THE CONDENSATION OF SOME BROMO BENZYL ALCOHOLS WITH PHENOLS

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THE CONDENSATION OF SOME HIGHER ALIPHATIC ALDEHYDES WITH PHENOLS

By

Du Yung Pu

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Abstract of Thesis

THE CONDENSATION OF SOME BROMOBENZYL ALCOHOLS WITH PHENOLS

by

WU DU YUNG

Para-bromo benzyl alcohol was prepared by the reaction of formaldehyde with p-brome phenyl magnesium bromide and subsequent hydrolysis. Ortho-bromo benzyl alcohol was prepared by the electrolytic reduction of o-bromo benzoic acid.

The para and ortho bromo benzyl alcohols were condensed with phenol in presence of aluminum chloride to give 4-hydroxy-4 bromo diphenyl methane and 4-hydroxy-2 bromo diphenyl methane respectively. The structure of these two compounds were confirmed by the direct bromination into 4-hydroxy-3,5,4-tribromo diphenyl methane and 4-hydroxy-3,5,2-tribromo diphenyl methane which were identical with the products obtained by the condensation of para and ortho bromo benzyl alcohols with 2,6-dibromo phenol.

The condensations took place para to the phenolic hydroxyl groups with the formation of benzylated phenols in 27-53% yields. No O-alkylation was observed.

The benzoyl and the benzene sulfonyl esters of the above phenols were also prepared.

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INTRODUCTION

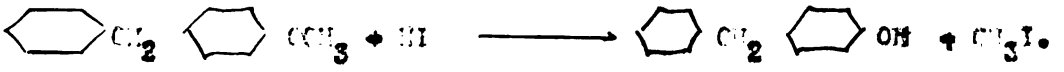
This thesis is a report on the condensation of ortho and para bromo benzyl alcohols with phenols and 2,6-dibromo phenols.

Considerable work has been carried out in this laboratory by Huston and coworkers on the condensation by aluminum chloride. Benzyl alcohol, α alkyl substituted benzyl alcohols and halo ring substituted benzyl halides have been condensed with phenols. As an addition to this work, it was considered desirable to condense certain bromo ring substituted benzyl alcohols with phenols.

A comparison was to be made between the yields and products obtained b use of bromo benzyl alcohols and those reported by other workers using the corresponding ring substituted benzyl halides.

HISTORICAL

The earliest work on benzylation of phenol was probably by E. Paterno (1) in 1872 who prepared benzyl phenol by heating gently a mixture of benzyl chloride and phenol in the presence of zinc dust. The benzyl phenol obtained had a boiling point of 175°-180°C. at 4-5 mm and crystallised out in white needles melting at 84°C. Benzyl anisole was prepared by the same method substituting anisole for phenol. The benzyl anisole thus prepared when treated with hydroiodic acid, gave methyl iodide and a benzyl phenol identical with the benzyl phenol by direct condensation.

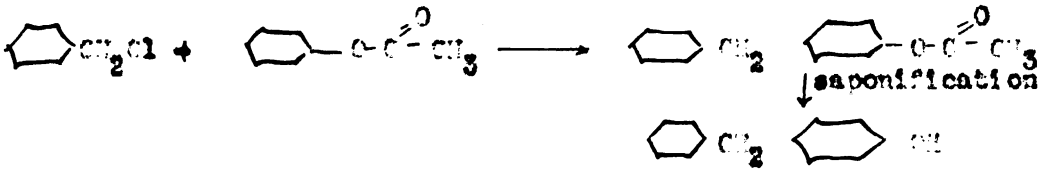


In 1874, Paterno and Filoti (2) prepared the derivatives of benzyl phenol with acetyl chloride, benzoyl chloride and bromine. By adding excess bromine to a solution of benzyl phenol in carbon disulfide, they obtained a compound melting at 175°C. which they assumed was a dibromide. Later workers (7) however questioned this compound.

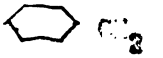
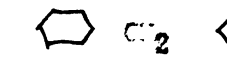
In 1875, Paterno and Filoti (3) prepared benzyl phenol by condensing benzyl alcohol and phenol with a mixture of sulfuric and acetic acids. They obtained a mixture of crystals and oils. Later, Rennie (4) showed that the principal crystalline compound in the mixture melted at 84°C. and was para benzyl phenol. The oil was shown to be ortho benzyl phenol.

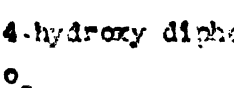
Perkins and Hodgkinson (5) in 1880, obtained benzyl phenyl acetate by the action of benzyl chloride on phenyl acetate. Saponification

of the benzyl phenyl acetate yielded benzyl phenol.



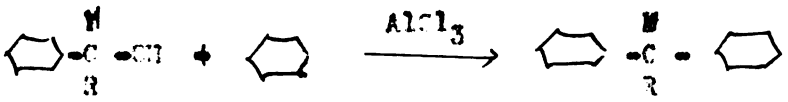
Leibmann (6) in 1882 used zinc chloride as a condensing agent in the condensation of benzyl alcohol with phenol.

In 1904, Zincke and Walter (7) prepared 4 hydroxy diphenyl methane () by condensing benzyl chloride and phenol with zinc dust. This compound was then brominated by the gradual addition of the calculated amount of bromine to its chloroform solution. They obtained a dibrominated product, 3,5-dibromo-4-hydroxy diphenyl methane () which melted at 87°C. It may be noted here that Zincke's dibromo compound did not have the same melting point as Paterno's (2).

Zincke and Walter also obtained a tribromo compound by adding an excess of bromine to 4 hydroxy diphenyl methane. They assumed that it was 3,5,4'-tribromo-4-hydroxy diphenyl methane () which melted at 88°C.

In 1910, Huston and Friedeman (8) condensed benzene and benzyl alcohol in the presence of aluminum chloride. The chief product was diphenyl methane.

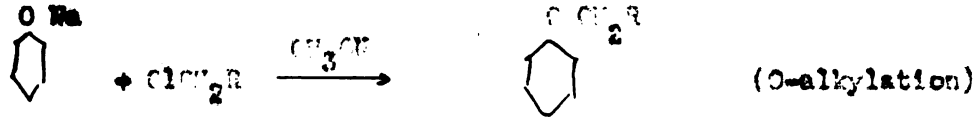
In 1918, Huston and Friedeman (9) studied the condensation of benzene with the ∝substituted benzyl alcohols (phenyl methyl carbinol, phenyl ethyl carbinol and diphenyl carbinol) in presence of aluminum chloride



They concluded that the presence of an α methyl or ethyl group gave lower yields while the presence of an α phenyl group gave better yields.

Huston (10), in 1920, condensed benzyl alcohol with phenol and obtained a good yield of p-brono benzyl phenol.

In 1923, Claisen (11) published work on the alkylation of phenol. He found that when the sodium derivative of a monohydric phenol was heated with an alkyl halide in a "nondissociating" medium, such as toluene, the predominating reaction was C-alkylation in a position ortho to the hydroxy group. However, when a "dissociating" medium, such as methyl alcohol was used, the predominating reaction was O-alkylation with the formation of an ether.



(O-alkylation)

(C-alkylation)

The ether and the phenol could be separated by treating with alcoholic potassium hydroxide. The alcoholic potassium hydroxide formed the potassium phenolate of the phenol which was soluble. The mixture was then extracted with petroleum ether to remove the ether product. Petroleum ether was better than ethyl ether since the latter also extracted a portion of the phenolic product. The petroleum ether

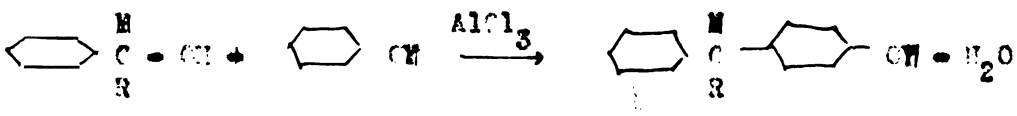
dissolved the other product and left the phenolic product in aqueous solution. The aqueous layer was then acidified with hydrochloric acid to liberate the phenol from the phenolate and then extracted with ethyl ether. The ether layer was separated, excess ether evaporated and the phenol isolated.

The Claisen method served as a process for the preparation of ortho benzyl phenols.

In 1924, Huston (12) condensed 1 mole of benzyl alcohol with 1.1 mole of phenol in petroleum ether using 0.5 mole of aluminum chloride as a condensing agent and a temperature below 30°C. P-benzyl phenol was obtained. The methyl and ethyl ethers of the p-benzyl phenol were also prepared in good yields by condensing benzyl alcohol with anisole and phenetole.

Huston and Sager (13) in 1924, studied the action of allyl alcohol in benzene in the presence of aluminum chloride.

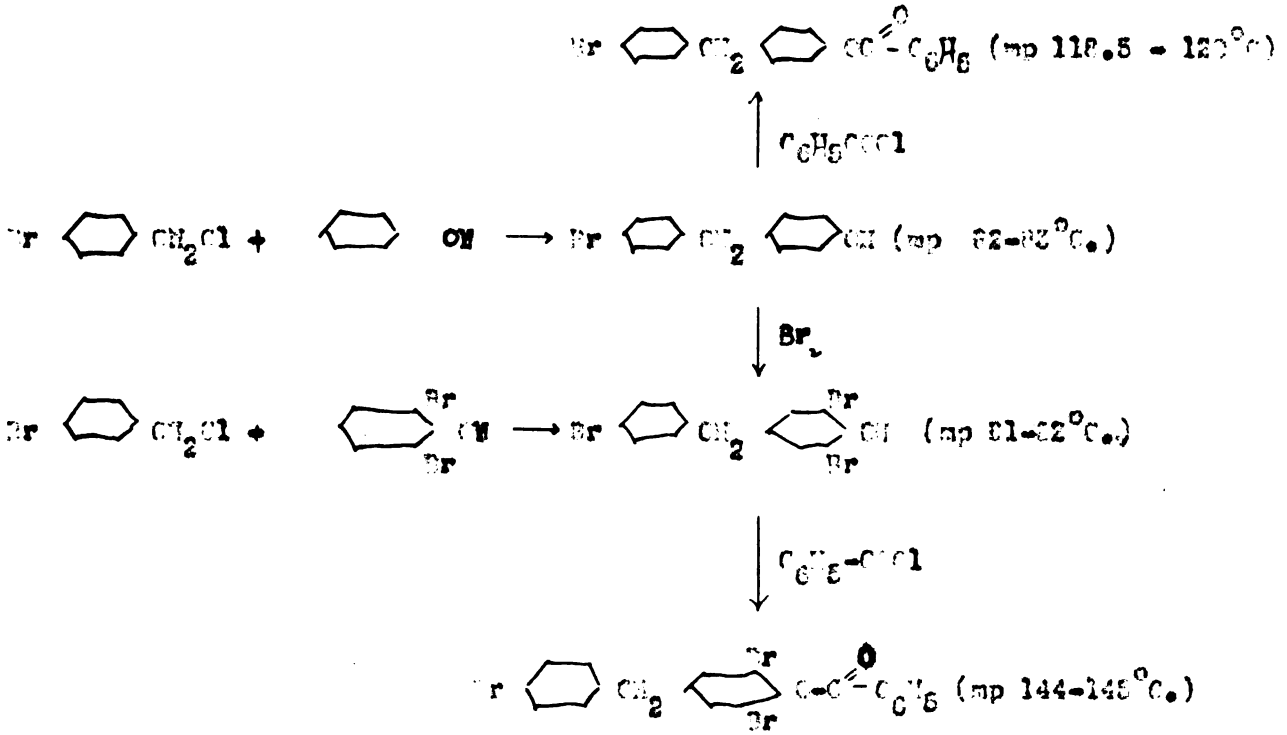
In 1927, Huston, Lewis and Grotemut (14) condensed methyl phenyl carbinol, ethyl phenyl carbinol and benzhydrol with phenol in presence of aluminum chloride.



A relatively large yield obtained in the condensation using benzhydrol confirmed the fact already observed (13) that unsaturation on the carbon atom, adjacent to the alcoholic group increased the reactivity of the hydroxyl toward the dehydrating effect of aluminum chloride.

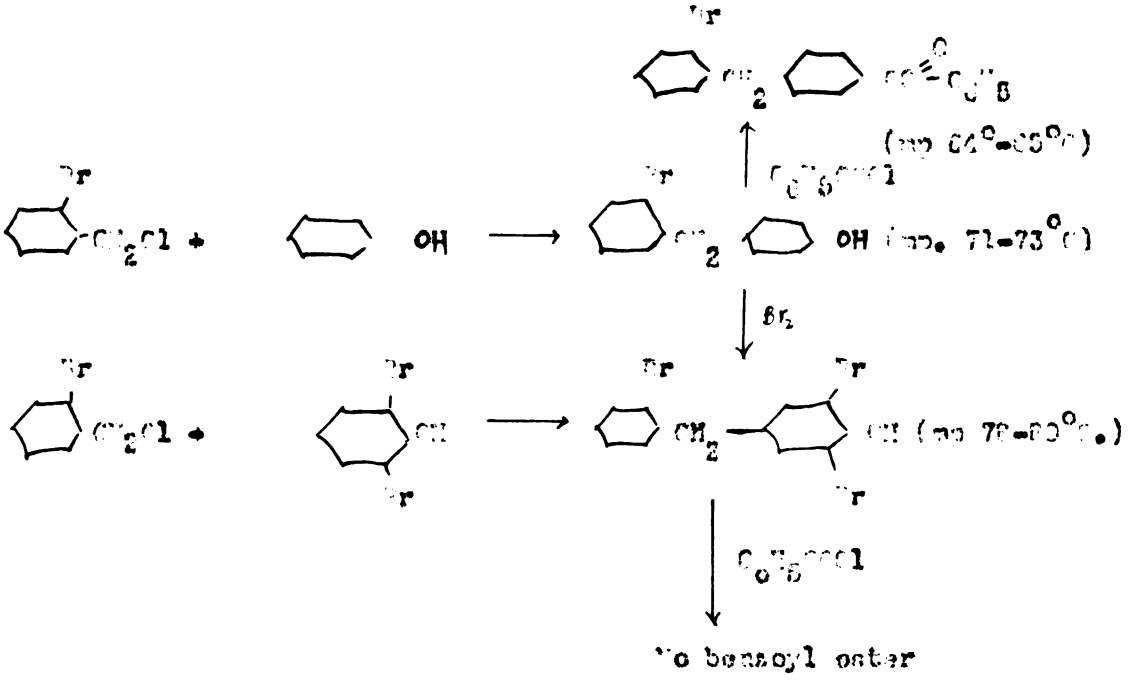
In 1920 (15) Maxfield studied the effect of varying proportions of phenol, benzyl alcohol and aluminum chloride on the yield and on the relative proportion of ortho and para benzyl alcohol obtained. He found that three moles of phenol, one mole of benzyl alcohol and half mole of aluminum chloride gave the highest yield.

D'Arcy (16) in 1930, prepared the bromo-derivatives of benzyl phenol. He condensed phenol and 2,6-dibromo phenol with para bromo benzyl chloride and obtained 4 hydroxy 4' bromo diphenyl methane and 4-hydroxy 3,5,4'-tribromo diphenyl methane respectively. The latter could also be prepared by the direct bromination of 4 hydroxy 4' bromo diphenyl methane. The benzoyl esters of both compounds were also prepared.



Mayerweather (17) in 1931 prepared the ortho bromo benzyl phenols. He condensed phenol and 2,6-dibromo phenol with ortho bromo benzyl

chloride and obtained 4-hydroxy-2'-bromo diphenyl methane and 4-hydroxy-3,5,2'-tribromo diphenyl methane respectively. The latter could also be obtained by the direct bromination of the former. The benzoyl ester of 4 hydroxy 2' bromo diphenyl methane was prepared but no benzoyl ester could be prepared from 4-hydroxy-3,5,2'-tribromo diphenyl methane.



In 1932, Klarmann, Gates and Shternov (18) studied the anti bacterial action of different halogen substituted benzyl phenols. A number of mono and dihalogen derivatives of the 2 and 4 hydroxy diphenyl methanes and their alkyl homologs had been synthesized either by direct benzylation of halogen phenols or by halogenation of benzylated phenols. The benzyl group was directed to either the ortho or para position by using the Claisen method or by zinc chloride as a condensating agent.

In 1933, Huston, Neely, Mayerweather, D'Arcy, Warfield, Pallard and Lewis (19) published an article on bromo derivatives of benzyl

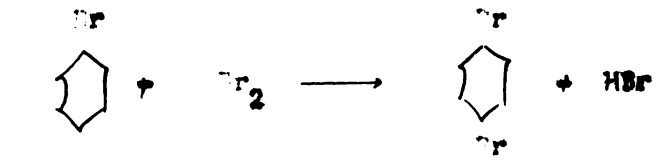
phenols. Phenol was condensed with 2-bromo benzyl chloride, 3-bromo benzyl chloride and 4-bromo benzyl chloride by the Claisen and by the aluminum chloride method.

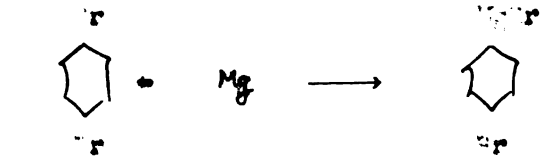
As a means of determining the structure of the compounds prepared in these reactions, condensations of each of three bromo substituted benzyl chlorides were made with 2,4-dibromo phenol by the Claisen method and with 2,6-dibromophenol by the aluminum chloride method. The tribromo benzyl phenols obtained by these condensations were also prepared by the cold bromination of the corresponding monobromo benzyl phenol in chloroform. In no case was it possible to introduce bromine into the benzyl nucleus, the bromine entered only the unoccupied ortho or para position of the phenolic ring.

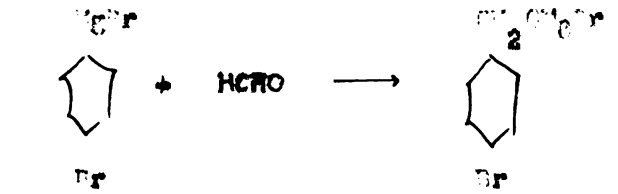
I Materials

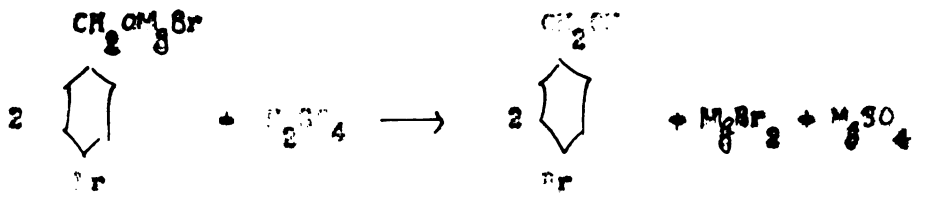
1. p-bromo benzyl alcohol

p-bromo benzyl alcohol was prepared through the following reactions.









(a) Preparation of dibromobenzene

Seven hundred and thirty grams of bromo benzene and 20 g. of iron filing were placed in a three neck three liter round bottom flask

fitted with a reflux condenser and a dropping funnel. Eight hundred and twenty grams of bromine were then added to the reaction by means of the dropping funnel in the following fashion. Ten cc of bromine were added and the flask heated on a steam bath for a few minutes in order to start the reaction. As soon as the reaction had started, bromine was added gradually over a four hour period. The reaction was exothermic and cooling was necessary. A cold towel wrapped around the neck of the flask helped control the reaction as it facilitated condensation without materially decreasing the reaction rate.

After all the bromine had been added, the flask was heated for 15-20 minutes on a steam bath to complete the reaction. Upon cooling, the reaction product separated as a solid mass. The mass was washed first with 5% sodium bisulfite solution to destroy any excess bromine, then with 5% Na_2CO_3 and then with water. The liquid was removed from the solid mass by decantation. The solid was pressed on a porous plate to remove any adhering water and unreacted bromobenzene.

The crude product was then distilled. It distilled without decomposition at 218°C. at 700 mm. The distilled product was recrystallized from alcohol. m.p. 86°C. The yield was 770 gm. (71% of the theoretical amount).

(b) Preparation of p-bromo phenyl magnesium bromide

In a three liter three neck round bottom flask fitted with 500 cc dropping funnel, mechanical stirrer and reflux condenser were placed 36.5 gm. of magnesium (1.5 mole) in 250 cc anhydrous ether (the anhydrous ether from the stock room was dried over sodium before use).

The reaction was protected from moisture and carbon dioxide by a drying tube at the top of condenser filled with soda lime and by a glycerine sealed stirrer. A few crystals of iodine were then added as a catalyst.

A mixture of 354 gm (1.5 mols) of *p*-dibromobenzene in 500 cc anhydrous ether (or enough anhydrous ether to dissolve the dibromobenzene) were then placed in the dropping funnel. Thirty to fifty cc were added without stirring. The flask was warmed with hot water until the iodine color disappeared which was an indication that the reaction had started.

The remainder of the halide solution was then added slowly with stirring at a rate that was just fast enough to maintain a gentle reflux. Some external cooling with water was employed but the reaction mixture was kept warm to facilitate the reaction.

After all the halide had been added, stirring was continued for fifteen minutes or until the ether no longer refluxed. The resulting product for the most part was a homogeneous solution but there remained traces of unreacted magnesium.

(c) The preparation of p-bromo benzyl alcohol

The dropping funnel was now replaced by a wide glass tube about 18 mm internal diameter which reached almost to but not below the surface of the liquid. The tube connected directly with a 500 cc round bottom flask containing 90 gm. of paraformaldehyde which had been previously dried for two days in a vacuum desiccator over phosphorus pentoxide. This drying is important since commercial paraformaldehyde contained 3-5% water.

The stirrer was started and the flask containing the paraformaldehyde was heated in an oil bath or by a mantle to 150-200°C. The formaldehyde formed was carried over into the Grignard reagent by a slow current of dry nitrogen. The inert atmosphere of nitrogen was found to partially inhibit the polymerization of formaldehyde.

The reaction was carried to completion as shown by a negative reaction to Michler's ketone. To half cc sample of the reaction mixture, one half cc of 1% Michler's ketone in dry benzene was added. To this mixture, 1 cc of water was added slowly and then several drops of 0.2% solution of iodine in glacial acetic acid. A characteristic greenish blue color is a positive test for the presence of Grignard reagent.

After the reaction was complete, the reaction mixture was poured into a 3 L. beaker containing 500 gm. of crushed ice. When hydrolysis was complete, as shown by lack of further reaction, 100 gm. of sulfuric acid (300 cc of 30% H_2SO_4) was added to dissolve the magnesium hydroxide. An excess of sulfuric acid was usually required in order to hydrolyse the formal formed if an excess of formaldehyde was used.

The solution was then extracted with ether, the ether layer separated and the aqueous layer was extracted several times with ether. The other extracts and the ether layer were combined and the ether was removed by distillation.

The crude product was subjected to vacum distillation at 15 mm. The results of one fractionation were as follows:

up to 100°C. 8 gm.

100° - 110°C. 17 gm.

110° - 130°C. 52 gm.

130° - 140°C. 27 gm.

140° - 143°C. 20 gm.

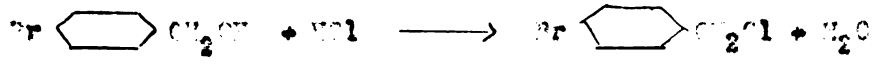
143° - 148°C. 22 gm.

148° - 170°C. 13 gm.

The lower boiling fractions were bromobenzene and p-dibromobenzene the higher fractions might be p-xylylene glycol  . The fraction boiling between 140-143°C. at 12 mm. was considered to be the p-bromo benzyl alcohol. This fraction crystallized on standing and was recrystallized from ethyl alcohol yielding 92 gm. of a pure product melting at 76-77°C. The fractions boiling between 130-140°C. and 143-148°C. at 15 mm. also crystallized and were combined and recrystallized twice from alcohol to give 38 gm. of p-bromo benzyl alcohol melting at 75-76°C. Total yield of p-bromo benzyl alcohol was 130 gm. or 40% based on dibromobenzene.

Another two trials were carried out with 47% and 43% yield respectively.

2. <u>p-bromo benzyl chloride</u>



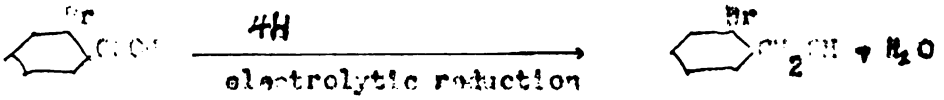
Twenty grams of p-bromo benzyl alcohol were allowed to react with 100 cc of concentrated hydrochloric acid first by shaking reactants together for one hour and then refluxing them on a steam bath for

another one hour. Since the CH_2Cl group is activated by the benzene nucleus and the substituted Br, ready reaction with hydrochloric acid was expected. The product was then cooled, washed with cold 5% Na_2CO_3 solution and then with water. The crude crystalline product was recrystallized from alcohol to yield 20 gm. of o-bromo benzyl chloride m.p. 41°C. The yield was 91% based on o-bromo benzyl alcohol.

The crude product was purified by distillation. Distillation at atmospheric pressure at 235°C. caused slight decomposition.

In order to test for chlorine, a sample was refluxed with alcoholic potassium hydroxide for a few minutes. The resulting solution after acidifying with dilute nitric acid gave a positive test for chloride with silver nitrate.

3. <u>o-Bromo benzyl alcohol</u>



The o-bromo benzyl alcohol was prepared by the electrolytic reduction of o-bromo benzoic acid. The apparatus used was nearly the same as that given by Solomon and Johnson (20) with the exception that one cell was used instead of four cells connected in series, a 15 volts D. C. current was used instead of 110 volts, and 200 cm^2 cathode surface area was used instead of 100 cm^2.

Thirty-five grams of o-bromo benzoic acid, prepared from anthranilic acid through diazotization and Sandmeyer reaction (21) and purified by dissolving in alkali and reprecipitated in acid were dissolved

in 200 cc of 80% alcohol. Twenty-seven cc of concentrated sulfuric acid were then added. The solution was placed in a 1000 cc beaker and served as the cathode liquid. One hundred and twenty cc of 20% H_2SO_4 were then placed in a porous cup and used as the anode liquid. As the porous cup may contain some iron salts which inhibit reduction, it was thoroughly cleaned by forcing first a dilute solution of sodium hydroxide and then dilute sulfuric acid through the walls to remove any metallic impurities.

The stirrer was started, the current turned on and the resistance so adjusted that the ammeter recorded 10-12 amp. The temperature was kept at about 30°C. by surrounding the beaker with a cold water bath.

The theoretical ampere hours required were $\frac{4 \times 96500 \times 25}{3200} =$ 18.8 amp. hrs.

As the current efficiency was very low, 3-4 times the amp. hrs was usually required. After the determined amount of current had been passed, the current was stopped and the cathode liquid was used for the isolation of o-bromo benzyl alcohol.

The alcohol was first evaporated off at low temperature. The solution was then neutralized with ammonium hydroxide. After neutralization, the solution usually separated into two layers. The upper layer was an alcoholic solution of o-bromo benzyl alcohol and the lower layer an aqueous layer containing ammonium sulfate and any unreacted o-bromo benzoic acid as its ammonium salt.

The two layers were then separated and the alcoholic layer was evaporated at low temperature to a small volume and precipitated with ice water. The o-bromo benzyl alcohol separated as a solid mass and was filtered off. The filtrate was saturated with ammonium sulfate and extracted several times with ether. The ether was evaporated and the residue combined with the main precipitate. The crude product was purified by suspending in water, neutralizing with ammonium hydroxide and filtering off the precipitate. The precipitate was washed with water and recrystallised from alcohol m.p. 82.4-83°C. (literature 80°C.). The yield was 13 gm or 40% based on o-bromo benzoic acid.

The aqueous layer was then acidified with sulfuric acid. During acidification, the unreacted o-bromo benzoic acid was precipitated. The precipitate was filtered off, washed with water and then recrystallised from hot water, m.p. 148°C. The recovered o-bromo benzoic acid could be used again for reduction.

Another two trials were carried out with yields of 15% and 30% respectively.

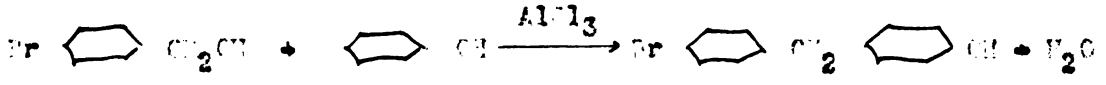
4. 2,6-dibromo phenol

The 2,6-dibromo phenol used in this experiment was prepared according to the method of Huston and Neeley (22). A redistilled and recrystallised product boiling at 130°C. at 15 mm. and melting at 56°C. was used in the following experiments.

II Condensation

All condensations were carried out by a standard procedure developed in this laboratory for aluminum chloride condensation. The bromo benzyl alcohol and phenol were suspended in petroleum ether kept below 30°C. and finely divided aluminum chloride was added in portions.

1. Condensation of p-bromo benzyl alcohol with phenol



Twenty-four grams of p-bromo benzyl alcohol and 30 gm of phenol were suspended in 100 cc petroleum ether in a 500 cc three neck flask fitted with a mechanical stirrer, a reflux condenser and a thermometer. Ten grams of aluminum chloride were added in small portions at such a rate that the temperature was maintained between 20-30°C.

After all the aluminum chloride had been added, stirring was continued for another hour and then the reaction mixture was allowed to stand over night. The reaction mass was decomposed with ice and hydrochloric acid. The organic layer was separated and the aqueous layer extracted three times with ether. The organic layer and the ether extracts were combined and the ether removed by distillation. The residue obtained was subjected to vacuum distillation (3 mm).

Fractions collected were as follows:

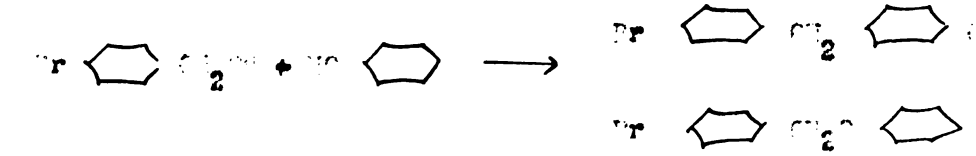
up to 90°C.	17 gm.
90° - 170°C.	2 gm.

170° - 173°C.	21.5 gm.
173°C. up	3 gm.

The first fraction was unreacted phenol. The 170-173°C. fraction was the expected product which solidified on cooling. Recrystallization from petroleum ether gave a product melting at 64.0-65.2°C. A yield of 18 gm. corresponding to 37% of theoretical was obtained. Since the melting point of the product did not check with that reported by Murray (11) two more condensations were carried out to yield products m.p. 65°C. in yields of 31 and 41% respectively.

The product was again subjected to repeated vacuum distillation. Four redistillation and two recrystallization from petroleum ether gave a product still melting at 65°C.

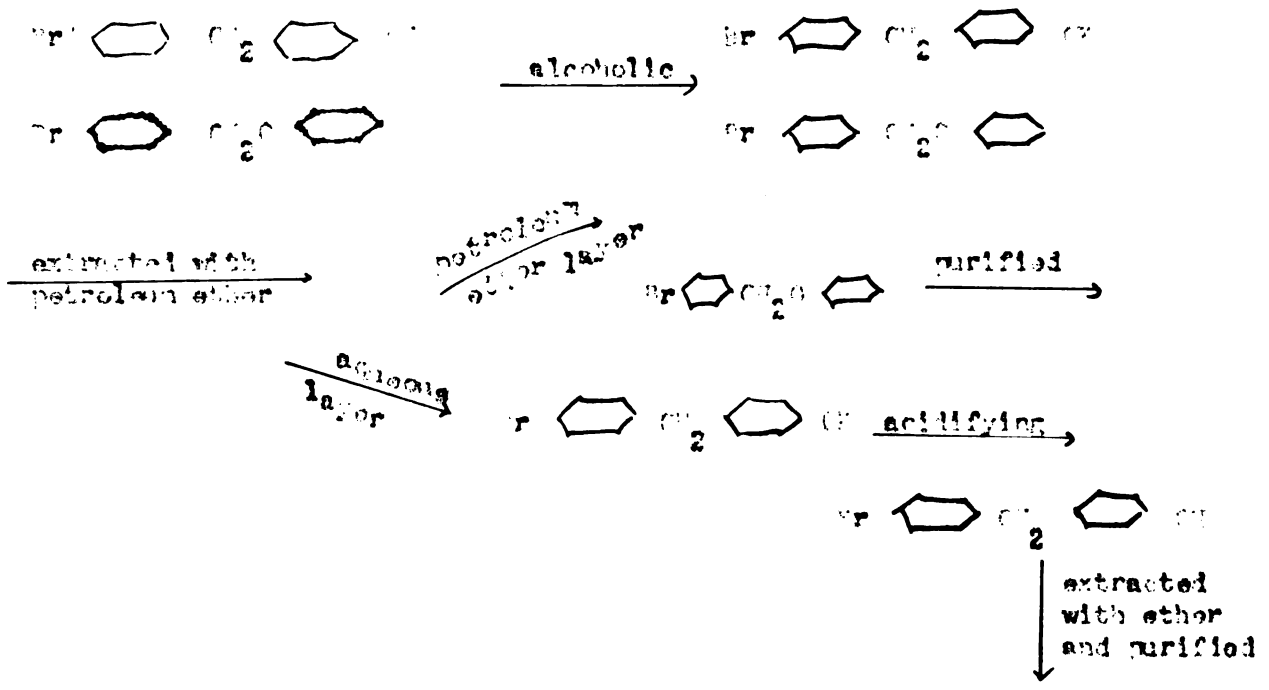
As there might have been some o-alkylation together with C-alkylation to yield a mixture of phenols and ethers,



the product from the aluminum chloride condensation was treated with an excess of Claisen alcoholic potash solution (350 gm. KOH dissolved in 600 cc. of water and made up to one liter with methyl alcohol) and then extracted with petroleum ether. The potassium salt of phenol is insoluble in petroleum ether while the ether is soluble. The petroleum ether was separated and evaporated but contained no ether product. This indicated that no o-alkylation had occurred.

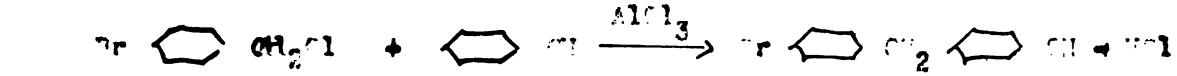
The lower phenolic layer was then treated with ice and neutralized with concentrated hydrochloric acid. After cooling, the phenol derivative

was removed by extraction with ether, the excess ether distilled off and the remaining solid product recrystallized from petroleum ether m.p. 64.0-65.2°C.



2. Condensation of p-bromo benzyl chloride with phenol

Since D'Arcy used p-bromo benzyl chloride in condensation with phenol, another trial was made using this substance as the starting material.

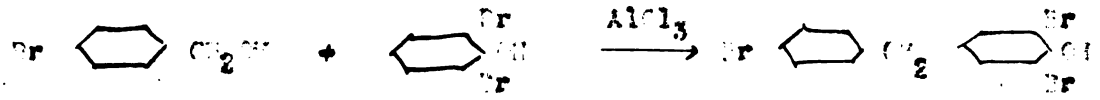


Twenty grams of p-bromo benzyl chloride and 30 gm. of phenol were condensed in presence of 10 gm. of $AlCl_3$ by the already outlined procedure. Upon fractionation at 3 mm. the following fractions were obtained:

up to 170°C.	22.6 gm.
170° - 175°C.	14.4 gm.
175° up	8 gm.

The 170-175°C. fraction solidified and was recrystallized twice from petroleum ether to yield 12.4 gm. (40%) of a product melting at 64.6-65.2°C. Mixed melting point with the product obtained from the condensation of p-bromo benzyl alcohol with phenol gave no depression.

3. Condensation of p-bromo benzyl alcohol with 2,6 dibromophenol



Twenty grams of p-bromo benzyl alcohol were condensed with 32.4 gm. of 2,6-dibromophenol (20% excess) in presence of 10 gm. of aluminum chloride according to the already outlined procedure.

The following fractions were obtained by vacuum distillation at 3 mm.

up to 100°C.	13.5 gm.
100° - 120°C.	2 gm.
120° - 210°C.	1 gm.
210° - 220°C.	23.5 gm.
220° up	0 gm.

Since decomposition was noted on the first distillation of this type of high boiling reaction mixture, the following precautions were observed:

(a) A metal alloy bath was used instead of mantle since a mantle causes more local heating than a metal bath.

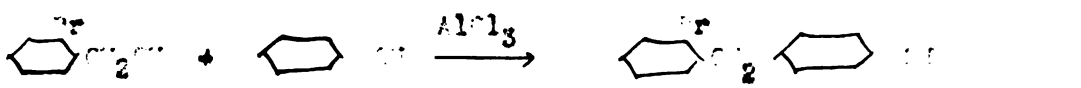
(b) The flask was cooled to room temperature before breaking the vacuum and each time after the receiver was changed, the distillation apparatus was evacuated before heat was applied to the distilling flask. In one case where these precautions were not observed, considerable decomposition was noted.

The fraction boiling between 210°-220°C. was then recrystallised twice from petroleum ether to yield 20 gms. of a product melting at 72. - 73.5°C. This corresponds to a 41% yield based on p-bromo benzyl alcohol.

In order to determine whether there was any other product formed during the condensation, the product was treated with Claisen reagent and then extracted with petroleum ether. No other product could be isolated from the petroleum ether layer.

Two more condensations were carried out and gave a product melting at 73°C. with yields of 43 and 40% respectively.

4. Condensation of p-bromo benzyl alcohol with phenol



Ten grams of p-bromo benzyl alcohol were condensed with 20 gm. of phenol in presence of 8 gm. of aluminum chloride. After decomposition and extraction, the residue was subjected to vacuum distillation at 3 mm. The fractions collected were:

up to 70°C.	11.3 gm.
90° - 100°.	1.5 gm.

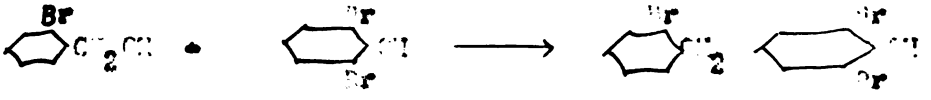
150° - 160°C.	1.5 gm.
160° - 170°C.	7.2 gm.
170°C. up	5 gm.

The fraction boiling between 160-170°C. was recrystallised several times from petroleum ether to yield 5.7 gm. (41%) of a compound melting at 84.6-85.2°C.

Some oily product was isolated from the 160-170°C. fraction but the amount was very small and therefore it was not identified.

No other product could be isolated from the 160°-170°C. fraction by treating with Claisen reagent followed by extraction with petroleum ether.

5. Condensation of o-bromo benzyl alcohol with 2,6-dibromo phenol



Ten grams of ortho bromo benzyl alcohol were condensed with 27 gm. of 2,6-dibromo phenol in presence of 7 gm. of aluminum chloride. After decomposition and extraction, the residue was subjected to vacuum distillation at 3 mm. The fractions collected were:

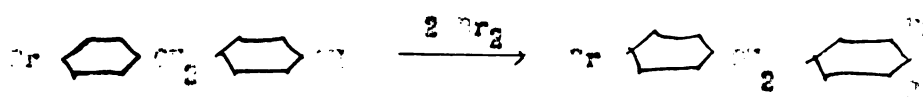
up to 130°C.	16 gm.
130° - 205°C.	4 gm.
205° - 215°C.	7.7 gm.
215° up	4 gm.

The fraction boiling between 205-215°C. solidified and was recrystallised several times from petroleum ether to yield 6.0 gm. (27%) of a compound melting at 81.6-82.0°C.

The product was then treated with Claisen reagent followed by extraction with petroleum ether. No other product could be isolated.

III Bromination

1. Bromination of 4-hydroxy-4'-bromo-diphenyl methane

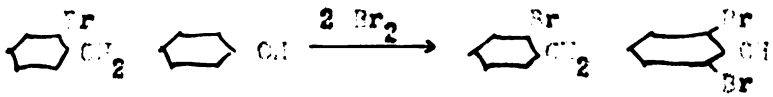


Five grams of 4-hydroxy-4'-bromo-di-phenyl methane were dissolved in 40 cc. of chloroform in an erlenmeyer flask and placed in an ice salt water bath. Twelve grams of bromine (about 10% excess for the preparation of tribromo derivative) were dissolved in chloroform and added bromine into the phenol solution. The solution was stirred continuously and then allowed to stand over night. The mixture was then poured into a beaker and the chloroform removed by evaporation. The residue was washed with 5% sodium bisulfite to destroy any excess bromine, then with 3% Na_2CO_3 to remove any HBr and finally with water to free it from any alkali. If the crude material was colored, it was dissolved in ether and decolorized with charcoal. The charcoal was filtered off and the ether solution evaporated to dryness. The product was then recrystallized from petroleum ether to form colorless needles melting at 84°C. A yield of 12.6 gm (87%) was obtained.

The product was purified through the formation of crystalline benzoyl and benzene sulfonyl esters followed by subsequent hydrolysis to a compound melting at 88.4-89.4°C. The details will be discussed later. Mixed melting point with the product obtained from condensation

of p-bromo benzyl alcohol with 2,6-dibromo phenol gave no depression.

2. Bromination of 4-hydroxy-2'-bromo diphenyl methane



Three grams of 4-hydroxy-2'-bromo diphenyl methane were brominated with 4 gm. of bromine according to the procedure already described. The product after recrystallization from petroleum ether melted at 91.0-91.6°C. Four grams of colorless needles were obtained which was an 83% yield. Mixed melting point with the product obtained from condensation of o-bromo benzyl alcohol with 2,6-dibromo phenol gave no depression.

DATA ON SYNTHESIZED 4-HYDROXY DIPHENYL METHANES

Substituted 4-hydroxy diphenyl methanes	Method of preparation	Yield	Melting point In this work	Melting point literature
4'-bromo	Condensation of p-bromo benzyl alcohol with phenol	48-53%	84.6-85.2°C.	82-83°C. (19)
4'-bromo	Condensation of p-bromo benzyl chloride with phenol	48%	84.6-85.2°C.	82-83°C. (19)
3,4'-tribromo	Bromination of 4-hydroxy-4'-bromo diphenyl methane	87%	80.4-80.4°C.	81-82°C. (19)
3,5,4'-tribromo	Condensation of p-bromo benzyl alcohol with 2,6-dibromophenol	40-44%	89.8-90.4°C.	81-82°C. (19)
2'-bromo	Condensation of o-bromo benzyl alcohol with phenol	41%	84.6-85.2°C.	71-73°C. (19)
3,2'-tribromo	Bromination of 4-hydroxy-2'-bromo diphenyl methane	83%	81.0-81.6°C.	78-80°C. (19)
3,5,2'-tribromo	Condensation of o-bromo benzyl alcohol with 2,6-dibromophenol	27%	81.0-82.0°C.	78-80°C. (19)

IV Derivatives

1. Benzoyl Esters

The benzoyl esters of all the phenols were prepared as follows:

To 0.5 gm. of the phenol, 10% excess of benzoyl chloride was added and then 5-10 cc. of 10% sodium hydroxide. The mixture was shaken vigorously and the benzoyl esters usually crystallised out after several minutes. The crystals were filtered off, washed with water, then with dilute acid and finally with water and then recrystallized from alcohol to a constant melting point. In some cases, the esters did not crystallize out readily but adhered to the glass tube as a sticky mass. This sticky material was washed with water and then extracted with ether, after which the ether was evaporated and the residue recrystallized from alcohol to a constant melting point.

The sticky mass, after being thoroughly washed with water by decantation, could be changed into a nonsticky form by treatment with a few cc of alcohol followed by stirring. The solution was then diluted with water, washed with dilute alkali and water and recrystallised from alcohol.

2. Benzene sulfonyl esters

The benzene sulfonyl esters of the various phenols were prepared either by the same procedure as that for the benzoyl esters using benzene sulfonyl chloride as the acylating agent or by the pyridine method in the case of easily hydrolyzable esters.

The procedure for the pyridine method was as follows:

Two grams of the phenol were dissolved in 5 gm. of dry pyridine and a 10% excess of the calculated amount of benzene sulfonyl chloride was added. After standing over night, an equal volume of water was added slowly and the mixture shaken until all the benzene sulfonyl chloride had hydrolyzed. The mixture was poured into dilute sulfuric acid and extracted with ether. After being washed with cold dilute sodium carbonate, the ether was removed from the ether extract by distillation and the product recrystallized from ethyl alcohol to a constant melting point.

"[illegible] (of the [illegible] and [illegible] of the [illegible] of the [illegible] 4-hydroxy [illegible])

Substituted 4-hydroxy diphenyl methanes	Purpose of diphenyl methanes	Esters prepared	Melting point In this work	Literature
4'-bromo	condensation	benzoyl	127-128°C.	118.5-120°C.(19)
3,5,4'-tribromo	condensation	benzoyl	143-144.5°C.	144-145°C. (19)
3,5,4'-tribromo	bromination	benzoyl	143-143°C.	144-145°C. (19)
2'-bromo	condensation	benzoyl	77.0-78.4°C.	84-85°C. (19)
3,5,2'-tribromo	condensation	benzoyl	106.5-108.2°C.	--
3,5,2'-tribromo	bromination	benzoyl	107-108°C.	--
4'-bromo	condensation	benzene sulfonyl	92.0-92.2°C.	--
3,5,4'-tribromo	condensation	benzene sulfonyl	143.0-143.2°C.	--
3,5,4'-tribromo	bromination	benzene sulfonyl	142.5-143°C.	--

V Hydrolysis of Derivatives

1. Hydrolysis of Benzoyl Esters

Three grams of the benzoyl ester were added to a solution of 10 cc of diethylene glycol, 2 gm. of potassium hydroxide and 4 cc. of water. The mixture was refluxed for one hour under a reflux condenser. The solution was then cooled, diluted with water and acidified with dilute sulfuric acid. A mixture of benzoic acid and the original phenol separated out after cooling. The separated precipitate was filtered off and the filtrate extracted with ether. The ether was evaporated and the residue combined with the original precipitate. The combined precipitates were then treated with dilute ammonium hydroxide or sodium bicarbonate to dissolve the benzoic acid. The phenol was filtered off, washed with water and recrystallized from alcohol to a constant melting point.

2. Hydrolysis of benzene sulfonyl esters

The benzene sulfonyl esters were hydrolyzed by the same procedure as previously outlined. After acidifying, the benzene sulfonic acid formed is soluble in water and thus can be separated from phenol by filtration. The filtrate was extracted with ether, the ether evaporated and the residue combined with the main precipitate. The combined precipitates were washed with water and recrystallized from alcohol to a constant melting point.

MELTING POINTS OF PHENOLS OBTAINED BY THE HYDROLYSIS OF ESTERS

Esters hydrolysed	Method of which the esters were made	Phenols isolated	Melting points of phenols
Benzene sulfonyl ester of 4-hydroxy-4'-bromo diphenyl methane	Condensation	4-hydroxy 4'-bromo diphenyl methane	64.5-65.5°C.
Benzoyl ester of 4-hydroxy-3,5,4'-tribromo diphenyl methane	Condensation	4-hydroxy 3,5,4'-tribromo diphenyl methane	89.5-90.5°C.
Benzene sulfonyl ester of 4-hydroxy-3,5,4'-tribromo diphenyl methane	Bromination	4-hydroxy 3,5,4'-tribromo diphenyl methane	89.5-90.5°C.
Benzene sulfonyl ester of 4-hydroxy-3,5,4'-tribromo diphenyl methane	Condensation	4-hydroxy 3,5,4'-tribromo diphenyl methane	89.5-90.5°C.

VI Analysis

The bromine content of the various compounds prepared in this work was determined by Parr Bomb according to the following procedure (23).

Approximately 10 gm. of sodium peroxide was mixed with 1.2 gm of potassium nitrate and 0.45 gm. of sucrose. A sample of 0.20-0.25 gm. was then added and mixed thoroughly with the other ingredients. The bomb was heated by the hottest flame of a Bunsen burner until some sound was heard which indicated complete fusion of the mixture. This usually required 2-3 minutes. The bomb was cooled, opened and its contents extracted quantitatively with hot water into a 400 cc. beaker. The solution was then acidified with nitric acid and an excess of standard 0.1 N silver nitrate was added. The solution was boiled to coagulate the precipitate, cooled and the excess silver nitrate back titrated with standard 0.1 N ammonium thiocyanate using ferric alum as indicator.

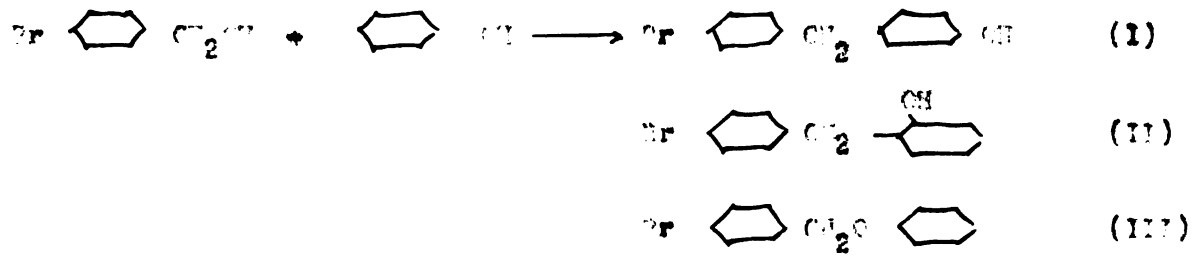
ANALYSIS OF THE COMPOUNDS

Name of the compound	Sources of the compound	Br determined	Br theoretical
p-bromo benzyl alcohol	from dibromobenzene	42.02	42.72
o-bromo benzyl alcohol	from o-bromo-benzoic acid	42.04	42.72
4-hydroxy-4'bromo diphenyl methane	from condensation of p-bromo benzyl alcohol with phenol	30.27 30.19	30.23 30.37
4-hydroxy-4'bromo diphenyl methane	from condensation of p-bromo benzyl chloride with phenol	30.30	30.37
4-hydroxy-3,4'- tribromo diphenyl methane	from bromination of 4-hydroxy-4'- bromo diphenyl methane	57.67 58.00	57.27 58.06
4-hydroxy-3,5,4'- tribromo diphenyl methane	from condensation of p-bromo benzyl alcohol with 2,6-dibromo phenol	58.61 58.44	58.52 58.95
4-hydroxy 2'-bromo-diphenyl methane	from condensation of o-bromo benzyl alcohol with phenol	30.37 30.39	30.38 30.37
4-hydroxy-3,5,2'- tribromo diphenyl methane	from bromination of 4-hydroxy-2'- bromo diphenyl methane	57.15 58.88	57.02 58.95
4-hydroxy-3,5,2'- tribromo diphenyl methane	from condensation of o-bromo benzyl alcohol with 2,6-dibromo-phenol	58.40 58.35	58.38 58.95

DISCUSSION

1. Identification of 4-hydroxy-4'-bromo diphenyl methane

During the condensation of p-bromo benzyl alcohol with phenol, three isomeric products may be obtained, i.e.,



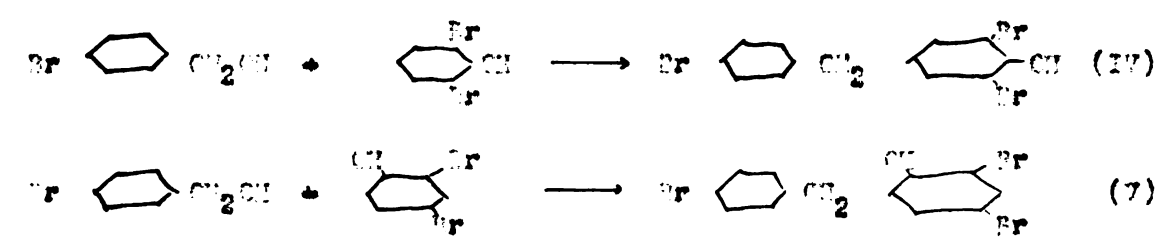
(I)

(II)

(III)

(III) could be separated from (I) and (II) by extracting with Claisen reagent. (I) and (II) could be differentiated or identified through bromination of the product obtained by condensing p-bromo-benzyl alcohol with phenol and condensation of p-bromo benzyl alcohol with 2,6-dibromo phenol or 2,4-dibromo phenol.

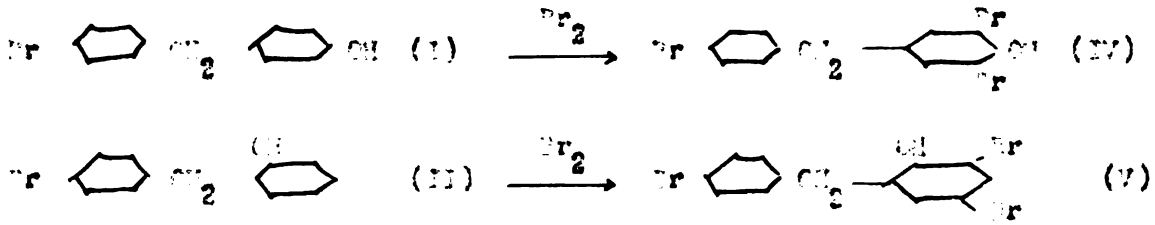
Due to the powerful ortho and para directing influence of phenolic OH group, the condensation or the alkylation of p-bromo benzyl alcohol with 2,6-and 2,4-dibromo phenol give (IV) and (V) respectively



(IV)

(V)

According to D'Arcy (16), during bromination, bromine entered into benzyl phenols in the unoccupied ortho or para position of the phenolic ring.



This, if (I) were the product in the condensation of p-bromo benzyl alcohol with phenol, after bromination, it would give(IV)which would be identical with the product obtained by condensing p-bromo benzyl alcohol with 2,6-dibromo phenol. If (II) were the product in the condensation of p-bromo benzyl alcohol with phenol, after bromination, it would give (V) which would be identical with the product obtained by condensing p-bromo benzyl alcohol with 2,6-dibromo phenol. However, if the product after bromination was identical with the product (IV) obtained by the condensation of p-bromo benzyl alcohol with 2,6-dibromo phenol, it would not be (II). Since if it were (II), after bromination, it would give (V) instead of (IV).

(I) was the expected product in the condensation of p-bromo benzyl alcohol with phenol. Bromination of (I) should yield a product identical with the product obtained by the condensation of p-bromo benzyl alcohol with 2,6-dibromo phenol. However, the brominated product obtained melted at 84°C. whereas the product by the condensation melted at 90°C. It seemed that these two compounds were different but the mixed melting point of the two (85°C) did not show any depression and furthermore, both gave the same benzoyl ester (m.p. 140°C) and the same benzene sulfonyl ester (m.p. 145°C.). Thus it was assumed that these two products were identical but the brominated product was slightly impure.

Several attempts were made to purify the brominated product. The bromination was repeated several times. The products were redistilled repeatedly under reduced pressure and recrystallized several times from different solvents. The products were rebrominated with excess bromine in order to assure complete bromination, redissolved in excess sodium hydroxide and reprecipitated with acid. This approach was without success.

As the brominated product and the condensed product gave the same benzoyl and benzene sulfonyl esters and the mixed melting point of these esters did not show a depression, the esterification and subsequent hydrolysis was another suggested method for obtaining pure phenols.

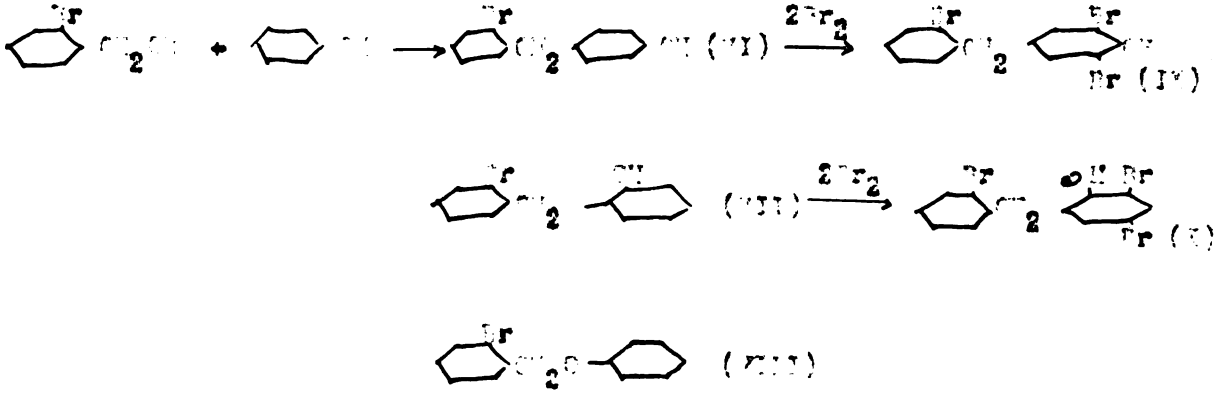
The benzoyl esters were hydrolyzed first, but it was somewhat difficult to separate the benzoic acid from the tribromophenol since poly bromo substitution makes the phenol more acidic and soluble in dilute alkali. Hydrolysis of the benzene sulfonyl esters was then tried and since the benzene sulfonic acid is soluble in water, it was easily separated from the tribromo phenol.

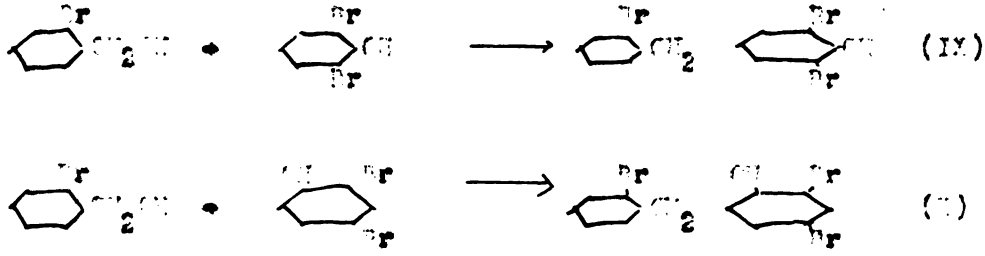
The hydrolysis of the benzene sulfonyl ester of the brominated and the condensed product gave two phenols melting at 89°C. and 90°C. respectively. The mixed melting point of these two phenols did not show any depression. Thus the two phenols must be the same and the esterification and subsequent hydrolysis appears to be a good method of purification.

Since the only product obtainable from the condensation of p-bromo benzyl alcohol with 2,6-dibromo phenol is (I'), the brominated product should also be (I'') and consequently, the product obtained in the condensation of p-bromo benzyl alcohol with phenol should be (I), that is, 4-hydroxy-4'-bromo diphenyl methane. In other words, in the condensation of p-bromo benzyl alcohol with phenol, the condensation takes place para to the phenolic hydroxyl group.

2. Identification of 4-hydroxy-4'-bromo diphenyl methane

The identification of 4-hydroxy-4'-bromo diphenyl methane was carried out according to the same principle as that described for 4-hydroxy-3'-bromo diphenyl methane





The bromination of the product obtained by the condensation of ortho bromo benzyl alcohol with phenol gave a product identical with that obtained by the condensation of ortho bromo benzyl alcohol with 2,6-dibromo phenol. This indicated that in the condensation of o-bromo benzyl alcohol with phenol, the condensation took place para to the phenolic hydroxyl group and gave 4-hydroxy-2'-bromo diphenyl methane as the main product.

3. The preparation of ortho and para bromo benzyl alcohols

The ortho and para bromo benzyl alcohols can be prepared by the direct chlorination of ortho and para bromo toluene followed by the hydrolysis of the benzyl chloride into the corresponding benzyl alcohol. This method introduces the use of chlorine into the preparation of the benzyl alcohol and the chlorination of bromo toluene might give instead of bromo benzyl alcohol, some side chain disubstituted products, some ring substituted products and some chloro benzyl chloride due to the replacement of bromine by chlorine in the ring. It is inconvenient to separate these impurities from the product. This probably accounts for several melting points (62°C., 81°C., and 80°C.) being reported in the literature (24) for p-bromo benzyl chloride.

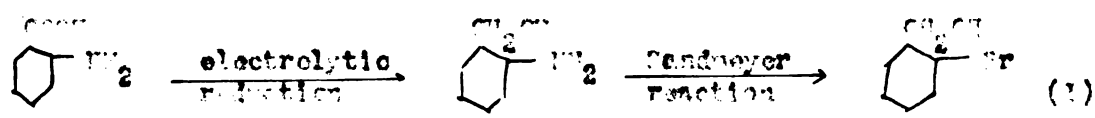
Modified preparations have been made in this laboratory using sulfuryl chloride as the chlorinating agent and benzoyl peroxide as catalyst (25).

The p-bromo benzyl alcohol used in this work, however, was prepared by the reaction of formaldehyde with p-bromo phenyl magnesium bromide which was in turn prepared from magnesium and p-dibromo benzene.

According to Gilman, Beaber and Jones (26), the reaction between p-dibromo benzene and magnesium in ether is confined to one of the bromine atoms with the di-Grignard formed only in traces. Thus, after the reaction of the mono-Grignard with formaldehyde, p-bromo benzyl alcohol was obtained in good yield without the possibility of formation of ortho or other ring substituted by products.

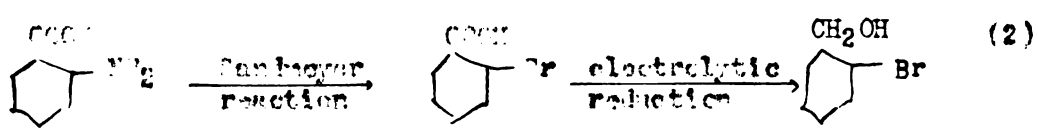
The ortho bromo benzyl alcohol could not be prepared by the same method as p-bromo benzyl alcohol because the bromination of bromo benzene gives p-dibromo benzene and o-dibromo benzene in the ratio of 6:1. Separation of pure ortho dibromo benzene from the mixture is impracticable.

A method for the preparation of o-amino benzyl alcohol through the electrolytic reduction of anthranilic acid is given by Coleman and Johnson (20). The ortho amino benzyl alcohol could then be converted into ortho bromo benzyl alcohol through a Sandmeyer reaction.



(1)

Another alternative procedure was also possible. This would be by the conversion of anthranilic acid into ortho bromo benzoic acid through a Sandmeyer reaction and then conversion of o-bromo benzoic acid into o-bromo benzyl alcohol through electrolytic reduction.



(2)

The second procedure was preferred since electrolytic reduction is most conveniently carried out in small quantities in the laboratory and the Sandmeyer reaction could be carried out on a large scale. Furthermore, Reissert and Cramer (27) showed that diazonium salts of o-amino benzyl alcohol were extremely labile. The diazotized hydrochloric acid solution of o-amino benzyl alcohol decomposes so rapidly at 0°, that in three hours, the decomposition into nitrogen and saligenin is complete.

Several electrolytic reduction of o-bromo-benzoic acid were carried out. In two cases no yield was obtained. A complete survey of literature showed that the presence of some metallic salts in the porous cup would inhibit the reduction. This was actually the case. After thoroughly cleaning the porous cup by forcing first a dilute solution of sodium hydroxide and then dilute sulfuric acid through the walls to remove the metallic impurities, a 40% yield was obtained.

The catalytic reduction of bromo benzaldehyde using platinum oxide as catalyst gives the corresponding bromo benzyl alcohol (28). If the bromo benzaldehyde is prepared through the usual hydrolysis of bromo benzal chloride which in turn is obtained by the chlorination of bromo toluene, there remains the possibility that by products already discussed in connection with direct chlorination procedures will be contaminated in the bromo benzyl alcohol.

The catalytic reduction of esters of substituted benzoic acids usually leads to the corresponding toluenes due to the activating influence of the benzene nucleus. Mozingo and Folkers (29), however,

recently published an article on the catalytic reduction of esters of alkyl substituted benzoic acids into the corresponding benzyl alcohols over copper chromite at 135-175°C. and 200 atmospheric pressure. This procedure may serve as a feasible method for the reduction of esters of halogen substituted benzoic acids, but at high temperature and high pressure, there might be some replacement of bromine by hydrogen.

4. Yields obtained in the condensation of bromo benzyl alcohols with phenols

The condensation of ortho and para bromo benzyl alcohols with phenols in the above experiments gave yields of 27 to 57% which are 10 to 25% higher than those obtained by previous workers (16, 17) using bromo benzyl chlorides.

SUMMARY

1. 4 hydroxy 4' bromo diphenyl methane and 4 hydroxy 2' bromo diphenyl methane were prepared by the condensation of p and o-bromo benzyl alcohol with phenol in the presence of aluminum chloride.
2. The condensation took place para to the phenolic hydroxyl group.
3. 4-hydroxy 3,4' tribromo diphenyl methane and 4-hydroxy 3,2'-tribromo diphenyl methane were prepared by the condensation of para and ortho bromo benzyl alcohol with 2-dibromo phenol.
4. No o-alkylation was observed in all these condensations.
5. The structure of 4 hydroxy 4' bromo diphenyl methane and 4-hydroxy 2'-bromo diphenyl methane were identified by the direct bromination of these two compounds into 4 hydroxy 3,4' tribromo diphenyl methane and 4-hydroxy 3,2' tribromo diphenyl methane.
6. The benzoyl ester of the four phenols and the benzene sulfonyl ester of 4 hydroxy 4' bromo diphenyl methane and 4-hydroxy 3,4' tri bromo diphenyl methane were prepared.
7. The esterification and subsequent hydrolysis of the ester was used as a method for the purification of certain of the phenols.
8. The presence of impurities in the porous cup inhibits the electrolytic reduction of o-bromo-benzoic acid to o-bromo benzyl alcohol.
9. Condensation of the o-and p-bromo benzyl alcohols with phenols gave larger yields than those reported using the ortho and para bromo benzyl chlorides.

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