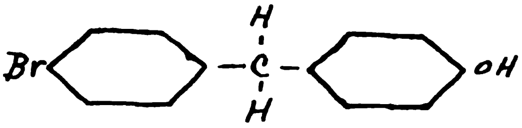


M. P. 144-145°

These benzoyl esters were crystallized from alcohol and water. The ortho compounds gave much more trouble in crystallizing than do the corresponding para isomer. The ortho benzoyl esters are oils and take a great deal of caution to separate them out in the alcohol-water solution.

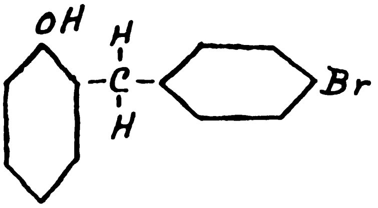
All of the above compounds found in this thesis were analyzed for bromine content, by the Parr bomb method. (J. F.

Lemp and H. J. Broderson, J. Am. Chem. Soc; 39, 2069 (1917)).



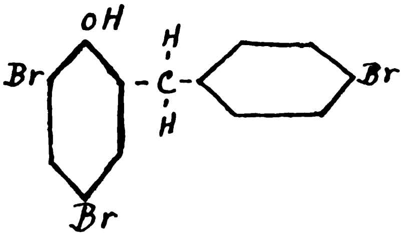
4 hydroxy 4' brom diphenyl methane

	Sample	Wt. bromine in sample	% Deter.	% Calc.
I	0.2230	0.06759	30.31	
II	0.2065	0.06114	29.60	
	Average		29.955	30.01



2 hydroxy 4' brom diphenyl methane

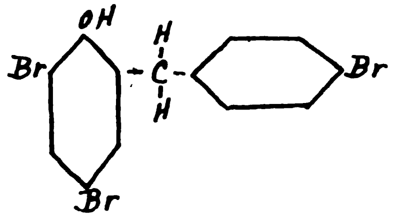
	Sample	Wt. bromine in sample	% Deter.	% Calc.
I	0.2079	0.06229	29.96	
II	0.2120	0.06356	29.98	
	Average		29.97	30.01



(By bromination)

2 hydroxy 3-5-4' tri brom diphenyl methane

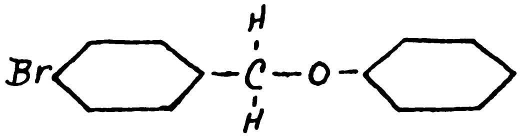
	Sample	Wt. bromine in sample	% Deter.	% Calc.
I	0.2101	0.11923	56.75	
II	0.2063	0.11731	56.86	
	Average		56.935	56.97



(By phenol and 2-4 di brom phenol)

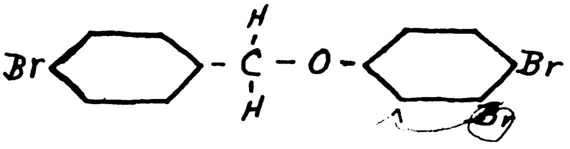
2 hydroxy 3-5-4' tri brom diphenyl methane

	Sample	Wt. bromine in sample	% Deter.	% Calc.
I	0.1989	0.11321	56.92	
II	0.2021	0.11509	56.95	
		Average	56.935	56.97



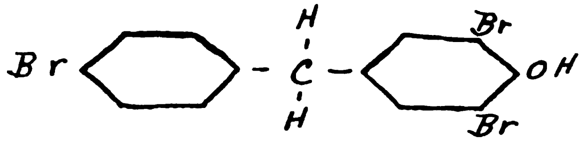
4brom benzyl phenyl ether

	Sample	Wt. bromine in sample	% Deter.	% Calc.
I	0.2104	0.06306	29.97	
II	0.2056	0.06168	30.00	
		Average	29.985	30.01



4 brom benzyl 2'-4' di brom phenyl ether

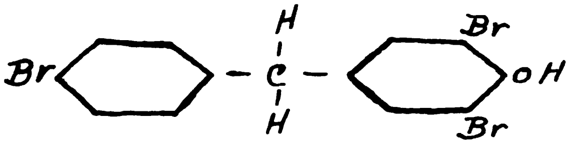
	Sample	Wt. bromine in sample	% Deter.	% Calc.
I	0.2031	0.11524	56.74	
II	o. 2025	0.11439	56.49	
		Average	56.615	56.97



(By bromination)

4 hydroxy 3-5-4' tri brom diphenyl methane

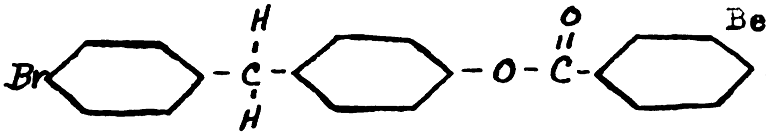
	Sample	Wt. bromine in sample	% Deter.	% Calc.
I	0.2122	0.11949	56.31	
II	0.2541	0.14415	56.73	
		Average	56.52	56.97



(By phenol and 2-6 di brom phenol)

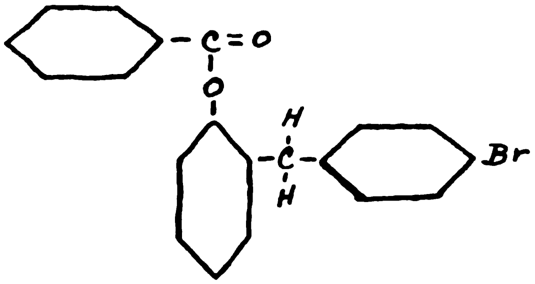
4 hydroxy 3-5-4' tribrom diphenyl methane

	Sample	Wt. bromine in sample	% Deter.	% calc.
I	0.1834	0.10546	57.50	
		Average	57.50	56.97



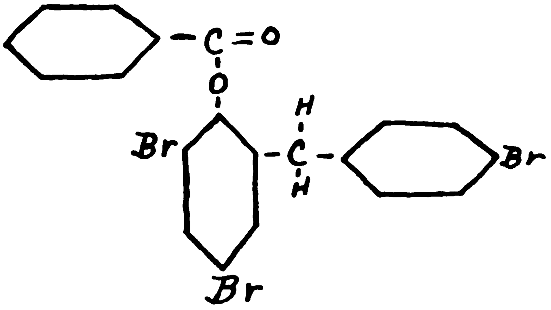
Benzoyl ester of 4 hydroxy 4' brom diphenyl methane

	Sample	Wt. bromine in sample	% Deter.	% Calc.
I	0.2014	0.04418	21.93	
II	0.2445	0.15064	21.61	
		Average	21.77	22.2006



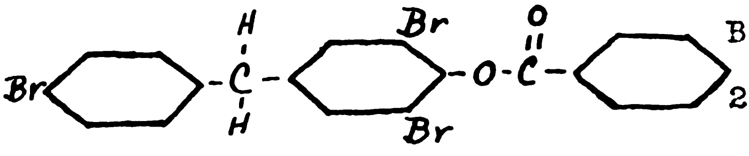
Benzoyl ester of 2 hydroxy 4' brom diphenyl methane

	Sample	Wt. bromine in sample	% Deter.	% Calc.
I	0.2291	0.05134	22.40	
II	0.2143	0.04710	21.98	
	Average		22.19	22.2006



Benzoyl ester of 2 hydroxy 3-5-4' tri brom diphenyl methane

	Sample	Wt. bromine in sample	% Deter.	% Calc.
I	0.2183	0.09891	45.31	
II	0.2016	0.09308	46.17	
	Average		45.74	45.85



Benzoyl ester of 4 hydroxy 2-6-4' tribrom diphenyl methane

	Sample	Wt. bromine in sample	% Deter.	% Calc.
I	0.2250	0.10397	46.21	
II	0.2125	0.09663	45.47	
	Average		45.84	45.85

Summary

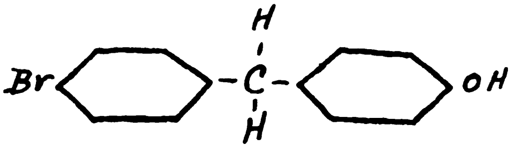
(1) Did not show the presence of a ortho substitution in the aluminum chloride condensations of p- brom benzyl chloride with phenol.

(2) Prepared and identified the following compounds:

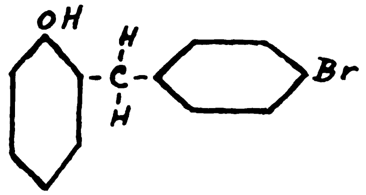
a. 4 hydroxy 4' brom diphenyl methane
b. 2 hydroxy 4' brom diphenyl methane
c. 2 hydroxy 3-5-4' tri brom diphenyl methane
d. 4 brom benzyl phenyl ether
e. 4 brom benzyl 2'-4' di brom phenyl ether
f. 4 hydroxy 2-6-4' tri brom diphenyl methane

A review of literature shows the preparation of 4 hydroxy 2-6-4' tri brom diphenyl methane (Zincke and Walter, Ann. <u>334</u>, 367-385 (1904)), but they did not give any proof of the structure. For the above formulas consult "Scheme of Condensation."

(3) Bromine entered into the following compounds,



and



in the unoccupied ortho and para positions of the phenolic ring.

Scheme of Condensation