THE PREPARATION AND CHARACTERIZATION OF THE ORTHO AND PARA MONOBROMOBENZYLATED ORTHO AND PARA CRESOLS

By

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A THESIS

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INTRODUCTION

When it was shown that a group of diphenylmethanes prepared in this laboratory under the direction of Dr. R.C. Huston (1) showed promising specific bactericidal activity (2) a program was begun to expand the series.

The compounds tested to date consist mainly of the chloro- and bromoderivatives of o- and p-benzylated phenols.

This work is to extend the series to include the o- and p-monobromobenzylated o- and p-cresols, as well as the evaluation of activity of the phenyl benzyl ethers produced as biproducts.

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HISTORICAL

The preparation of diphenylmethanes has been accomplished by a variety of means. Of these the oldest is that of Jena (3), who obtained diphenylmethane by heating diphenylacetic acid in the presence of sodium carbonate.

A more common method is that of Zincke (4), who refluxed benzyl chloride and benzene with a large amount of zinc dust. This reaction was utilized successfully with a large number of benzene homologs (5). It has also been applied to the benzylation of toluene to yield the 4- and 2-methyldiphenylmethanes (6).

In addition, the reaction has been found useful in the preparation of the phenolic derivatives of the diphenylmethane series (7). In this method one mole of the benzyl chloride and two moles of the phenol are combined, using mossy zinc as catalyst to achieve a less violent reaction than is obtained with the zinc dust used previously. However, in this reaction the reducing action of the zinc on the benzyl chloride caused low yields, and severely limited its application.

To overcome this, Meister (8), in a method suggested by v. Baeyer (9), used a sulfuric-acetic acid mixture as a condensing agent for benzyl alcohol and benzene (10).

This reaction was also used to condense benzyl-alcohol and phenol (11).

Later Liebmann (12) condensed benzyl alcohol with phenol in the presence of zinc chloride, and reported only p-benzylation.

Liebmann also suggested that zinc chloride, not zinc, was the active catalyst. This thesis was supported by the fact that the use of the chloride rather than the metal resulted in a better yield of diphenylmethane from benzene and benzyl chloride (13).

Zinc chloride was also used by Rennie (14) to prepare benzylphenols. He had stated that $AlCl_3$ and $FeCl_3$ exerted the same influence as the $ZnCl_2$. From the products of the zinc chloride distillation Rennie was also able to obtain a small amount of the o-isomer by precipitating the p-benzylphenol as the barium salt, and recovering the o-benzylphenol in the aqueous filtrate (15).

Nef (16) used phosphorous pentoxide to condense both benzyl alcohol and benzyl ethyl ether with benzene.

The best-known and one of the most useful methods of benzylation was developed in 1877 by Friedel and Crafts (17). It is discussed in a separate section.

A lesser known method, also using an acidic type catalyst was developed by v. Baeyer (18). This reaction concerns the condensation of two moles of benzene, or one of its homologs, with methylal, in the presence of concentrated sulfuric acid. It has been used to obtain a number of sym-

metrical, phenolic diphenylmethanes (19) by condensation of formaldehyde and the phenols, as well as a considerable number of nitro- and aminoderivatives. The reaction has been further investigated by Niederl and coworkers (20).

A more recent addition to the list of acidic condensing agents is hydrogen fluoride. Calcott, Tinker and Weimayer (21) benzylated o-cresol with dibenzyl ether in the presence of hydrogen fluoride to obtain 54 percent monobenzyl o-cresol and 10.4 percent dibenzyl o-cresol yield.

The boron trifluoride catalyzed reaction between benzyl alcohol and benzene resulted in a 23 percent yield of the monobenzylated product, 15 percent of the dibenzylated product, and 34 percent of polybenzylated product (22).

A benzylation method using sulfonic acid esters was reported by Foeldi (23). By refluxing benzene sulfonic acid esters with benzene and phenol at high temperatures he was able to isolate the benzylation products, but only in fair yield.

Perkin and Hodgkinson (24) refluxed benzyl chloride and phenyl acetate for fourteen days to obtain, upon saponification, the same benzyl phenol reported by Paterno (25). This was later identified by Remmie (14) as the p-benzylphenol.

Auwers developed a method for the preparation of diphenylmethane derivatives from pseudophenols (26) using pyridine. By treating 3,5-dibromo-4-hydroxy-benzylbromide with

pyridine and subsequent treatment of the intermediate with sodium carbonate and sodium hydroxide, he reported the products as 3,5,3',5'-tetrabromo-4,4'-dihydroxydiphenylmethane (27) and formaldehyde (the latter was not isolated), rather than the stilbene derivatives obtained when potassium hydroxide was used instead of pyridine (28).

Auwers and Rietz (29) and Kohn and Jawetz (30) have described the condensation of various pseudophenols with phenols. The former, using no condensing agent, heated equimolar quantities of 3,5-dibromo-4-hydroxybenzylbromide and a phenol to 100-150° until the evolution of hydrogen bromide ceased. This reaction yielded o- and p-derivatives in the case of phenol and o-cresol, as well as the dibenzylated products of p-cresol and p-xylenol.

Kohn and Jawetz (30) used equimolar quantities of 2-hydroxy-3,5-dibromobenzylbromide and potassium hydroxide with an excess of dihydric phenol in the presence of water.

Harden and Brewer (31) used this aqueous alkali method in the condensation of 2-hydroxy-3,5-dibromobenzylbromide with a series of substituted phenols. They found that this method gave higher yields than those using either boiling toluene and zinc, or boiling toluene and anhydrous sodium carbonate.

A method frequently utilized in the preparation of diphenylmethanes is the production of the benzophenone derivative and subsequent reduction to the desired product.

Kollaritz and Merz (32) obtained benzophenone by condensing benzoic acid with benzene, using an excess of phosphorous pentoxide at elevated temperature.

A more common method for the preparation of the ketones introduces the acyl group into the phenolic nucleus by condensing the proper fatty acid with phenol in the presence of zinc chloride, sometimes using glacial acetic acid as a solvent. This is known as the Nencki Reaction (33) and was used by Johnson and Lane (34) and by Dohme, Cox and Miller (35) to prepare a series of acyl derivatives of resorcinol which were reduced by the Clemmensen method (36) to the alkyl derivatives. Kemarowsky and Kostanecki (37) obtained benzoylresorcinol by condensing benzoic acid with resorcinol, using the above method.

This reaction is little used with monohydric phenols, although p-acetylphenol (38) and p-propionylphenol (39) have been prepared by it.

Another method for obtaining the ketone is the Hoesch Synthesis (40). It has been used extensively by Klarmann and coworkers in the preparation of diphenylmethane derivatives. By condensing p-chlorobenzonitrile with resorcinol in ether under a current of hydrogen chloride and in the presence of zinc chloride, he obtained a 65 percent yield of 4'-chloro-2,4-dihydroxybenzophenone imide. This gave the ketone when boiled with water; and reduction of this by Clemmensen's method gave a 33 percent yield of the 4'-chloro-2,4,-dihydroxydiphenylmethane (41).

The same authors applied this method to a number of similar condensations (42).

The well-known preparation of ketones from acyl halides and aromatic compounds in the presence of aluminum chloride has been used extensively (43). A 98 percent yield of benzophenone was obtained by reacting equimolar quantities of benzoyl chloride and aluminum chloride with benzene in carbon disulfide (44). Toluene and benzoyl chloride yield phenyl p-tolyl ketone in yields up to 92 percent (45).

Heller (46) obtained an 83 percent yield of 4-methyl-3-chlorobenzophenone from o-chlorotoluene and benzoyl chloride. With o-bromotoluene, however, he obtained only 3-hydroxy-4-methylbenzophenone, the bromine atom having been replaced during hydrolysis.

The reaction of o-bromobenzoyl chloride and m-dichlorobenzene with aluminum chloride gave a 43 percent yield of 2-bromo-2'4'-dichlorobenzophenone (47).

Friedel, Crafts and coworkers also developed a method for the preparation of symmetrical benzophenones using benzene, or benzene homologs and phosgene in the presence of aluminum chloride (48).

In the case of unsubstituted alkyl ethers of phenols, the reaction with acid chlorides usually gives p-acyl substitution.

Although early reports stated that aluminum chloride

could not be used as a condensing agent with phenolic compounds (49) Behn (50) obtained thymyl methyl ketone by the reaction of thymol with acetyl chloride in the presence of aluminum chloride. Nitrobenzene was used as a solvent. This reaction, which gives good yields if the position p- to the phenolic hydroxyl group is open, was later improved by Rosenmund and Schulz (51).

Although the direct acylation of phenols has been shown to be satisfactory, good yields are obtained only if the reaction is carried out in nitrobenzene, or if the hydroxyl group has been protected previously (52). Better yields frequently are achieved by preparing the phenolic ester, and converting this, through treatment with aluminum chloride, to the o- or p-hydroxyketone. This is known as the Fries Reaction (53). Pope (54) was able to rearrange resorcinol monoacyl esters in 80 to 90 percent yield using zinc chloride instead of the aluminum chloride. However, this method gave only poor yields with esters of phenol, m-cresol or guaiacol.

Cox (55) rearranged the benzoyl esters of o- and p-cresol to give over 90 percent yields of the ketones. The rearrangement of the benzoyl ester of m-cresol gave 32 percent p-benzoyl-m-cresol and 50 percent of o-benzoyl-m-cresol.

This work was repeated by Rosenmund and Schnurr (56). These workers also prepared o-(2-bromobenzoyl) p-cresol and o-(4-bromobenzoyl) p-cresol from the corresponding esters in practically quantitative yield.

Klarmann and coworkers (57) used this method to prepare a series of o-alkyl-p-chlorophenols, p-alkyl-o-chlorophenols, as well as the corresponding bromophenols.

Thus it can be seen that the reaction gives a rapid and useful method for either o- or p-benzylation, depending, however, on one of these two positions being blocked. If both are open, although the percentage of o- and p-substitution can be controlled somewhat by the temperature of reaction, a difficultly separable mixture will result.

A comparison of four of the methods mentioned can be found in the work of Coulthard, Marshall and Pyman (58). They used the Nenski and Fries Reactions, as well as the isomerization of phenyl esters by zinc chloride and the condensation of acids with phenols using phosphorous pentoxide. The ketones obtained by these methods were then reduced by the Clemmensen method to the desired alkyl derivatives.

The above is by no means a complete survey of the methods used for the preparation of diphenylmethane derivatives. Of those methods mentioned the best known and most completely studied is that of Friedel and Crafts.

BENZYLATION BY THE FRIEDEL CRAFTS SYNTHESIS

This synthesis has been discussed thoroughly in the literature (59); therefore a complete review here seems unnecessary. For this reason the discussion below will be limited to the utilization of the reaction in the benzylation of aromatic nuclei.

The reaction as developed by Friedel and Crafts was first described in 1877 (60). It then made possible the synthesis of a large number of diphenylmethane derivatives (61).

The reaction of benzyl chloride with benzene yields as the major product diphenylmethane (62), with anthracene a biproduct in small yield (63). This reaction, which can take place at high temperatures without catalyst, can be carried out easily at much lower temperatures (64) in the presence of catalytic quantities of aluminum chloride (65).

A further biproduct is the result of the self-condensation of benzyl chloride catalyzed by aluminum chloride to give a resinous, polymeric product (66). This led Boeseken (67) to the conclusion that benzyl chloride would be unsuitable for the Friedel-Crafts synthesis. This condensation of benzyl chloride may also only involve two molecules, as shown by Wertyporoch and Farnik (68), when carried out in nitrobenzene solution, to yield o- and p-chloromethyldiphenylmethanes.

These side reactions can be minimized by running the reaction at a low temperature and adding the catalyst in small

portions. However, after the desired diphenylmethane derivatives have been obtained, further biproducts may be produced by the effect of aluminum chloride on the product. The treatment of diphenylmethane with 66 percent of aluminum chloride at room temperature resulted in the formation of benzene and anthracene (69).

An alternate method for the production of symmetrical diphenylmethanes utilizes the reaction of two moles of benzene with one of dichloromethane using the aluminum chloride catalyst (70).

The use of benzyl alcohol, rather than the chloride, as the benzylation agent was first accomplished by Nef (71). He obtained diphenylmethane by treating an excess of benzene with equal weights of benzyl alcohol and aluminum chloride.

By using less than a molar equivalent of aluminum chloride, Huston and Friedemann (72) were able to isolate a 30 percent yield of diphenylmethane as well as 8 percent p-dibenzylbenzene, some o-dibenzylbenzene and 20 percent of anthracene. When an excess of benzene was used it was found that the yield of diphenylmethane was increased and that of anthracene reduced.

The effect of aluminum chloride on phenols was first investigated by Merz and Weith (73), who obtained a 12 percent yield of the diphenylether. This reaction was carried out by refluxing phenol and the catalyst; it will not take place to an appreciable extent if the phenol is suspended in petroleum ether and the temperature kept below 30° (74).

The benzylation of phenols has been studied extensively by Huston and coworkers (75). The best yields of condensation products were obtained when one mole of the benzyl chloride was condensed with 3 moles of the phenol in the presence of ½ mole of aluminum chloride at 20-35°, using petroleum ether as solvent. In the case of halogen substituted reactants benzylation usually took place p- to the phenolic hydroxyl group to give the 4-hydroxydiphenylmethane derivatives. However, in the reaction of the 2-chloro-, or 2-bromobenzyl chlorides with phenol equal quantities of the o- and p-benzylated phenols were obtained. When the nucleus of the benzyl chloride contained bromine, appreciable yields of the halogenated phenyl benzyl ether were isolated, in addition to the diphenylmethane derivatives.

The benzylation of phenol by means of benzyl alcohols and aluminum chloride was first reported by Huston (76). By treating 1 mole of benzyl alcohol and 1.1 mole of the phenol with 0.5 ml. of aluminum chloride at 20-30°, a 45 percent yield of p-benzylphenol was obtained. Slightly higher yields of the p-benzylated product were reported when anisole or phenetole were substituted for phenol. Petroleum ether or carbon disulfide were used as solvents.

Similar treatment of o-cresol yielded not only the 2-methyl-4-benzylphenol, but also small quantities of the o-benzylated 2-methyl-6-benzylphenol, and the dibenzylated 2-methyl-4,6-dibenzylphenol (77).

Condensation of three moles of p-cresol with one mole of benzyl alcohol in petroleum ether solution gave a 53 percent yield of 2-benzyl-4-methylphenol, and 30 percent of 2,6-dibenzyl-4-methylphenol (78). These proportions of the reactants were found to give the highest yield of monobenzylated product (79).

The same reaction with m-cresol gave two monobenzylated products: 3-methyl-4-benzylphenol and 3-methyl-6-benzylphenol in approximately equal quantities, as well as the dibenzylated 3-methyl-4,6-dibenzylphenol (80).

When benzyl alcohol was used to benzylate 2,6-dichlorophenol, 3,5-dichloro-4-hydroxydiphenylmethane was obtained, with 2,6-dichlorophenylbenzyl ether as biproduct.

The condensation of alcohols other than benzyl alcohol gave similar results. Methylphenyl carbinol gave a 35 percent yield of p-hydroxy-1,1-diphenylethane, ethylphenyl carbinol a 30 percent yield of p-hydroxy-1,1-diphenylpropane; and benzhydrol in carbon disulfide gave a 40 percent yield of p-hydroxytriphenylmethane. No o- substitution products were isolated (81).

Phenylpropyl carbinol gave a 20 percent yield of 4-(α phenylbutyl) phenol and 6 percent of 2-(α phenylbutyl) phenol (82).

Dimethylphenyl carbinol was condensed with phenol, using aluminum chloride at 100° to obtain a 72 percent yield of p-(α , α -dimethylbenzyl) phenol (83). When methyldiphenyl carbinol was used, the yield of p-alkylated product increased to 80

percent; with triphenylcarbinol, to 95 percent.

These reactions supply additional evidence of the accelerating effect of unsaturation of the carbon adjacent to the alcoholic hydroxyl group on the reactivity of this hydroxyl toward the catalytic effect of aluminum chloride (84).

No thorough comparison has been made of the yields obtained using either the benzyl chlorides or benzyl alcohols to obtain diphenylmethane derivatives. If the work was carried out under identical conditions it appears that the yields are not significantly different (85). The examples above, as well as the work of Rennie (86), Gattermann (87) and Senkowski (88) indicate that in the condensations with phenol the benzyl and benzoyl groups will predominantly go p- to the phenolic hydroxyl. It should be noted, however, that in the acylation of phenols the relative yields of o- and p-derivatives can be controlled by the choice of solvent. Thus the mild reaction conditions using nitrobenzene result mainly in the formation of p-derivatives; while carbon disulfide is conducive to the formation of o-hydroxyalkyl aryl ketones (89).

Theory:

The mechanism of the Friedel-Crafts synthesis has been the concern of a large number of workers. It was originally suggested by Friedel and Crafts (90) that the reaction proceeded by way of an intermediate organoaluminum compound. Although evidence is inadequate to rule out this possibility, no such organometallic compound has yet been isolated.

A theme which has undergone many variations and has been applied widely is that of the intermediate carbonium ion. This cationoid theory, first suggested by Walker (91) and completely reviewed by Price (92), proceeds as shown below:

1. $RCl + AlCl_3 \rightleftharpoons R^+ + AlCl_4^-$

2. $AlCl_4^- + R^+ + C_6H_6 \rightleftharpoons RC_6H_5 + HCl + AlCl_3$

If, as shown, the displacement 2. occurs in one step, the resonance energy of the aromatic substance need not be overcome.

In the presence of such electrophilic agents as aluminum chloride, boron fluoride, and others, this mechanism is not only applicable to the reaction of alkyl halides, but can also be used in the case of alcohols, ethers, esters, or olefins, which can all be converted to the necessary carbonium ion.

The presence of the carbonium ion has also been used widely to explain the rearranged products obtained from alkyl halide and aliphatic alcohol condensations (93).

This mechanism is further supported by the fact that aluminum chloride reacts with ethyl chloride to give conducting solutions. Transference experiments show that the aluminum is contained in the anion (94).

The electrophilic character of the substituent group in this synthesis is shown also by the fact that the reaction usually takes place at the points of high electron density - that is, o- or p- to o-, p-orienting groups present in the aromatic nucleus. In the case of nitrobenzene the deactivation of the nucleus is sufficient to prevent the reaction.

The activation of the aromatic nucleus by aluminum chloride is a debatable subject. Prins (95) assumed that the catalyst polarizes or ionizes benzene to give a negative phenyl ion. Price and Ciskowski (96), and many others, believe that the carbonium ion is able to react with an aromatic nucleus without activation. This may be expected, due to the basic properties exhibited by aromatic nuclei in several reactions (97). However, this basic character may also cause the formation of active complexes with the acidic catalysts. This type of activation of the ring may explain the mechanism of the Scholl reaction, in which ring closure in polynuclear ketones is accomplished by the elimination of hydrogen in the presence of aluminum chloride.

Actual attempts to isolate these complexes have concerned a number of workers. Gustavson has observed the formation of Al_2Cl_6, $6C_6H_6$ and Al_2Cl_6, $6C_6H_5CH_3$ by allowing benzene or toluene to react with aluminum chloride and hydrogen chloride (98).

Norris and coworkers (99) claimed that no isolatable complex could be obtained unless a third component, a hydrogen halide or alkyl halide, were added to the hydrocarbon-aluminum halide mixture.

These data were used by Schaarschmidt (100) as an explanation of the activation of aromatic rings; but there is as yet no evidence that these complexes play a part in the actual reaction.

Nuclear Halogen Replacement and Migration in the Presence of Aluminum Chloride:

The problem of the mobility of nuclear halogens in the presence of aluminum chloride has concerned a number of workers.

The replacement of halogen in the Friedel-Crafts Reaction with subsequent condensation will occur only when the halogen is sufficiently labile to permit replacement. As the reactivity of the halogen in halogenated polynuclear hydrocarbons is higher than in benzene, these condensation reactions take place mainly in the former. These may condense with themselves as shown in the reaction of 9-bromophenanthrene in benzene at room temperature to yield 2,3,10,11-dibenzoperylene (101).

Chattaway (102) noted a similar condensation of bromobenzene and naphthalene, carried out at 70-80°, which gave a 20 percent yield of alpha phenylnaphthalene. This reaction may have taken place by the halogen migrating to the naphthalene and subsequent reaction with benzene.

The migration of halogens, under the influence of aluminum chloride, in compounds containing ether, carbonyl, and carboxyl groups, has been investigated by Nenitzescu and coworkers (103).

The first evidence of migration of nuclear halogens was found in the methylation of o-dichlorobenzene with aluminum chloride and methyl chloride (104). The major products were

hexamethyl benzene and trichloromesitylene.

In the ethylation of bromobenzene using an eight to one molar ratio of bromobenzene to aluminum chloride, and treating with ethylene, 43 percent of the products isolated consisted of bromine-free benzene, ethylbenzene and diethylbenzenes (105).

Leroy (106) treated p-dibromobenzene with aluminum chloride (five to one ratio by weight) at 110°. He obtained mainly bromobenzene, some m-dibromobenzene, unchanged p-dibromobenzene, and two tribromobenzenes.

Dumreicher (107) found that a vigorous reaction occurred when bromobenzene was treated with 50 percent of its weight of aluminum chloride. When it was heated to 130° for 8-12 hours the products were mainly the unchanged starting material, but also some benzene, dibromobenzene and hydrogen bromide.

Iodobenzene treated similarly at 70-80° yielded much iodine, some benzene, unchanged iodobenzene, and a little diiodobenzene, most of which was the p-di-iodobenzene. Some hydrogen chloride was also isolated.

Chlorobenzene was unaffected under similar conditions, even after being heated several days.

In the case of chlorotoluene appreciable rearrangement is noted when it is treated with aluminum chloride and hydrogen chloride. This rearrangement is ascribed to the shift of the methyl radical, and not the chlorine atom (108). It was

found, in the limited number of compounds studied, that the o- and p-orienting groups CH_3, OH and Cl produce in a methyl radical sufficient reactivity to permit a change of position of the latter in the molecule.

p-chlorotoluene undergoes a rapid rearrangement (41.8 percent) and disproportionation when treated with a 1 to 1 molar ratio of aluminum chloride in the presence of hydrogen chloride. The same treatment at 55° gave a 67.8 percent rearrangement (o-chlorotoluene 29.3 percent, m-chlorotoluene 38.5 percent) and considerable disproportionation. The authors found o-chlorotoluene to be most stable at 96° (78 percent unchanged), m- less so (49 percent unchanged), and p-chlorotoluene least stable (26 percent unchanged).

As is stated above, the hydroxyl group is also capable of causing such a shift. By treating p-cresol with a double molar quantity of aluminum chloride at 200° a rearrangement took place to form the m-isomer in appreciable quantities.

Copisarow (109) found that when two parts of bromobenzene were treated with one part of aluminum chloride at 100° for eight hours there were formed benzene (7-8 percent); the three dibromobenzenes (below 8 percent, mainly p-); 1,3,5-tribromobenzene; and a small amount of 1,2,4-tribromobenzene (together less than 5 percent).

However, when the benzene formed is distilled off, in a reaction using four parts bromobenzene to one part aluminum chloride, its yield is increased to 20 percent, leaving 40

percent of the unchanged bromobenzene. When nitrogen is passed through the reaction, the yield of benzene is increased to 42 percent; with hydrogen chloride, to 78 percent benzene; and with hydrogen, to 83 percent benzene (and 10.5 percent unchanged bromobenzene). In the presence of phenol 35 percent benzene was isolated, very little dibromobenzene, and some tribromophenol. Chlorobenzene was not affected when treated as above.

The p-dibromobenzene yielded benzene; bromobenzene; a mixture of dibromobenzenes; 1,3,5 and 1,2,4 tribromobenzenes; as well as bromo derivatives of condensation products.

At a lower temperature of reaction, with a smaller proportion of aluminum chloride, or in the presence of a volatile solvent such as carbon disulfide, the mobility of the bromine is markedly decreased. The rearrangement of alpha bromo- or chloronaphthalene to the beta isomer was noted by Roux (110). Using alpha iodonaphthalene he obtained free iodine and no rearrangement product.

In the case of dibromonaphthalenes, heating with aluminum chloride resulted in the production of small amounts of isomeric dibromonaphthalenes (111).

The reactions of halogenated phenols and aluminum chloride are very similar to those of the above halogenated hydrocarbons.

In the presence of a volatile solvent no halogen migration was noted by Perrier (112) when he heated o- and p-chlorophenols with aluminum chloride in dry carbon disulfide.

He obtained crystalline compounds to which he gave the formula: $(C_6H_3OCl)_2Al_2Cl_4$. These gave the original chlorophenols on hydrolysis.

Weston and Suter (113) produced p-hydroxydiphenyl in 22 percent yield by the reaction of one mole p-fluorophenol with two moles of aluminum chloride refluxed in an excess of benzene for 2.5 hours.

An extensive series of papers on the mobility of halogens in phenols was published by Kohn and coworkers.

When tribromophenol in benzene was treated with aluminum chloride, a good yield of bromobenzene was obtained, as well as a small amount of phenol. Under similar conditions trichlorophenol was not affected (114).

The treatment of p-bromophenol with aluminum chloride in benzene (80°) gave little bromobenzene; the replacement of the benzene with toluene at 100° increased the rate of reaction to give m-bromotoluene and phenol.

Tribromophenol when treated as above gave the same products (115).

Increasing the extent of bromination to tetra- and pentabromophenols shows that the bromine atoms o- and p- to the hydroxyl group are removed to give bromobenzene and m-bromophenol.

If both chlorine and bromine atoms are present, preferential debromination takes place (116).

In their investigations of the bromo derivatives of cresols (117), behavior similar to that of the phenols was observed. Tetrabromo-o-cresol when refluxed in benzene with aluminum chloride yielded 3,5-dibromo-2-methyl phenol and bromobenzene (118).

Tetrabromo-p-cresol treated with an equal weight of aluminum chloride and refluxed in benzene gives 3,5-dibromo-4-methyl phenol. Prolonged heating removes even the remaining two halogens m- to the hydroxyl group to give p-cresol (119). Tetrabromo m-cresol when allowed to react as above gives 3-bromo-5-methyl phenol. Tribromoresorcinol was also debrominated by similar treatment (120).

3,5-dibromo-2-hydroxybenzylbromide does not give the expected Friedel-Crafts reaction with benzene, but yields only phenol and bromobenzene (121).

The reaction of 3,5-dibromo-4-hydroxybenzyl bromide with benzene and aluminum chloride gives the diphenylmethane derivative, which on further heating splits and loses the halogens to produce phenol.

It must be emphasized that in the above reactions Kohn et al usually used three moles of aluminum chloride to one mole of the halogenated phenol, and a temperature of about 80°.

The usual procedure of carrying out the Friedel-Crafts condensation in this laboratory employs petroleum ether as a solvent, is kept below 30°, and uses in most instances only

catalytic amounts of aluminum chloride. For this reason it may be expected that the bromine compounds used will be less liable to halogen migration. The chlorine derivatives, as shown previously, will be stable.

Huston and D'Arcy (122) reacted p-bromobenzyl chloride and 2,6-dibromophenol to obtain 4-hydroxy-3,5,4'-tribromodiphenylmethane in 19 percent yield. No dehalogenation products were reported.

The production of 4-hydroxy-2'-bromodiphenylmethane and 2-hydroxy-2'-bromodiphenylmethane in yields of 15 percent and 5 percent respectively was also accomplished without apparent migration of the halogen (123).

Guile and Wu (85) prepared 4-hydroxy-4'-bromodiphenylmethane in 48 percent yield by condensing p-bromobenzyl chloride or alcohol with phenol in the presence of aluminum chloride. As in the previous work, no migration of the halogen was reported in this, or in the preparation of 4-hydroxy-2'-bromodiphenylmethane (41 percent yield) and 4-hydroxy-3,5,2'-bromodiphenylmethane (27 percent yield).

Huston and Eldridge (124) reacted 2,6-dichlorophenol and benzyl alcohol, using aluminum chloride as catalyst, to give 4-hydroxy-3,5-dichlorodiphenylmethane and the corresponding ether.

In this, and in further work, no migration of the halogen is expected nor was found, due to the evident stability of chlorine under these conditions.

Huston and Headley (125) prepared 4-chloro-4'-hydroxydiphenylmethane (24 percent yield) and 2-chloro-4'-hydroxydiphenylmethane (31 percent yield) without evident dehalogenation.

Nor was there dehalogenation in the work of Huston and Chen (126), who reacted o-chlorobenzyl chloride and phenol to give a small yield of 4-hydroxy-2'-chlorodiphenylmethane, as well as the o-benzylated product. On chlorination this yielded a product identical to that made by the condensation of o-chlorobenzyl chloride and 2,6-dichlorophenol.

Huston and Warren (127) obtained 4-benzyl-2-chlorophenol and 6-benzyl-2-chlorophenol in the benzylation of o-chlorophenol, using aluminum chloride.

Huston and Guile (128) reacted m-chlorobenzyl chloride and 2,6-dichlorophenol to yield 4-hydroxy-3,5,3'-trichloromethane.

Nor was any halogen migration noted in the preparation of the bromine derivatives shown below. Huston and Neeley (129) used m-bromobenzyl chloride with 2,6-dibromophenol in the presence of ½ mole of aluminum chloride to give a 17 percent yield of 4-hydroxy-3,5,3'-tribromodiphenylmethane.

Huston and Strickler (82) condensed n-propyl-phenylcarbinol and 2,6-dibromophenol to give 4-(alpha-phenylbutyl)-2,6-dibromophenol.

Huston and Coleman (130) attempted to condense tertiary butyl and tertiary amyl alcohols with o- and p-chlorophenols using aluminum chloride. They did obtain the p-tertiary-alkyl-o-

chlorophenols, but could not condense the alcohols with the p-chlorophenol under these conditions - indicating that this chlorine is not replaced.

In none of the above instances was any evidence of halogen migration or removal reported. However, when the work of Huston and Coleman was investigated further by Huston and Larsen (131) it was found that by using a 0.6 molar quantity of aluminum chloride, in a one mole reaction, at about 30°, it was possible to obtain 50 percent yields of p-tertiaryalkyl o-chlorophenols; but in the case of the condensation of tertiary butyl alcohols with o-bromophenols, a 58 percent yield of p-tertiary butylphenol was obtained, and only 6 percent of the p-tertiary butyl-o-bromophenol. With tertiary amyl alcohol, a yield of 39 percent of the debrominated product, p-tertiary amyl phenol, and only 6.6 percent of the p-tertiary amyl-o-bromophenol, was isolated.

From the above data it may be concluded that bromine is most easily removed, or replaced by a cationoid agent, when o- or p- to a strong o,p-director. This is not the case if chlorine derivatives are used with aluminum chloride. In the utilization of bromobenzylchlorides in this problem it may be assumed that if the temperature is kept low, the reaction run in a volatile solvent, and the aluminum chloride used in only catalytic amounts, this type of migration or replacement, although it may occur, will be at a minimum.

The problem of nuclear halogen migration does not occur in the Claisen method of C-alkylation of phenols.

C-ALKYLATION OF PHENOLS BY THE CLAISEN METHOD *

As the Friedel-Crafts reaction yields predominantly the p-benzylated product, the isolation of pure o-substituted substances necessitates blocking of the p- position, or the difficult separation of the o-alkylated biproduct. For this reason the method of Claisen, although restricted to active halides only, has been found useful.

The nuclear alkylation of phenols is accomplished by treating the sodium phenoxide with an active halide of the allyl or benzyl type in an inert solvent such as toluene. The products are always the o-isomers; no definite examples of p-alkylation have been found. (In the alkylation of sodium phenolate with triphenylmethyl chloride Busch and Knoll (132) reported a 74 percent yield of the p-alkylated product. This is probably a typographical error. Claisen (133) mentions p-alkylation with ethyl iodide in the case of the sodium salt of anthranol.)

C-alkylation of phenols in basic medium had been noted previously in the treatment of resorcinol and phloroglucinol, et cetera, with alkyl halides (134). These phenols, due to their tendency to react in the tautomeric carbonyl form,

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* As the name "Claisen Reaction" has been applied to the aceto-acetic ester condensation, ketone-ester condensation to form 1,3 diketones and such aldol reactions as the condensations of ethyl acetate with benzaldehyde to form ethyl cinnamate, it is thought desirable not to give any other reactions this same name, although this reaction is already designated in the literature as such.

give both O- and C-alkylation. Claisen, in a footnote (135) stated that the reaction of allyl bromide, calcium carbonate and phenol in acetone, yields not only the allyl ether but also a little allyl phenol. As the conditions used caused no rearrangement of the ether, C-alkylation must have taken place. But in the reaction of the alkali salts of phenol (136) and α and β naphthol (137) with benzyl chloride, in alcohol, the expected phenyl benzyl ethers were obtained.

In 1920 Gomberg and Buchler (138) found that by allowing sodium phenolate to react with benzyl chloride (using no solvent) a 24 percent yield of benzyl phenol was obtained. The addition of copper increased this to 35 percent. The use of toluene gave only 13 percent of the benzyl phenol; but when the reaction was carried out in water only the ether, and no benzyl phenol, was obtained. The authors did not fully identify the products and did not pursue the reaction further.

Claisen and Roth (139) attempted to increase the amount of C-alkylation noted in the preparation of phenyl allyl ether. The use of potassium or sodium phenolate, rather than the calcium carbonate, in alcohol or acetone solution caused no improvement in the yield of the C-alkylated product. But when a "non-dissociating" medium such as benzene or toluene was used, the amount of C-alkylation increased from 1 to 3 percent to 60-70 percent, the formation of the allyl ether decreasing accordingly. The product formed was identified as o-allylphenol with a small amount of o,o-diallylphenol as biproduct (140).

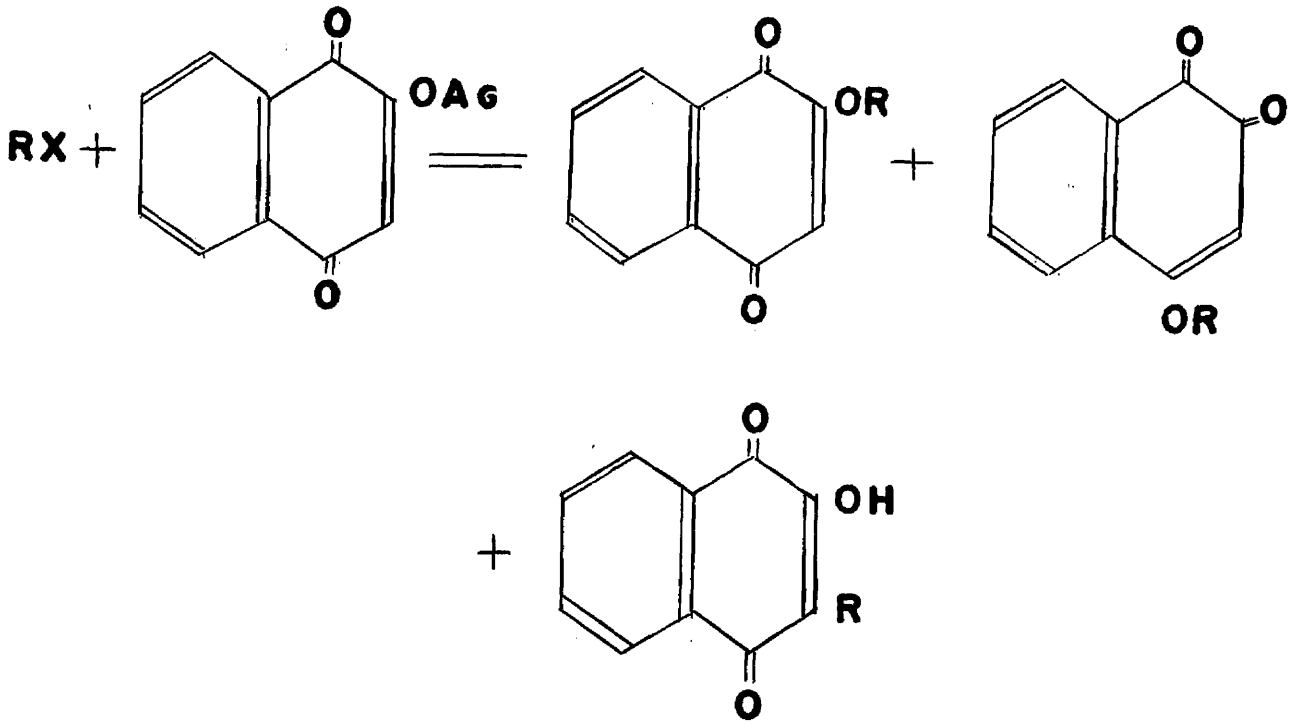
On more complete investigation (133) this o-alkylation was also found to occur with benzyl halides, 1-bromo-3-methyl-2-butene, 1-bromo-1-methyl-2-butene, and cinnamyl bromide. Busch (141) confirmed Claisen's work and also showed that while benzyl chloride and an alkali phenolate in a "non-dissociating" medium do react giving a little O-alkylation, the more reactive diphenylchloromethane exhibits no trace of O-alkylation.

Schorigin (142) and H.O. Swartout (143) used the reaction to prepare 2-methyl-6-benzyl phenol from sodium o-cresolate and benzyl chloride in toluene in 31 percent yield.

Lewis (144) obtained 2-benzyl-4-methylphenol in 49 percent yield, while Houk (145) when benzylating sodium m-cresolate obtained a mixture of equal amounts of the two possible o-benzylated products.

Schorigin (146) attempted to form o-hydroxytriphenylmethane from sodium phenolate, but obtained mainly O-alkylation. As he used an excess of phenol (147), which is a "dissociating solvent", this is to be expected; and when the work was repeated by Busch and Knoll (132) without excess phenol, the o-alkylated derivative was formed, with only a 0.5 percent yield of the ether. Fieser alkylated the silver salt of hydroxynaphthaquinone by a 1,2 addition of reactive alkyl halides (148). This reaction resembles the C-alkylation of the non-tautomeric phenols above in that only very reactive alkyl halides give C-alkylation; and as reported by Claisen, cinnamyl and benzyl halides give

higher yields of the C-alkyl derivative than does the allyl bromide.



A Claisen type alkylation has also been used in the synthesis of dihydrovitamin K_1. This was produced by the reaction of phytyl bromide and the monosodium salt of 2-methyl-1,4-naphthohydroquinone, using benzene as a solvent (149).

The synthesis of benzylphenols in this laboratory has utilized the Claisen alkylation method to a great extent to obtain pure o-benzylated derivatives (150). In no case was the p-derivative isolated.

Theory:

No completely satisfactory mechanism has yet been proposed for Claisen's method of C-alkylation. Such a mechanism must take into account the following factors which influence the

reaction:

1. The type of phenol.
2. The type of alkyl halide.
3. The halogen used.
4. The metal used (Na, K or Ag).
5. The temperature.
6. The medium in which the reaction is carried out.
7. The amount of the O-alkylated product present in the reaction mixture.

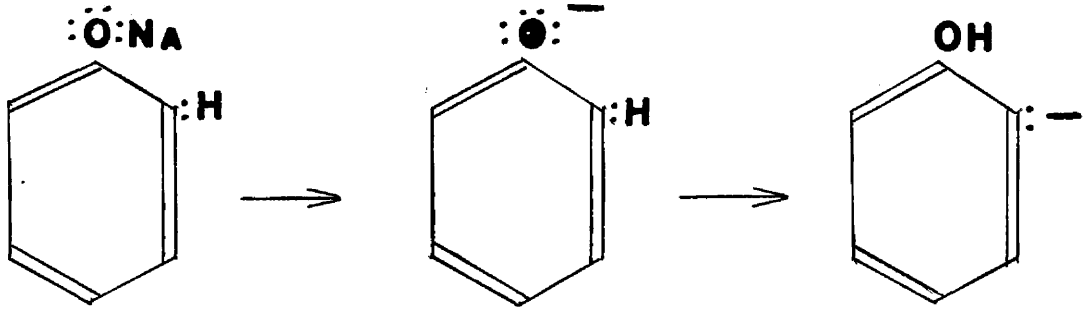
The tendency of the phenol to tautomerize influences the reaction. The alkyl halide used must be highly reactive. The effects of the halogen, metal and temperature have not been investigated thoroughly and are of much smaller importance than the effect of the medium in which the reaction is carried out. This is described above. As shown by Huston and coworkers (151) the addition of the corresponding benzyl phenyl ether, from a previous reaction, to the reaction mixture, materially increases the yield of benzylated phenol.

Claisen suggested three possible courses by which the reaction could take place:

1. The formation and subsequent shift of the ether.
2. The reaction of the metal and halogen to form the metal halide, leaving the free enol and alkyl radicals.
3. A 1-2 addition and subsequent splitting to form the alkylated aromatic nucleus.

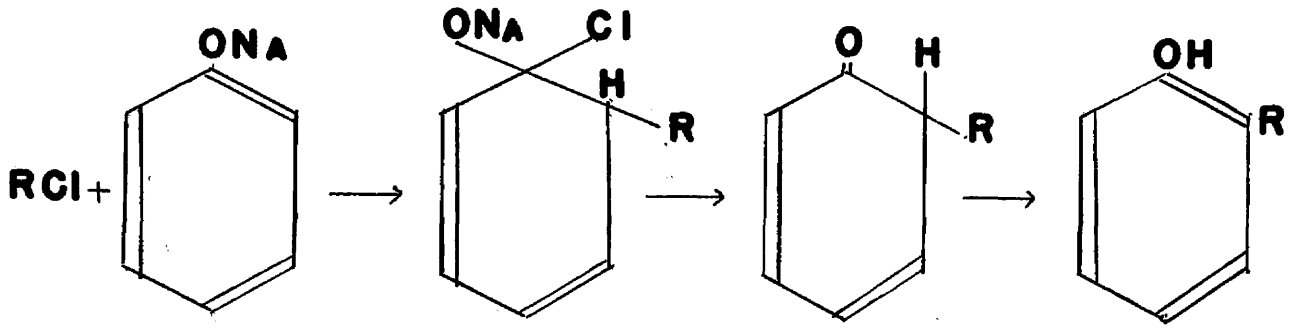
The first hypothesis is not correct, as the phenyl benzyl ether will not rearrange under the conditions of the reaction. (The work of Schorigin indicates that in the presence of sodium, and under extreme conditions, some rearrangement occurs, but not to yield the O-benzylated phenols (152). If such a rearrangement should occur it may be expected that some p-alkylation would be found.)

The second mechanism, suggested by the work of Wislicenus (153) requires the removal of the metallic ion to leave a carbanion activated in the o- position by a proton shift.



This does not explain the fact that there is no p-alkylation, and that the difference in reactivity of the alkyl halides causes either predominantly O- or C-alkylation. This mechanism should show the highest O-alkylation for the most reactive alkyl halides (154), which is not the case.

For this reason Claisen (133) and other workers (155) favored the addition-hypothesis which was developed by Michael to explain the formation of methyl isocyanide from silver cyanide and methyl iodide (156). Using this mechanism the reaction would proceed as shown:



The production of the O-alkylated phenol in a "non-dissociating" medium may possibly be explained by the presence of phenol produced in the reaction:

$2C_6H_5ONa + 2C_6H_5CH_2Cl \longrightarrow (C_6H_5CH_2)_2C_6H_3OH + C_6H_5OH + 2NaCl.$

As this is a dissociating solvent it will promote the formation of O-alkyl derivatives from sodium phenoxides and active alkyl halides.

CHEMICALS

Aluminum Chloride Anhydrous Sublimed.
General Chem. B. & A.

Benzene Sulfonyl Chloride E.K. 32

Benzoyl Chloride E.K. 293

Benzoyl Peroxide E.K. 713

o-Bromotoluene E.K. 47 and Dow (Redistilled)

m-Bromotoluene E.K. 1142 and prepared (Redistilled)

p-Bromotoluene E.K. 48 and Dow (Redistilled)

Copper Powder - By Hydrogen - Baker

o-Cresol E.K. P81 (Redistilled)

p-Cresol E.K. P449 (Redistilled)

p-Dibromobenzene (Benzene Dibromide CP (Para))
B247 Fisher Scientific Co.

3,5 Dinitrobenzoyl Chloride E.K. 2654

Ethyl Alcohol 95 percent, Commercial Solvents

Ethyl Ether Merk 71633

"Hexane" (from Petroleum) E.K. P1135

Methanol CP E. & A. A-412

Paraformaldehyde E.K. 421 (Dried over P_2O_5)

Petroleum Ether (Benzine) CP Baker

Pyridine E.K. P214 (Distilled from BaO)

Raney Catalyst Powder No. 23020B

Sodium Peroxide CP Baker

Sulfuryl Chloride E.K. P322

p-Toluene Sulfonic Acid E.K. 984

p-Toluene Sulfonyl Chloride E.K. 523

m-Toluidine E.K. P862

p-Toluidine E.K. 254

Zinc Chloride, General Chemical, Lot C-262

PREPARATION OF m-BROMOTOLUENE

Two common methods are available for the preparation of m-bromotoluene. The first, a Sandmeyer reaction replacing the amino group of m-toluidine with bromine by the use of a hydrobromic acid-cuprous bromide solution (157), gave only a 15-16 percent yield.

The second method, although lengthier, gave better yields. p-toluidine was acetylated, to modify the directing influence of the amino group, then brominated, the acetyl group removed by hydrolysis, the amino group diazotized and the diazonium group replaced by a hydrogen atom through reduction with ethyl alcohol and copper powder (158). Below is given a more detailed description of the method than is found in the literature.

EXPERIMENTAL

Two moles (214 g.) of p-toluidine were dissolved in 800 ml. of glacial acetic acid in a three liter, three neck flask. This was refluxed for two hours, then cooled. While it was being stirred a slight excess of bromine (325 g., 102 ml., 2.03 moles) was added; then the stirring was continued for one-half hour with the temperature being kept at 50-55°. The reaction mixture was poured into 10 liters of cold water in a battery jar to which had been added 25 g. of sodium bisulfite. The product was filtered off, washed with water and dried in the Buechner funnel to about 500 g. It was then returned to the 3 liter flask and refluxed with 500 ml. of 95 percent ethyl

alcohol. To this 500 ml. of concentrated hydrochloric acid was added slowly, and reflux continued. After three hours the mixture was poured into a beaker and the hydrochloride filtered off. This was washed with chilled alcohol. The hydrochloride was then suspended in 800 ml. of water in a two liter beaker; and a solution of 140 g. sodium hydroxide in 700 ml. of water was added slowly with continual stirring. The oil, 3-bromo-4-aminotoluene, was isolated and added to a cold mixture of 800 ml. of 95 percent ethanol and 200 ml. concentrated sulfuric acid in a five liter, three neck flask equipped with a stirrer. This was cooled to 10°; and a solution of 2.05 moles (148 g.) of sodium nitrite in 260 ml. of water was added. The reaction was stirred for twenty minutes. After the stirrer was removed a long bulb reflux condenser was put in its place and 35 g. of copper bronze was added slowly. (Reduced copper powder may also be used, but 50 g. to 60 g. are necessary.) The flask was kept free so that it could be moved easily. It was then heated on the steambath to accelerate the reaction. When the evolution of gases became too vigorous the reaction was cooled immediately in an icebath. When the reduction had subsided, it was heated on the steambath for ten minutes while being observed continually in case further cooling was necessary.

When the color of the solution had changed from a red-brown to a yellow, two liters of water were added, and the product was steam distilled. The resulting oil was washed twice with 200 ml. portions of 10 percent sodium hydroxide, once

with water, twice with 150 ml. portions of concentrated sulfuric acid, and finally with 100 ml. of a 5 percent sodium carbonate solution. The sulfuric acid caused considerable charring to take place, and care was necessary in the separation of the product which constituted the upper layer.

The m-bromotoluene was dried over calcium chloride, filtered through glass wool and distilled at 180-183°/750 mm., (85-89°/34 mm.).

This six-step process gave, in ten reactions, an average yield of 30 percent of the crude product; after purification, a 25 percent yield.

As the use of ethanol makes possible the formation of an ether, the yield may be increased by using reducing agents such as hypophosphorous acid or alkaline formaldehyde (159).

THE PREPARATION OF BROMOBENZYL CHLORIDES

The major problem in the production of the necessary benzyl chlorides is the prevention of over-chlorination, mainly in the sidechain, but also in the nucleus.

One method yielding pure p-bromobenzyl chloride is the chloromethylation (160) of bromobenzene. Regrettably, the presence of a halogen on the ring makes this reaction difficult and decreases the yields (161).

In this chloromethylation method a crude oil, formed by the reaction of formalin and hydrogen chloride in a tower at 60° and in the presence of zinc chloride monohydrate, is treated with bromobenzene to give a 45 percent yield of p-bromobenzyl chloride. 4,4'-Dibromodiphenylmethane (M.P. 64°) was also isolated. A further disadvantage of this method is that it is limited to the p-compound.

The replacement of the hydroxyl groups in the three isomeric bromobenzyl alcohols yields the three benzyl chlorides in a pure state. p-Bromobenzyl alcohol yields 91 percent of the p-bromobenzyl chloride when refluxed with concentrated hydrochloric acid (85). The o- and m-bromobenzyl alcohols can be expected to react similarly. Although the method will result in a pure product, it is severely limited by the difficulty of the preparation of the alcohols.

Dippy and Williams (162) brominated benzyl chloride in the presence of a trace of iodine. They obtained a 60 percent yield of p-bromobenzyl chloride (M.P. 50°). However, the purity

of this product is highly debatable.

Another method for promoting sidechain chlorination is by conducting the reaction in the vapor phase at 200-600° (163).

The method most commonly used is the direct chlorination of the bromotoluenes using a combination of light (below 5000 Å in wavelength) and thermal activation (67).

This photochlorination involves the dissociation of chlorine by light into free chlorine atoms, which then initiate reaction chains by substitution at the aliphatic carbon-hydrogen bond. In the case of the toluenes an appreciable amount of chlorination will occur in the absence of light (164).

Jacobs and Heidelberger (165) passed the theoretical amount of chlorine gas into boiling o-bromotoluene to produce o-bromobenzyl chloride.

Erdmann (166) used 0.1 mole phosphorous pentachloride to six moles of o-chlorotoluene and chlorinated the sidechain in the light at 150-180°. This procedure has been used in this laboratory (128, 129) for the production of halogenated benzyl chlorides. To prevent overchlorination the reaction was continued until 75 percent complete, as determined by the weight of the vessel.

However, Quelet (167) found that in the sidechain chlorination of p-bromotoluene, the use of phosphorous pentachloride as a catalyst was not to be recommended, as it increased the yield of biproducts.

A source of molecular chlorine, other than the gas, is sulfuryl chloride. Dubois (168) allowed toluene and sulfuryl

chloride to react at 115° to form benzyl chloride and chlorotoluene. Wohl (169) used the same reaction at 130° to obtain a 50 percent yield of benzyl chloride.

It was felt that these chlorination methods led to the formation of impurities, especially benzal chloride and benzotrichloride, as well as possible nuclear chlorination, making difficult the purification of the bromobenzyl chlorides.

The use of sulfuryl chloride in the presence of an organic peroxide, as a source of atomic chlorine, makes possible a rapid and smooth sidechain chlorination (170).

The peroxide catalyzed reaction proceeds rapidly in the dark, whereas the light promoted reaction with sulfuryl chloride is much slower, as is the light promoted Cl_2 gas chlorination. The reaction is typified by the equation:

$$RH + SO_2Cl_2 \xrightarrow[\text{peroxide}]{\text{heat}} RCl + SO_2 + HCl$$

The mechanism postulated by Kharash and coworkers depends on the heat decomposition of the peroxides to form free radicals (171).

This slow decomposition initiates a vigorous chain reaction by removal of a reactive halogen from the sulfuryl chloride:

$$C_6H_5\overset{O}{\overset{\|}{C}}-O-O-\overset{O}{\overset{\|}{C}}-C_6H_5 \rightarrow 2C_6H_5^{\cdot} + 2CO_2$$

$$C_6H_5^{\cdot} + SO_2Cl_2 \rightarrow SO_2Cl + C_6H_5Cl$$

$$\cdot SO_2Cl \rightarrow SO_2 + Cl\cdot$$

$$Cl\cdot + RH \rightarrow R\cdot + HCl$$

$$R\cdot + SO_2Cl_2 \rightarrow RCl + \cdot SO_2Cl$$

This chlorination is less successful in the neighborhood of groups or atoms showing strong electron repulsion ($-I_s$ effects); thus the introduction of a second halogen into the benzyl chloride sidechain, while possible, is difficult; and a third halogen cannot be added. A bromine substituent is not displaced, and no nuclear halogenation takes place. The reaction is inhibited by small quantities of sulfur, iodine or oxygen. The inhibiting effect of oxygen is overcome by the vigorous evolution of gases.

This reaction was used for the preparation of the o-, m- and p-bromobenzyl chlorides.

EXPERIMENTAL

All reactions, including the purification of the final products, must be carried out in the hood.

The yield depends in large part on the efficiency of the reflux condenser. By trapping the gases given off in an ice-salt bath and returning the condensed liquids to the reaction, a nearly quantitative yield can be obtained.

However, the reaction proved to be so violent that it was found best to let the gases escape freely. For a one mole run, a 2 liter single neck flask and a reflux condenser were used with a thermometer held in the reaction mixture through the reflux condenser.

The reactants had to be redistilled, as the crude products contained impurities which poisoned the free radical reaction. In the case of the sulfuryl chloride this redistillation had to be accomplished shortly before use. A one foot Fenske column was used, and the 65-67°/750 mm. fraction taken for the reaction.

The bromotoluene and sulfuryl chloride were mixed and the exact amount of benzoyl peroxide added. (Excess peroxide causes an extremely violent reaction.) The reaction was heated cautiously to 93-97°. At this point a vigorous evolution of gas took place, and rapid cooling of the mixture was necessary. When the reaction had subsided, heat was reapplied and reflux was continued until gases were no longer given off. At this point the reaction was complete and the mixture was

fractionated.

The total time for the reaction was 20 to 30 minutes.

Reactants:

3 moles bromotoluene 514 g.

1 mole sulfuryl chloride 135 g.

0.002 mole benzoyl peroxide 0.5 g.

Products: Bromobenzyl chlorides

Bromotoluene	Initiation Temp.	Chlorides, Yield	B.P.	M.P.
para	93°	78%	115-120°/12 mm.	40-42°
ortho	93-95°	63%	123-125°/20 mm.	------
meta	95-97°	57%	118-121°/18 mm.	------

p-Bromobenzyl Chloride:

The p-bromotoluene was melted to facilitate addition. The reaction proved to be very vigorous, and rapid cooling was necessary.

The excess p-bromotoluene was removed at 70-75°/12 mm. 93 percent of one mole used); the major portion of the p-bromobenzyl chloride distilled over at 115-120°/12 mm. It was necessary to heat the sidearm, as the product crystallized very easily.

Recrystallization was accomplished from 95 percent ethanol, giving fine, white needles in an average yield of 78 percent (based on the pure crystalline product). It melted in the range of 40-42°. Literature values vary from 38-39° (172), 40° (173), 41° (174), to 50° (162).

Some high boiling product was isolated and crystallized from ethanol to give fine, white needles, M.P. 54-55°. This constituted only 2 percent of the yield.

In attempts to harvest further crops from the filtrate there resulted a brown liquid which was insoluble in cold ethanol and could not be crystallized. This liquid was not identified.

o-Bromobenzyl Chloride:

After initiation at 93-95° the reaction progressed less violently than the production of the p-bromobenzyl chloride, but some cooling was still necessary.

After removal of the o-bromotoluene (70-72°/20 mm., n_D^{20} 1.5550) the product was collected at 115-125°/20 mm. The straw-colored liquid was redistilled through a 6 inch Fenske column to give a colorless, stable liquid in an average yield of 63 percent which boiled at 123-125°/20 mm. This agrees with the value given by Jacobs and Heidelberger (124-126°/20 mm.) (165).

m-Bromobenzyl Chloride:

In order to start the reaction it was necessary to heat the mixture to 95-97°, after which the reaction took place smoothly and with less violence than was noted in the two previous reactions. However, in some cases the reaction had to be cooled.

The excess m-bromotoluene was removed by distillation at 81-84°/12 mm., the m-bromobenzyl chloride at 118-121°/18 mm., through a 6 inch Fenske column. A small fraction was obtained

in the intermediate range, boiling mainly at 103-105°/12 mm. This was not identified.

The average yield of m-bromobenzyl chloride was 56.5 percent. Its boiling point agreed with that given by Olivier (119°/18 mm.) (175). However, the m-bromobenzyl chloride did not solidify, and thus did not give the melting point of 22-23° cited in the above reference.

A small amount of high boiling material was isolated and crystallized from alcohol to give white flakes melting at 30-31°. This was not further identified.

In all the above reactions a small amount of red fumes was noted in the condenser. This was especially true in the case of p-bromotoluene, least so in the case of m-bromotoluene. It seems possible that this is bromine removed during the reaction.

It should also be pointed out that in the case of m-bromotoluene a much more violent reaction was obtained when the sulfuryl chloride was not predistilled.

For these reasons it seems advisable to investigate this reaction further.

THE PREPARATION OF p-BROMOBENZYL ALCOHOL

This alcohol is most commonly prepared by the hydrolysis of the corresponding benzyl halide. Jackson and Lowery (176) refluxed p-bromobenzyl bromide in water until no further lachrymatory properties were evident. Bodroux (177) used alcoholic potassium hydroxide to hydrolyze p-bromobenzyl chloride, and obtained an alcohol melting at 77°. The hydrolysis of p-bromobenzyl chloride using dilute potassium carbonate, and refluxing, proved successful. It gave a pleasant-smelling product, which on crystallization from ligroin gave white needles having a melting point of 76-77°.

Carothers and Adams (178) obtained the alcohol by the catalytic reduction of p-bromobenzaldehyde. The latter may be prepared by the reaction of ethyl orthoformate with p-bromophenylmagnesium bromide and subsequent hydrolysis.

In order to prevent the presence of chlorinated impurities, the p-bromobenzyl alcohol for this reaction was prepared from p-dibromobenzene by the Grignard reaction.

According to Gilman, Beater and Jones (179), the preparation of the Grignard reagent from p-dibromobenzene at normal temperatures in ether will yield little other than the p-bromophenylmagnesium bromide. This makes possible the preparation of p-bromobenzyl alcohol by reaction of the Grignard reagent with formaldehyde and subsequent hydrolysis.

A major difficulty encountered in the reaction is

the addition of the formaldehyde without excessive repolymerization. The method of Ziegler (180) as modified by Gilman and Catlin (181) proved fairly successful.

In this procedure paraformaldehyde is depolymerized at about 300° and driven into the reaction by a stream of nitrogen. It was found that by using trioxane (α trioxymethylene) as a source of formaldehyde, and heating the inlet tube as far as possible, less difficulty with polymerization was encountered.

EXPERIMENTAL

For a three mole run a five liter, three neck flask was used; it was fitted with reflux condenser, dropping funnel and stirrer.

Reactants:

3 moles magnesium 73 g.

3 moles p-dibromobenzene 708 g.

2800 ml. ether (dried over sodium)

9 moles formaldehyde (trioxane) 270 g.

The trioxane was dried over phosphorous pentoxide for two days.

Fifty ml. of the solution of dibromobenzene solution in ether was run into the reaction flask, and the reaction started by the addition of a small amount of ethyl bromide. The remainder of the halide solution was added as rapidly as the reflux rate would permit (3.5 hrs.) without cooling. The mixture was left overnight, then filtered under a stream of nitrogen. No unreacted magnesium was found.

The dropping funnel was then replaced with a 12 mm. inlet tube for formaldehyde addition. In a 500 ml. flask attached to the inlet tube the trioxane was heated in order to depolymerize it, and the formaldehyde was driven into the reaction flask by a stream of dry nitrogen. (Care must be taken to keep the inlet tube above the reaction mixture.) After 6 to 7 hours the reaction was found to be completed, as shown by a negative Michler's ketone test. The reaction mix-

ture was hydrolyzed in the flask, using ice and 25 percent sulfuric acid. It was extracted with ether and dried over anhydrous sodium sulfate; and the ether was removed by distillation through a one foot Fenske column. The product was distilled at 135-145°/15 mm. and crystallized on standing. Recrystallization from ligroin gave large, flat white needles melting at 76-77°.

A yield of only 25 percent was obtained in the one reaction, although yields of 40 percent to 50 percent have been reported (85). A mixed melting point with the product obtained by the hydrolysis of p-bromobenzyl chloride gave no depression.

CONDENSATION REACTIONS, EXPERIMENTAL

Apparatus

All condensation reactions were carried out in a one liter round bottom standard taper three neck (24/40 - 34/45 - 24/40) flask. This was equipped with a dropping funnel and reflux condenser. Stirring was accomplished by means of a Hershberg stirrer (182) of nichrome wire.

To assure adequate mixing it was found necessary to use two glass-rod rings with attached wire stirrers. The stirrer was placed in the flask through a glycerine seal.

For the Claisen type condensations adequate greasing of the glass joints with silicone stopcock grease was found to be essential to prevent "freezing". The use of rubber stoppers is not to be recommended, due to the corrosive action of the reactants.

Distillations were carried out in a 250 ml. and a 50 ml. distillation flask with straight, heated columns. Heating of the flasks was accomplished by means of Glasco mantles, care being taken not to heat the product when it was not under vacuum. In order to be able to collect three fractions without breaking the vacuum an inclined rotating receiver was used (183), the fractions being collected in 50 ml. Erlenmeyer flasks.

Other apparatus, similar to the usual distillation heads, was not found to be suitable, due to the high viscosity of the products. The use of rotating receivers utilizing an Erlen-

meyer flask with attached receivers, such as the modified Pauly receiver (184) was also found to be unsuitable, as some of the products crystallized out in the sidearm, making the application of heat necessary.

FRIEDEL-CRAFTS BENZYLATION, EXPERIMENTAL

Reactants:

1.5 moles cresol (163 g.)

0.5 mole bromobenzyl chloride (105 g.)

400 ml. petroleum ether

0.25 mole aluminum chloride (33.4 g.)

The one and one-half moles of the cresol were dissolved in 400 ml. of petroleum ether. To this solution one-half mole of the bromobenzyl chloride was added rapidly. This mixture in the one liter reaction flask was stirred vigorously. To this was added one-quarter mole of aluminum chloride in small portions, over a two hour period. The reaction was carried out at room temperature (24-35°). Cooling was not found to be necessary. The stirring was continued for the times shown under the specific reactions.

At the conclusion of the reaction the red, oily aluminum chloride addition product settled out of the mixture. This was hydrolyzed by being poured, with continuous stirring, into a mixture of 500 g. of ice and 300 ml. of concentrated hydrochloric acid. The reaction products were then extracted with four 100 ml. portions of ethyl ether.

After removal of the solvent the remaining oil was treated with 250 ml. of Claisen solution (See Claisen Method, Experimental.) and extracted with four 100 ml. portions of petroleum ether to remove any O-benzylated products.

The alkaline, aqueous fraction was then acidified, in 500 g. of crushed ice, with 6 N hydrochloric acid. This solution was extracted with four 100 ml. portions of ethyl ether to remove the phenolic products.

The ethers used to extract both the O- and the C-alkylated fractions were removed on the steambath. In no case was there sufficient O-benzylated product isolated to be able to purify it and determine its identity.

The C-benzylated fraction obtained by the extraction of the acidified Claisen solution was fractionally distilled. The results of these distillations are given below; but it must be noted that the accuracy of the temperatures and pressures given is open to question, due to the ease with which these compounds superheat, as well as to the possible inaccuracy of the finger manometer (Corning Glass 6950) used. Correct values are given with the summarized physical constants of these compounds.

The fractions containing the desired phenolic product were redistilled at least once, then crystallized from hexane. This solvent caused less loss of product, due to solubility in the cold solvent, than did petroleum ether, which, however, may also be used. These crystallizations were continued until the products reached a constant melting point. The crystals were then redistilled, using a McLeod gauge to determine the pressure. The products were crystallized from hexane and their melting points determined by the capillary-tube method (185).

o-CRESOL AND o-BROMOBENZYL CHLORIDE:

These reactants were condensed, using the general procedure described in the preceding section. The reactions were run at 29-32° for periods of 60 to 72 hours.

Extraction of the Claisen solution with petroleum ether yielded only a trace of O-alkylated products. The phenolic fraction obtained by the acidification and extraction of the Claisen solution was purified as shown below.

4-HYDROXY-3-METHYL-2'-BROMODIPHENYLMETHANE

After removal of the excess and unreacted o-cresol (90-98 g.) by distillation under a slightly reduced pressure the reaction products were separated.

Distillation:

160-170°/2 mm.	3.8 g.
170-180°/2 mm.	9.7 g.
180-184°/2 mm.	18.4 g.
183-184°/2 mm.	24.9 g.
184-185°/2 mm.	11.4 g.
185-186°/2 mm.	16.8 g.
186-220°/2 mm.	7.0 g.
Tar	21.7 g.

All fractions boiling from 170-186°/2 mm. were redistilled. This compound crystallized very easily, making it necessary to heat the sidearm with a microburner during the distillation. The solid obtained was crystallized from hexane until the long, white fluffy needles had reached a constant melting

point. Considerable heating was necessary to dissolve this compound in hexane. From the filtrate of the crystallization there was isolated 32 g. of an unidentified oil. This probably contains some impure product; but it could not be separated in the pure state.

The average yield of pure product of four of the reactions was 21 percent (27.6 g.). One reaction, carried out under a stream of nitrogen, was run at 23° and gave a yield of only 10.1 percent (14 g.).

The product had the following physical constants:

B.P.	173-176°/2 mm.
M.P.	65.4-65.8°
Br calcd	28.83 percent
Br found	28.68, 28.94 percent

o-CRESOL AND m-BROMOBENZYL CHLORIDE:

Two reactions were run using these substances in the quantities and under the procedure given in the general reaction. For these condensations a reaction time of 72 hours at a temperature of 35° was used.

The separation of O-bromobenzylated product yielded only 2 g. of an unidentified oil.

4-HYDROXY-3-METHYL-3'-BROMODIPHENYLMETHANE

After removal of 102 g. of the unused o-cresol at 85-90°/16 mm. the product was distilled.

Distillation:

75-183°/3 mm.	10.1 g.
183-185°/3 mm.	20.8 g.
185-195°/3 mm.	26.9 g.
195-210°/3 mm.	23.7 g.
210-225°/3 mm.	8.6 g.
225-260°/3 mm.	2.5 g.
Tar	15.0 g.

All fractions boiling from 75-225°/2 mm. were redistilled twice and the high and low boiling portions of each fraction discarded. The intermediate fractions were then crystallized with difficulty at 0-10°. As the crystals contained a considerable amount of oil, they were dried on clay plates. The white, crystalline product was then recrystallized and again dried on clay plates until the crystals had reached a constant melting point. This purification procedure decreased the yield of pure product to 5.4 percent (7.5 g.). The combined filtrates, on evaporation of the solvent, yielded 25.3 g. of an unidentified oil. The product, which was obtained in the form of short, white fluffy needles, was found to have the following physical constants:

B.P.	172-175°/3 mm.
M.P.	46.4-46.8°
Br calcd	28.83 percent
Br found	28.85, 29.07 percent

The clay plates used to absorb the oily impurity from this crystalline product were extracted with ethyl ether. The oil obtained was purified by distillation and subsequent crystallization from hexane. It yielded only 1.5 g. of a white powder melting at 40-41°.

o-CRESOL AND p-BROMOBENZYL CHLORIDE:

These reactants were used in three condensations. The two successful reactions were carried out at 25-30° for 30 hours. The third reaction, which was run at 10-15°, was found to give a much smaller yield of the desired product.

The deep red-colored reaction mixture was hydrolyzed and extracted as described in the general procedure. The treatment with Claisen solution and subsequent extraction gave only a trace of an oil. The quantity was insufficient for identification.

The phenolic fraction was purified as shown below:

4-HYDROXY-3-METHYL-4'-BROMODIPHENYLMETHANE

Distillation:

57-58°/2 mm.	91.5 g.
58-85°/2 mm.	10.0 g.
85-140°/2 mm.	5.7 g.
140-180°/2 mm.	4.0 g.
180-190°/2 mm.	44.7 g.
190-200°/2 mm.	33.1 g.
200-205°/2 mm.	9.1 g.

205-210°/2 mm.	5.1 g.
210-225°/2 mm.	9.5 g.
Tar	10.3 g.

The fractions boiling from 180-210°/2 mm., a total of 92 g., crystallized into an oily solid. This was redistilled twice, with some difficulty, due to the ease with which it solidifies; and was then crystallized from hexane four times. A total of 42.2 g. of pure product, and 29.5 g. of an unidentified oil, were isolated. The average yield for the two reactions, based on the pure product, was 30.4 percent (42.2 g.) isolated in the form of fine, matted white needles.

B.P.	183-185°/2 mm.
M.P.	75.4-76.0°
Br calcd	28.83 percent
Br found	28.60, 29.14 percent

The one reaction run at 10-15° yielded only 10.5 percent (14.6 g.) of the same product.

o-CRESOL AND p-BROMOBENZYL ALCOHOL:

In order to compare both the products and the yields of the aluminum chloride catalyzed condensation of o-cresol with p-bromobenzyl chloride and with p-bromobenzyl alcohol, both condensations were run. The results, using p-bromobenzyl chloride, are given in the preceding section. The condensation using p-bromobenzyl alcohol was carried out as follows:

Reactants:

.33 mole p-bromobenzyl alcohol (62.4 g.)

.37 mole o-cresol (40.0 g.)

.25 mole aluminum chloride (33.4 g.)

200 ml. petroleum ether

The o-cresol was dissolved in 200 ml. petroleum ether; and the p-bromobenzyl alcohol, which proved to be only slightly soluble in the solvent, was added as a solid. With vigorous stirring the aluminum chloride was added over a 1.5 hour period with the reaction at 21-27°.

After 16 hours the reaction mixture was hydrolyzed in ice and concentrated hydrochloric acid. The product was extracted from the hydrolysis mixture with four 250 ml. portions of ethyl ether. This was dried over anhydrous potassium carbonate. After removal of the solvent the resultant oil was purified, as in all previous cases.

4-HYDROXY-3-METHYL-4'-BROMODIPHENYLMETHANE

Distillation:

62-70°/3 mm.	12.0 g.
70-165°/3 mm.	4.9 g.
165-180°/3 mm.	7.8 g.
180-190°/3 mm.	13.6 g.
190-215°/3 mm.	28.6 g.
215-300°/3 mm.	5.8 g.
Tar	21.0 g.

The fractions boiling from 165-215°/3 mm. were redistilled.

Repeated crystallization from hexane gave fine, matted white needles melting at 75.5-76.0°. A mixed melting point with 4-hydroxy-3-methyl-4'-bromodiphenylmethane, which had been prepared by the condensation of p-bromobenzyl chloride and o-cresol, showed no depression.

The yield of this condensation, using p-bromobenzyl alcohol, was 26 percent (24 g.), which is slightly less than that obtained by the condensation of o-cresol and p-bromobenzyl chloride.

o-CRESOL AND BENZYL CHLORIDE:

In this reaction an excess of o-cresol (162 g., 1.5 moles) was condensed with one-half mole of benzyl chloride (64 g.). The condensation was catalyzed by one-quarter mole of aluminum chloride (33.4 g.) and carried out in 200 ml. of petroleum ether at 26-31°. The isolation and purification of the desired product was carried out as in the condensations mentioned previously. No O-benzylated product was found.

4-HYDROXY-3-METHYLDIPHENYLMETHANE

Distillation:

60-95°/3 mm.

95-150°/3 mm.

150-160°/3 mm.

160-180°/3 mm.

180-195°/3 mm.

195-215°/3 mm.

The three fractions boiling from 150-195° were redistilled

twice, then crystallized from hexane. The product was obtained in short, white fluffy needles.

B.P.	155-156°/3 mm.
M.P.	49.6-50.2°
Br calcd	None
Br found	None

These data agree with those given by Huston, Swartout and Wardwell (77).

p-CRESOL AND p-BROMOBENZYL CHLORIDE:

In order to determine the yield of o-bromobenzylated compound obtained by the Friedel-Crafts reaction if the position para to the phenolic hydroxyl is blocked, two reactions were run to condense p-cresol and p-bromobenzyl chloride.

The reaction mixture was treated with 150 ml. Claisen solution and extracted with five 200 ml. portions of petroleum ether to remove the considerable quantity of oxygen-bromobenzylated product. The phenolic and ether fractions were then purified as in all previous cases.

2-HYDROXY-5-METHYL-4'-BROMODIPHENYLMETHANE

Distillation:

65-70°/2 mm.	110.0 g.
70-115°/2 mm.	1.5 g.
115-155°/2 mm.	1.0 g.
155-165°/2 mm.	5.2 g.
165-170°/2 mm.	12.0 g.
170-175°/2 mm.	18.4 g.

175-200°/2 mm.	2.6 g.
Tar	7.7 g.

The fraction boiling from 165-170°/2 mm. was crystallized from hexane to give 6.1 g. of product melting at 60-61°. A mixed melting point with a sample of 2-hydroxy-5-methyl-4'-bromodiphenylmethane, prepared by the Claisen method (B.P. 172-175°/2 mm., M.P. 61.6-62.2°) showed only a small depression (M.P. 60-61°).

The fraction isolated at 170-175°/2 mm., yielded 9.4 g. of white needles after crystallization from hexane. These crystals melted at 75.5-79.0°. Further crystallization did not shorten the range of this melting point. Both the benzoate (M.P. 42.0-43.5°) and the p-toluene sulfonate (M.P. 48.0-51.0°) of this compound were prepared. These do not agree with the melting points of the corresponding derivatives of 2-hydroxy-5-methyl-4'-bromodiphenylmethane (63.5-64.0° and 69.5-71.0° respectively). No further attempt was made to identify this product.

4-METHYLPHENYL-4-BROMOBENZYL ETHER

This product, extracted from the basic Claisen solution with petroleum ether, was distilled as shown:

Distillation:

71-100°/2 mm.	3.2 g.
100-155°/2 mm.	1.0 g.
155-165°/2 mm.	21.7 g.
165°/2 mm.	13.1 g.

165-250°/2 mm.	1.3 g.
250-255°/2 mm.	7.5 g.
255-260°/2 mm.	1.1 g.
Tar	4.0 g.

All fractions boiling from 155-255°/2 mm. were crystallized from 95 percent ethanol to give a total of 24 percent (33 g.) of product melting at 101.0-101.5°. A mixed melting point with 4-methylphenyl-4-bromobenzyl ether, obtained as a by-product in the o-benzylation by the Claisen method (B.P. 161-165°/2 mm., M.P. 101.5-102.0°) showed no depression.

CLAISEN C-ALKYLATION OF PHENOLS, EXPERIMENTAL

Reactants:

0.5 mole sodium (11.5 g.)

0.5 mole cresol (54.7 g.)

0.5 mole bromobenzyl chloride (103 g.)

300 ml. toluene (dry)

The sodium, freshly cut into small cubes, was placed in the one liter flask with 100 ml. of toluene. It was refluxed, with continual stirring, for 1.5 hours until it had formed small fluid pellets. At this time one-half mole of the cresol, dissolved in 100 ml. of toluene, was added slowly and with caution*. This addition was most effectively accomplished without removing the heat from the flask; but for this reason it must be run carefully for approximately 1.5 hours. (It has recently been pointed out (187) that for the syntheses of sodium phenolates sodium hydride is more conveniently handled than is sodium.)

The sodium cresolate formed a white, pasty mass which was refluxed for a period of from one to two hours at 110° to insure completeness of the reaction. To this well stirred, viscous suspension was added one-half mole of the bromobenzyl chloride, dissolved in 100 ml. of toluene. Heating was also continued during this addition, which required one hour.

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* Phenolic burn antidotes: Limewater or a saturated solution of bromine in glycerol. (Let the undissolved bromine settle out before use.) (186) In no case use organic solvents.

The reaction was stirred and refluxed at 105-110° for the times shown under the specific reactions. A deeply colored reaction mixture resulted. It was acidified with 6 N hydrochloric acid in ice to remove the sodium chloride formed. This acidic extraction was found preferable to the usual water extraction, as the latter dissolved some of the sodium salts.

The toluene was separated and the aqueous layer further extracted with two 100 ml. portions of toluene. The toluene was then distilled off at atmospheric pressure, the last traces being removed by distillation under a slight vacuum to insure complete separation in the next step.

The residual liquid was cooled and treated with 250 ml. of Claisen's solution* (188) and the insoluble oxygen-benzylated product extracted from the potassium phenolates with four 100 ml. portions of petroleum ether. (Ethyl ether cannot be used, due to the solubility of the methanolic solution of the phenolates in it.) The presence of toluene in the reaction mixture causes the formation of an emulsion in this separation.

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* 350 g. KOH in 250 g. H_2O, diluted to one liter with methanol. Concentrated aqueous (50 percent) KOH cannot be used, as the potassium salts are insoluble in it. Therefore they form either an oily layer between the petroleum ether and the KOH, or partially dissolve in the ether.

The Claisen solution was then acidified in 500 g. of crushed ice with 6 N hydrochloric acid. The ice serves to dilute the methanol concentration, as well as to cool the reaction. It was then extracted with four 100 ml. portions of ethyl ether. The ethyl ether was removed on the steambath; then the residual oil was fractionally distilled. The results of these distillations are given below; but it must be noted that the accuracy of the temperatures and pressures given is open to question, due to the ease with which the distillate superheats, and the possible inaccuracy of the finger manometer used. Correct values are given with the summarized physical constants of these compounds. The fractions containing the desired products were redistilled at least once, then crystallized from hexane. The crystalline products were recrystallized until they reached a constant melting point. These were then redistilled using a McLeod gauge to determine the pressure. After crystallization from hexane the melting points were again determined.

In those runs in which the methylphenylbromobenzyl ether formed in previous reactions was added to the reaction mixture, this addition took place after the sodium cresolate had been formed, and before the bromobenzyl chloride had been added.

The O-bromobenzylated compounds extracted from the Claisen solution were purified in the same fashion as was the C-bromobenzylated compound. However, 95 percent ethanol, ra-

ther than hexane, was used as crystallization solvent for these ethers.

o-CRESOL AND o-BROMOBENZYL CHLORIDE:

These reactants were combined using the general procedure described above. Reaction times of 16 to 19 hours were used in the five reactions run.

The 2-hydroxy-3-methyl-2'-bromodiphenylmethane was separated from the 2-methylphenyl-2-bromobenzyl ether by extraction with Claisen solution. The two products were then purified by distillation and crystallization.

2-HYDROXY-3-METHYL-2'-BROMODIPHENYLMETHANE

Distillation:

Below 60°/2 mm.	13.4 g.
60-170°/2 mm.	0.6 g.
170-172°/2 mm.	3.5 g.
172-186°/2 mm.	27.7 g.
190-250°/2 mm.	2.9 g.
Tar	5.4 g.

The 172-186°/2 mm. fraction was redistilled twice, then crystallized from hexane as described above. Short, white matted needles were isolated in an average yield (3 reactions) of 13 percent (18 g.).

B.P.	157-160°/2 mm.
M.P.	41.4-42.0°
Br calcd	28.83 percent
Br found	29.13, 28.85 percent

When 18 grams of the 2-methylphenyl-2-bromobenzyl ether were added to the reaction mixture, yields of 4.4 percent (4.7 g.) and 5.2 percent (7.1 g.) of 2-hydroxy-3-methyl-2'-bromodiphenylmethane were isolated.

2-METHYLPHENYL-2-BROMOBENZYL ETHER

Distillation:

65-70°/2 mm.	9.6 g.
70-140°/2 mm.	5.2 g.
140-155°/2 mm.	29.4 g.
155-170°/2 mm.	4.2 g.
170-260°/2 mm.	3.0 g.
Tar	10.5 g.

The fractions boiling from 140-170°/2 mm. were redistilled and crystallized from 95 percent ethanol to give long, flat white needles in an average yield (3 reactions) of 18 percent (24.9 g.).

B.P.	136-140°/2 mm.
M.P.	46.6-47.2°
Br calcd	28.83 percent
Br found	28.93, 28.90 percent

Twelve grams of an unidentified oil were isolated from the filtrate of this crystallization. This may contain impure product, but further purification was not possible.

In the reactions in which this ether was added to the reaction mixture the yield of the 2-methylphenyl-2-bromobenzyl ether, after subtracting the added amount, was decreased to an

average yield of 11 percent (15 g.) in the two reactions.

o-CRESOL AND m-BROMOBENZYL CHLORIDE:

Reaction times of 26 to 85 hours were used in the four reactions in which these two compounds were condensed. During this time the creamy white reaction mixture had turned to a straw color which on cooling became a deep gray, then violet.

The phenolic and ether fractions were separated and purified as before.

2-HYDROXY-5-METHYL-3'-BROMODIPHENYLMETHANE

Distillation:

65-95°/2 mm.	14.2 g.
95-105°/2 mm.	1.0 g.
105-170°/2 mm.	0.5 g.
170-175°/2 mm.	5.8 g.
175-180°/2 mm.	9.4 g.
180-190°/2 mm.	5.0 g.
190-295°/2 mm.	0.5 g.
Tar	4.0 g.

The 170-190°/2 mm. fractions were redistilled and crystallized from hexane to give an average yield of 8 percent (11.1 g.). The two reactions, which were run for 85 hours, gave an average yield of 12 percent. The product was obtained in the form of matted, short white needles.

B.P.	162-167°/2 mm.
M.P.	48.8-49.4°
Br calcd	28.83 percent
Br found	28.58, 28.86 percent

2-METHYLPHENYL-3-BROMOBENZYL ETHER

Distillation:

70-150°/2 mm.	9.5 g.
150-160°/2 mm.	20.5 g.
160-170°/2 mm.	12.9 g.
170-190°/2 mm.	8.9 g.
190-250°/2 mm.	1.1 g.
Tar	12.0 g.

The fractions boiling from 150-170°/2 mm. were redistilled four times to give a colorless liquid in an average yield of 21 percent (29 g.) for those reactions which had been run 26 hours. In the case of the two reactions run for 85 hours an average yield of 18 percent (24.9 g.) of this ether was obtained.

B.P.	157-162°/3 mm.
n_D^{20}	1.5950
D_4^{20}	1.3398
Br calcd	28.83 percent
Br found	29.11, 28.80 percent

Cooling this liquid in a dry ice-acetone bath resulted in the formation of a glass-like solid which melted at room temperature. All attempts to crystallize it failed.

o-CRESOL AND p-BROMOBENZYL CHLORIDE:

This condensation, using the same quantities as were used in the previous reactions, was allowed to react for from four to fifteen hours. Of the five reactions, two were run in the presence of an added quantity of the p-bromobenzyl ether of o-cresol.

In all the reactions these white sodium cresolates turned a straw color on addition of the p-bromobenzyl chloride. After reflux there resulted a bright orange solution which turned purple on cooling.

After acidification and removal of the toluene used for extraction, an average of 148 g. of the crude products was isolated. The phenolic and ether fractions were separated and purified as before.

2-HYDROXY-3-METHYL-4'-BROMODIPHENYLMETHANE

Distillation:

56-60°/2 mm.	10.0 g.
60-140°/2 mm.	0.5 g.
140-180°/2 mm.	30.0 g.
180-300°/2 mm.	6.8 g.
Tar	10.6 g.

The fraction boiling from 140-180°/2 mm. was redistilled twice. During this distillation the sidearm had to be heated constantly, due to the ease with which this compound crystallized. After three crystallizations from hexane the product was isolated in the form of long, flat white needles

in 8.7 percent (12 g.) yield.

B.P.	162-164°/3 mm.
M.P.	50.6-51.0°
Br calcd	28.83 percent
Br found	28.89, 28.92 percent

It was noted that this crystallization caused a 34 percent loss from the redistilled product to the final, pure crystalline product.

The two reactions in which the 2-methylphenyl-4-bromobenzyl ether was added to the reaction mixture, as described under the general procedure, showed a marked increase in yield. In the reaction in which 15 g. of this ether was added the final yield of the C-bromobenzylated product was increased from the 8.7 percent to 22.8 percent (31.6 g.); however, increasing the quantity of the 2-methylphenyl-4-bromobenzyl ether added to 25 g. increased the yield to only 17 percent (23.6 g.). This effect has been noted previously by Guile (128) and Neeley (129).

2-METHYLPHENYL-4-BROMOBENZYL ETHER

Distillation:

85-122°/2 mm.	1.3 g.
122-150°/2 mm.	7.7 g.
150-170°/2 mm.	28.1 g.
170-185°/2 mm.	1.6 g.
185-275°/2 mm.	1.6 g.
Tar	20.0 g.

The 150-170°/2 mm. fraction was redistilled twice and crystallized from 95 percent ethanol to give long, flat white needles in an average yield of 18 percent (24.9 g.). In both reactions in which the 2-methylphenyl-4-bromobenzyl ether had been added to the reaction mixture the yield of this ether was increased to 22 percent (30.5 g.) after subtracting the quantity added from the amount obtained.

B.P.	152-155°/2 mm.
M.P.	70.8-71.2°
Br calcd	28.83 percent
Br found	28.53, 28.62 percent

This compound was also used to determine the accuracy of a Beckmann cryoscopic molecular weight apparatus (189). A molecular weight of 271.1 was found in the one determination run (Calcd 277.2).

o-CRESOL AND BENZYL CHLORIDE:

In this reaction one-half mole of the sodium o-cresolate was prepared as before. To this was added one-half mole (64 g.) of benzyl chloride over a one hour period. The reaction was refluxed for 6 hours.

The extraction and purification of the products was carried out as in the previous cases.

2-HYDROXY-3-METHYLDIPHENYLMETHANE

Distillation:

50-60°/2 mm.

60-120°/2 mm.

120-140°/2 mm.

140-165°/2 mm.

165-215°/2 mm.

215-240°/2 mm.

The fraction boiling at 140-165°/2 mm. was redistilled twice, and then was crystallized from hexane three times to give fine, matted white needles.

B.P.	148-152°/2 mm.
M.P.	50.2-50.6°
Br calcd	None
Br found	None

These data agree with those given by Schorigin (142) and by Huston, Swartout and Wardwell (77).

2-METHYLPHENYL BENZYL ETHER

Distillation:

37-60°/2 mm.

60-110°/2 mm.

110-152°/2 mm.

152-170°/2 mm.

170-240°/2 mm.

The fractions boiling from 110-170°/2 mm. were redistilled four times to give a clear, light straw colored liquid.

B.P.	118-124°/3 mm.
n_D^{20}	1.5750
D_4^{20}	1.0663
Br calcd	None
Br found	None

The boiling point of this compound is given by Staedel (190) and by Huston, Swartout and Wardwell (77) as 285-290°.

p-CRESOL AND o-BROMOBENZYL CHLORIDE:

Four one-half mole reactions were carried out to condense these two compounds. These reactions were allowed to run for 16 to 29 hours. Again the usual purification procedure was followed.

2-HYDROXY-5-METHYL-2'-BROMODIPHENYLMETHANE

Distillation:

65-130°/2 mm.	2 g.
130-170°/2 mm.	2 g.
170-180°/2 mm.	16 g.
180-187°/2 mm.	12 g.
187-197°/2 mm.	12 g.
197-220°/2 mm.	6 g.
220-280°/2 mm.	7 g.
Tar	20 g.

The fractions boiling from 170-197°/2 mm. were redistilled three times and the low and high boiling fractions discarded. The intermediate fractions were crystallized from hexane until the crystals reached a constant melting point. The average yield of the three reactions which had been run 16, 24 and 29 hours was 20 percent (27.2 g.). One reaction, which had been run 18 hours, gave a yield of only 8.5 percent (11.8 g.). The product consisted of short, white needles and had the following physical constants:

B.P.	158-161°/2 mm.
M.P.	47.5-48.1°
Br calcd	28.83 percent
Br found	28.79, 29.02 percent

The boiling point of this compound as determined by the careful distillation of the pure product is found to be considerably lower than the temperatures given in the distillation of the crude mixture. This superheating was consistently found in all four of the reactions run.

4-METHYLPHENYL-2-BROMOBENZYL ETHER

Distillation:

83-160°/4 mm.	3.0 g.
160-180°/4 mm.	17.1 g.
180-190°/4 mm.	7.3 g.
190-220°/4 mm.	2.0 g.
220-250°/4 mm.	6.4 g.
Tar	5.0 g.

The fractions boiling from 160-190°/4 mm. were redistilled. The distillate was crystallized, with difficulty, from 95 percent ethanol (at 0-10°). The product was filtered and dried in a vacuum dessicator at 10°. The ether, in the form of a flocculent, powdery mass, was obtained in an average yield of 14 percent (19.3 g.).

B.P. 142-146°/2 mm.

M.P. 25-26°

Br calcd 28.83 percent

Br found 29.17, 29.04 percent

The fraction boiling from 230-250°/4 mm. solidified to a gray, crystalline compound. This was crystallized from ethanol without difficulty to give flat white needles (3.5 g.) melting at 78-81°. The bromine content of this substance was found to be 35.89 percent. This value corresponds to the bromine content calculated for the 2-bromobenzyl ether of 2-hydroxy-5-methyl-2'-bromodiphenylmethane (35.82 percent).

p-CRESOL AND m-BROMOBENZYL CHLORIDE:

Two Claisen C-benzylations were run using these reactants. For both a reaction time of 24 hours was used. The separation and purification of the O- and C-bromobenzylated fractions (148 g. crude) was carried out as in all previous reactions.

2-HYDROXY-5-METHYL-3'-BROMODIPHENYLMETHANE

Distillation:

70-78°/3 mm.	18.3 g.
78-95°/3 mm.	1.7 g.
95-180°/3 mm.	2.2 g.
180-185°/3 mm.	26.2 g.
183-186°/3 mm.	8.0 g.
186-190°/3 mm.	1.2 g.
Tar	10.0 g.

The fractions boiling from 180-186°/3 mm. were redistilled twice. Some difficulty in distillation was encountered due to the tendency of the product to solidify in the side-arm. The resultant crystalline compound was recrystallized from hexane to give very short, white fluffy needles in an average yield of 16 percent (22 g.).

B.P.	174-176°/2 mm.
M.P.	58.6-59.2°
Br calcd	28.83 percent
Br found	28.98, 28.82 percent

4-METHYLPHENYL-3-BROMOBENZYL ETHER

An average of 51 g. of crude O-bromobenzylated compound were extracted by petroleum ether from the Claisen solution treated reaction mixture.

Distillation:

75-90°/3 mm.	5.5 g.
90-160°/3 mm.	4.0 g.
160-168°/3 mm.	7.4 g.
168-182°/3 mm.	11.0 g.
182-202°/3 mm.	7.0 g.
202-217°/3 mm.	2.5 g.
217-240°/3 mm.	1.4 g.
Tar	11.0 g.

The fractions boiling from 160-202°/3 mm. were redistilled. During this distillation it was necessary to heat the side-arm with a microburner to prevent crystallization of the

compound. The crystalline product was recrystallized twice from 95 percent ethanol to give short, flat white needles in 10.6 percent (15 g.) yield.

B.P.	157-161°/2 mm.
M.P.	53.0-53.6°
Br calcd	28.83 percent
Br found	29.12, 28.87 percent

p-CRESOL AND p-BROMOBENZYL CHLORIDE:

Due to the relatively excellent yield of this reaction only two such condensations were necessary. One of these was run without the addition of the 4-methylphenyl-4-bromobenzyl ether; in the other this ether was added to the reaction mixture.

2-HYDROXY-5-METHYL-4'-BROMODIPHENYLMETHANE

Distillation:

65-85°/3 mm.	9.2 g.
85-175°/3 mm.	28.8 g.
175-190°/3 mm.	15.4 g.
190-220°/3 mm.	26.9 g.
220-240°/3 mm.	2.2 g.
240-250°/3 mm.	7.1 g.
Tar	9.2 g.

The fractions boiling from 65-85°/3 mm. and 240-250°/3 mm. remained red oils; while all the other fractions boiling from 85-240°/3 mm. crystallized very easily, making it necessary to heat the sidearm during the distillation. These

latter fractions were redistilled twice and were then crystallized from hexane. Short, fluffy white needles were obtained in 41.9 percent (57.8 g.) yield. When 14 g. of the 4-methylphenyl-4-bromobenzyl ether were added to the reaction mixture, this yield of 2-hydroxy-5-methyl-4'-bromodiphenylmethane was decreased slightly to 39.7 percent (55.0 g.).

B.P.	173-175°/2 mm.
M.P.	61.6-62.2°
Br calcd	28.83 percent
Br found	28.76, 28.82 percent

4-METHYLPHENYL-4-BROMOBENZYL ETHER

Distillation:

100-145°/4 mm.	5.3 g.
145-185°/4 mm.	10.3 g.
185-195°/4 mm.	22.6 g.
195-220°/4 mm.	1.8 g.
Tar	7.3 g.

The fractions boiling from 145-195°/4 mm. crystallized very easily, making it necessary to heat the distillation apparatus continually with a microburner to prevent crystallization in the sidearm. The compound was crystallized from 95 percent ethanol. It showed remarkably low solubility in this solvent, even when heated.

Both reactions, the one with, and the one without, the addition of the ether, gave a 10 percent (13.9 g.) yield

of 4-methylphenyl-4-bromobenzyl ether. It was obtained in the form of short, fine, flat white needles.

B.P. 161-165°/2 mm.

M.P. 101.5-102.0°

Br calcd 28.83 percent

Br found 28.79, 28.68 percent

p-CRESOL AND BENZYL CHLORIDE:

As in the same reaction using o-cresol, one-half mole of sodium o-cresolate and one-half mole (64 g.) of benzyl chloride were allowed to react in toluene for a period of six hours.

The extraction and purification of the products were carried out as in the previous cases.

2-HYDROXY-5-METHYLDIPHENYLMETHANE

Distillation:

65-85°/3 mm.

85-135°/3 mm.

135-165°/3 mm.

165-210°/3 mm.

210-225°/3 mm.

225-235°/3 mm.

The fractions boiling from 135-210°/3 mm. were redistilled twice, and the low and high boiling fractions discarded. The intermediate fractions obtained were crystallized from hexane until a constant melting point was achieved. These crystallizations had to be carried out at about 10°. The

product was isolated in the form of fine, white, fluffy needles.

B.P.	144-147°/3 mm.
M.P.	36.2-36.8°
Br calcd	None
Br found	None

These data agree with those given by Huston and Lewis (78).

4-METHYLPHENYL BENZYL ETHER

Distillation:

40-125°/3 mm.	2.7 g.
125-150°/3 mm.	6.5 g.
150-190°/3 mm.	3.6 g.

The fraction boiling from 125-150°/3 mm. was redistilled once and then crystallized twice from 95 percent ethanol to give 3.5 g. of thin, white plates. The amount isolated was insufficient to determine the boiling point accurately.

M.P.	40.0-41.2°
Br calcd	None
Br found	None

This melting point agrees with that given by Staedel (190), and by Huston and Lewis (78).

SUMMARY OF YIELDS AND PHYSICAL CONSTANTS

In the table on the following page are given the yields and physical constants of the compounds prepared, and the by-products which were isolated.

The yields are based on the quantity of pure product obtained. As a considerable amount of the desired product is lost during purification, the yields reported are lower than those actually given by the reaction.

The boiling points given were obtained by the distillation of the pure product under reduced pressure. This pressure was measured using a tilting type McLeod gauge (Scientific Glass Co. No. 10-297).

The products of these distillations were crystallized from either hexane (for phenolic compounds), or from 95 percent ethanol (for the ethers), and dried at room temperature. The crystals obtained were used to determine the melting points given on the table, by the capillary-tube method (185).

All boiling points and melting points are uncorrected.

FRIEDEL-CRAFTS BENZYLATION

REACTANTS	PRODUCTS	YIELD %	B.P. °C	M.P. °C	BR CALCD %	BR FOUND %
o-cresol, o-bromobenzyl chloride	4-hydroxy-3-methyl-2'-bromodiphenylmethane	21.0	173-176/ 2 mm.	65.4-65.8	28.83	28.68 28.94
o-cresol, m-bromobenzyl chloride	4-hydroxy-3-methyl-3'-bromodiphenylmethane	5.4	172-175/ 3 mm.	46.4-46.8	28.83	28.85 29.07
o-cresol, p-bromobenzyl chloride	4-hydroxy-3-methyl-4'-bromodiphenylmethane	30.4	183-185/ 2 mm.	75.4-76.0	28.83	28.60 29.14
o-cresol, p-bromobenzyl alcohol	4-hydroxy-3-methyl-4'-bromodiphenylmethane	26.0	180-185/ 2 mm.	75.5-76.0	28.83	
o-cresol, benzyl chloride	4-hydroxy-3-methyldiphenylmethane	-----	155-158/ 3 mm.	49.6-50.2	0	0 -----
p-cresol, p-bromobenzyl chloride	2-hydroxy-5-methyl-4'-bromodiphenylmethane	4.5	165-170/ 2 mm.	60.0-61.0	28.83	
	4-methylphenyl-4-bromobenzyl ether	24.0	--------	101.0-101.5	28.83	

CLAISEN C-ALKYLATION OF PHENOLS

REACTANTS	PRODUCTS	YIELD %	B.P. °C	M.P. °C	BR CALCD %	BR FOUND %
o-cresol, o-bromobenzyl chloride	2-hydroxy-3-methyl-2'-bromodiphenylmethane	13.0	157-160/ 2 mm.	41.4-42.0	28.83	29.13 28.85
	2-methylphenyl-2-bromobenzyl ether	18.0	136-140/ 2 mm.	46.6-47.2	28.83	28.93 28.90
o-cresol, o-bromobenzyl chloride 2-methylphenyl-2-bromobenzyl ether	2-hydroxy-3-methyl-2'-bromodiphenylmethane	4.8		41.4-42.0		
	2-methylphenyl-2-bromobenzyl ether	11.0		46.6-47.2		
o-cresol, m-bromobenzyl chloride	2-hydroxy-3-methyl-3'-bromodiphenylmethane	12.0	162-167/ 2 mm.	48.8-49.4	28.83	28.58 28.86
	2-methylphenyl-3-bromobenzyl ether	18.0	157-162/ 3 mm.	liquid	28.83	29.11 28.80
o-cresol, p-bromobenzyl chloride	2-hydroxy-3-methyl-4'-bromodiphenylmethane	8.7	162-164/ 3 mm.	50.6-51.0	28.83	28.89 28.92
	2-methylphenyl-4-bromobenzyl ether	18.0	152-155/ 2 mm.	70.8-71.2	28.83	28.53 28.62
o-cresol, p-bromobenzyl chloride 2-methylphenyl-4-bromobenzyl ether	2-hydroxy-3-methyl-4'-bromodiphenylmethane	22.8		50.6-51.0		
	2-methylphenyl-4-bromobenzyl ether	22.0		70.8-71.2		

.8

o-cresol, benzyl chloride	2-hydroxy-3-methyldiphenylmethane	-----	148-152/ 2 mm.	50.2-50.6	0	0 -----
	2-methylphenylbenzyl ether	-----	118-124/ 3 mm.	liquid	0	0 -----
p-cresol, o-bromobenzyl chloride	2-hydroxy-5-methyl-2'-bromodiphenylmethane	20.0	158-161/ 2 mm.	47.5-48.1	28.83	28.79 29.02
	4-methylphenyl-2-bromobenzyl ether	14.0	142-146/ 2 mm.	25.0-26.0	28.83	29.17 29.04
p-cresol, m-bromobenzyl chloride	2-hydroxy-5-methyl-3'-bromodiphenylmethane	16.0	174-176/ 2 mm.	58.8-59.2	28.83	28.98 28.82
	4-methylphenyl-3-bromobenzyl ether	10.6	157-161/ 2 mm.	53.0-53.6	28.83	29.12 28.87
p-cresol, p-bromobenzyl chloride	2-hydroxy-5-methyl-4'-bromodiphenylmethane	41.9	172-175/ 2 mm.	61.6-62.2	28.83	28.76 28.82
	4-methylphenyl-4-bromobenzyl ether	10.0	161-165/ 2 mm.	101.5-102.0	28.83	28.79 28.68
p-cresol, p-bromobenzyl chloride 4-methylphenyl-4-bromobenzyl ether	2-hydroxy-5-methyl-4'-bromodiphenylmethane	39.7		61.6-62.2		
	4-methylphenyl-4-bromobenzyl ether	10.0		101.5-102.0		
p-cresol, benzyl chloride	2-hydroxy-5-methyldiphenylmethane	-----	144-147/ 3 mm.	36.2-36.8	0	0 -----
	4-methylphenylbenzyl ether	----	--------	40.0-41.2	0	0 -----

PROOF OF STRUCTURE

A number of methods are available which may be used to prove the structures of the compounds obtained.

To determine the structures of the o- and p-benzylated phenols prepared by Huston et al. (191), each of the bromobenzyl chlorides was condensed with 2,4-dibromophenol by the Claisen method, and with 2,6-dibromophenol by the Friedel-Crafts method. The condensation products were proved to be identical with those obtained by the bromination of the condensation products of phenol and the bromobenzyl chlorides.

A number of degradative methods are available. Oxidation to the benzophenones can be accomplished by chromic acid oxidation or alkaline potassium permanganate (192). To protect the phenolic hydroxyl group its methyl ether must be prepared previous to the oxidation. Although the methylene group is much more liable to oxidation than is the methyl group, the latter may be oxidized to give rise to a carboxylic acid by-product.

If the benzophenones can be prepared from the diphenylmethanes they can be split by treatment with sodium amide in benzene under reflux as shown by Haller: (209)

$$R-\underset{\underset{O}{\|}}{C}-R' \xrightarrow{NaNH_2} RH + R-\underset{\underset{ONa}{|}}{C}=NH + R'H + R'-\underset{\underset{ONa}{|}}{C}=NH$$

The problem of the separation of the four products would be considerable.

An alternate method of splitting of the benzophenones entails the preparation of their oximes. This may prove to be difficult, especially in cases where o-positions on both rings are occupied.

If these oximes can be prepared, their syn and anti forms may be separated partially by fractional crystallization from a glacial acetic acid-water mixture (193). These benzophenones can then be rearranged to the benzanilides by means of the Beckmann rearrangement. These can be hydrolized using concentrated hydrochloric acid at 160° (194) to give four possible products. In spite of the original separation of the isomers, the purification of these products would be difficult.

Because the above methods introduce difficulties in separation, a need for fairly large quantities of material, or the necessity for the syntheses of other compounds, simpler methods were found to be preferable.

These consisted of the dehalogenation of the bromobenzylated cresols to the known benzylated compounds; and in the case of o-cresol, the rearrangement of the ethers formed as by-products in the Claisen C-benzylation, to the parabromobenzylated products identical to those obtained by the Friedel-Crafts method.

THE REARRANGEMENT OF PHENYL BENZYL ETHERS

The Claisen Rearrangement of allyl ethers of enols and phenols (195) requires the following group of atoms in order to have the rearrangement take place:

As the benzyl ethers contain the requisite group of atoms, numerous attempts have been made to rearrange these.

Using conditions similar to those used for the allyl ethers did not affect rearrangement (196).

Gomberg and Buchler (138) believed that they were dealing with a rearrangement in the reaction of sodium phenolate and benzyl chloride to give benzylphenol. However, as shown by Claisen (197), this reaction is not due to a rearrangement of the ether. The phenyl benzyl ether, when formed, could not be rearranged by the conditions used by Gomberg and Buchler.

Braun (198) did obtain benzylphenol from benzyl phenyl ether; but as he worked in the presence of concentrated hydrochloric acid, it is probable that the reaction took place by splitting to give the benzyl chloride which subsequently reacted to give the benzylphenol.

Van Alphen (199) prepared a small quantity of 4-hydroxydiphenylmethane by heating the benzyl phenyl ether with zinc chloride. Short (200) treated the ether with anhydrous zinc chloride at 160°, or at 100° when a stream of hydrogen chloride was passed through. He obtained phenol, some o-

hydroxydiphenylmethane, more p-hydroxydiphenylmethane, and a considerable amount of high boiling products. Short and Stewart (201) found this reaction to be intermolecular with benzyl chloride an intermediate, as 2,4-dibenzylphenol was formed under all conditions tried, and as in the presence of anisole more than half the benzyl groups became attached to the anisole nucleus.

Schorigin (202) found that heating phenyl benzyl ethers to 100° with sodium for 28 hours usually resulted in a rearrangement to a carbinol. Thus, 22 g. of p-tolylbenzyl ether yielded 1.5 g. of toluene, 3 g. phenyl p-tolyl carbinol, and 5.7 g. p-cresol. This did not hold true for o-tolylbenzyl ether, which formed 2-hydroxydibenzyl.

Behaghel and Freiensehner (203) did succeed in rearranging phenyl benzyl ethers in small yield, without the presence of halogen, under drastic conditions. The ether was treated for eight hours under reflux at 250° to give a viscous red liquid which contained a 10 percent yield of phenol, 4 percent of p-benzylphenol, and some o-, p-dibenzylphenol.

The reaction was found to be much more rapid and complete when some zinc or copper was added to the ether. However, even then the reaction temperature must be kept at 250°, as at a lower temperature no rearrangement takes place. Refluxing the phenyl benzyl ether with a piece of zinc for 18 hours gave a yield of 27 percent of a mixture of o- and p-

benzylphenols and a 20 percent yield of o-, p-dibenzylphenol; while the rearrangement of phenyl benzyl ether proceeded slowly without zinc, that of ∝ naphthyl benzyl ether went rapidly. The possibility of halogen impurities in the compounds used must be considered.

o-cresyl benzyl ether treated as above, without catalyst, yielded 14 percent o-cresol and 30 percent p-benzyl-o-cresol, as well as some 2,4-dibenzyl-o-cresol shown to be the same as that obtained by Huston et al. (77).

In all these rearrangements the benzyl group shifts predominantly to the position p- to the hydroxyl. In the case of the p-cresyl benzyl ether the rearrangement does not take place, or takes place only very slowly.

EXPERIMENTAL

I. Rearrangement of the Ether using Zinc and Heat.

Fifty grams of 2-methylphenyl-2-bromobenzyl ether, and five grams of zinc, were heated to 240-250° for 23 hours. The tarry reaction mixture was then treated with Claisen solution and extraction with ethyl ether. After removal of the solvent the oil obtained was fractionated by distillation to give 9 grams of a yellow, viscous liquid boiling at 165-175°/3 mm. This could not be purified further and did not crystallize.

Due to the low yield and the large amount of charring resulting from the above reaction, the use of this method was abandoned.

II. Rearrangement of the Ether using $ZnCl_2$, HCl and Heat.

This method as developed by Short and Stewart (201) permits the reaction to be carried out at a lower temperature than the 250° used before. Therefore less decomposition would be expected.

Fifty grams of the 2-methylphenylbromobenzyl ether were combined with 2.5 grams of zinc chloride and heated to 100°. At this temperature anhydrous hydrogen chloride (run through concentrated sulfuric acid) was bubbled through the molten mixture. The reaction vessel was shaken occasionally. It was found that two hours was sufficient time in which to complete the reaction.

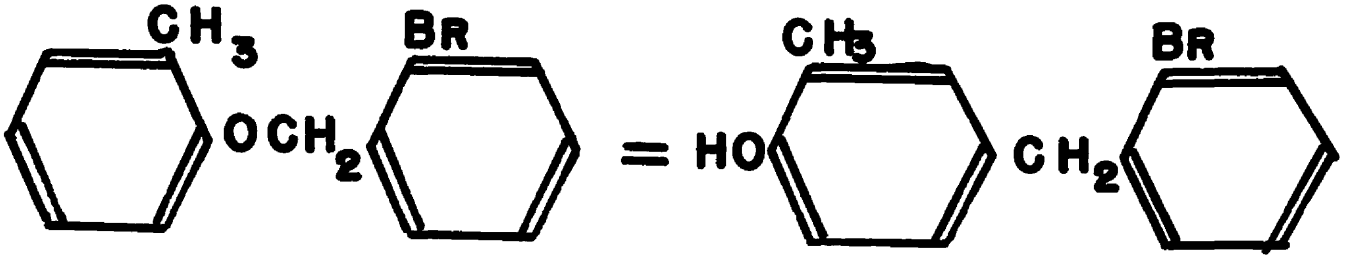
The hot mixture was than poured into 200 ml. of water, and the product was extracted from the acid solution with ethyl ether.

After removal of the solvent, treatment with Claisen solution showed no trace of the original oxygen alkylated compounds.

The phenolic fraction, recovered from the acidified Claisen solution, was fractionally distilled. In each case a low boiling fraction (B.P. 50-65°/3 mm., 185-189°/739 mm.) was isolated. This was shown to be o-cresol (B.P. 191°/760 mm.) by preparing its aryloxyacetic acid derivative (204), M.P. 152-153°. A mixed melting point with the same derivative prepared from a sample of o-cresol (M.P. 152-153°) showed no depression.

The higher boiling p-bromobenzylated o-cresols were distilled at least twice, then crystallized from hexane until a constant melting point was reached. These compounds were then redistilled and recrystallized. The physical constants are given on the next page.

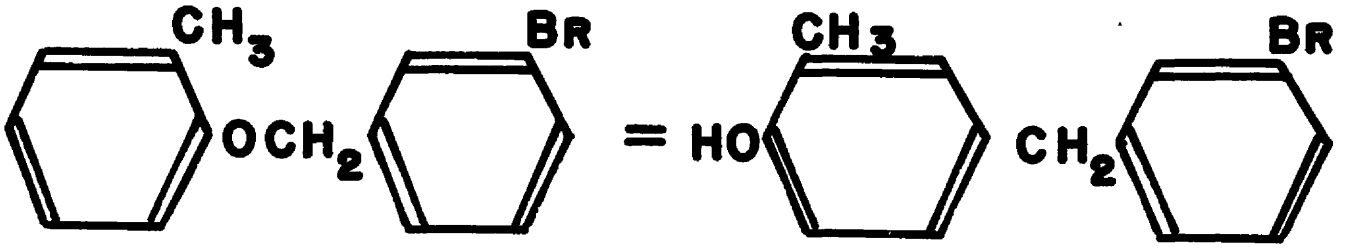
In each case oils which probably consist of the dibromobenzylated o-cresol, and tars were also isolated.



B.P. 136-140°/2 mm.

M.P. 46.6-47.2°

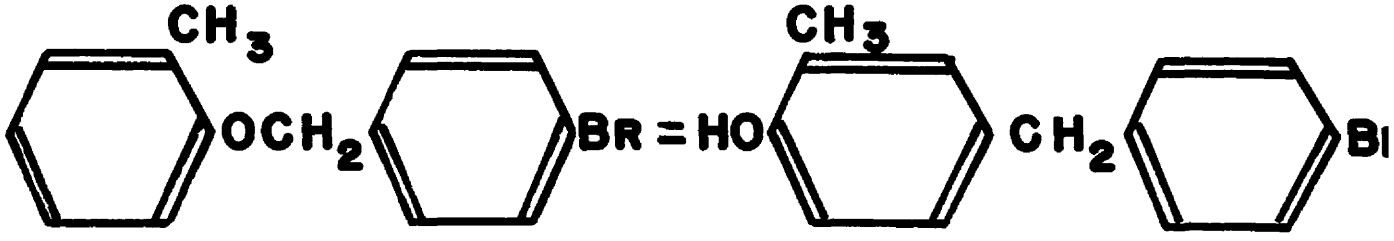
B.P. 173-176°/2 mm.
M.P. 65.4-65.8°



B.P. 157-162°/3 mm.

M.P. liquid

B.P. 172-175°/3 mm.
M.P. 46.4-46.8°



B.P. 152-155°/2 mm.

M.P. 70.8-71.2°

B.P. 183-185°/2 mm.
M.P. 75.4-76.0°

In all cases the products obtained by the rearrangement of the 2-methylphenylbromobenzyl ethers, which had been obtained as by-products of the Claisen method condensations, had the same melting points as the products of the Friedel-Crafts condensations. Mixed melting points of the rearrangement products and the Friedel-Crafts condensation products showed no depression.

No attempt was made to rearrange the bromobenzyl ethers of p-cresol.

DEHALOGENATION WITH Ni - Al ALLOY AND AQUEOUS ALKALI

This method, as developed by Papa and coworkers (205), was found to be applicable to this problem. The reduction, while removing the halogen, does not attack the phenolic hydroxy group.

EXPERIMENTAL

In this procedure ten grams of the phenolic compound was dissolved in 300 ml. of 10 percent sodium hydroxide and heated to 90° under reflux. Thirty grams of Raney's Ni - Al alloy was added cautiously to the solution, in small portions, and with stirring. The stirring was continued for an additional hour, the temperature being maintained at 90°.

The mixture was filtered while hot and the filtrate washed with water and a small amount of benzene, care being taken not to let the Ni residue become dry.

The filtrate was cooled and then acidified to congo red paper by pouring the alkaline solution into concentrated hydrochloric acid with stirring. (This prevents the precipitation of aluminum salts.) The reduction product was isolated by extraction with ethyl ether.

After removal of the ethyl ether the benzylated cresol was purified by distillation and crystallization, as in all previous cases.

No yields are given in these reactions, as small amounts of compound were used, and as each reaction was carried out only once. However, it may be stated that the yields were

excellent in all cases.

The physical constants of the three benzylated o- and p-cresols given in the literature are:

2-hydroxy-3-methyldiphenylmethane (I),

B.P. 150-152°/5 mm.

M.P. 49.5-50.5° (77)

M.P. 51.0-52.0° (142)

2-hydroxy-5-methyldiphenylmethane (II),

B.P. 165-185°/10 mm.

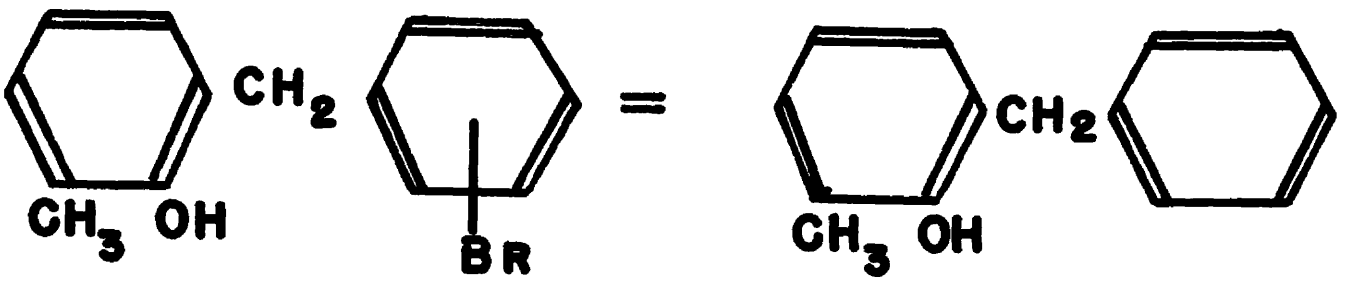
M.P. 35.0-36.0° (78)

4-hydroxy-3-methyldiphenylmethane (III),

B.P. 167-169°/5 mm.

M.P. 49.5-50.5° (77)

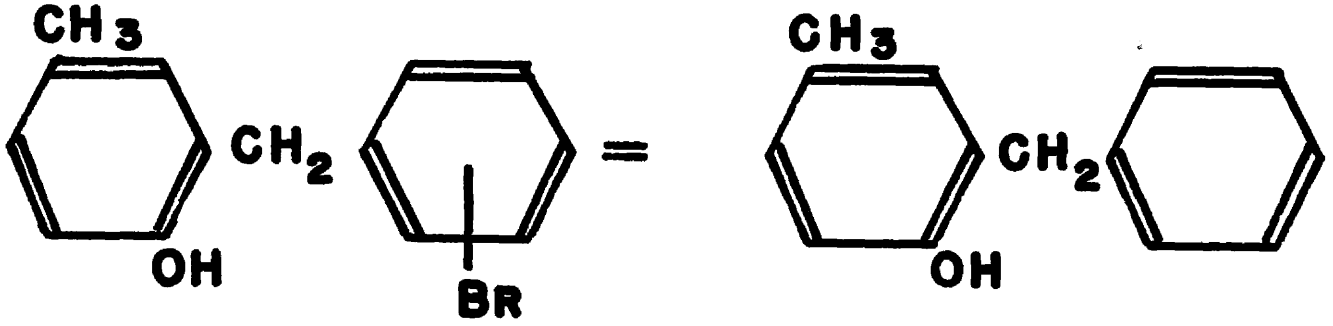
These constants agree with those of the three reduction products of the nine bromobenzylated cresols, as shown on the following page.



Bromine Position

(I)

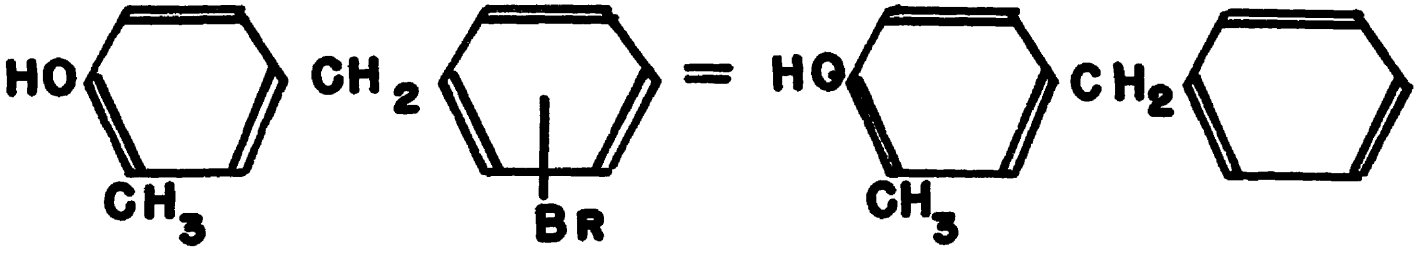
	2'	3'	4'	
B.P.	157-160°/ 2 mm.	162-167°/ 2 mm.	162-164°/ 2 mm.	B.P. 148-152°/2 mm.
M.P.	41.4-42.0°	48.8-49.4°	50.6-51.0°	M.P. 50.2-50.6°



Bromine Position

(II)

	2'	3'	4'	
B.P.	158-161°/ 2 mm.	174-176°/ 2 mm.	172-175°/ 2 mm.	B.P. 144-147°/3 mm.
M.P.	47.5-48.1°	58.8-59.2°	61.6-62.2°	M.P. 36.2-36.8°



Bromine Position

(III)

	2'	3'	4'	
B.P.	173-176°/ 2 mm.	172-175°/ 3 mm.	183-185°/ 2 mm.	B.P. 155-158°/3 mm.
M.P.	65.4-65.8°	46.4-46.8°	75.4-76.0°	M.P. 49.6-50.2°

In order further to prove the structures of the reduction products (I, II, III) the three benzylated cresols were prepared by the benzylation of the o- and p-cresols, as described previously. Mixed melting points using these products and those obtained by the reduction showed no depression.

DERIVATIVES

BENZOATES

To a solution of 3 ml. of pyridine and 1 ml. of benzoyl chloride (in a ten inch test tube) was added 1 gram of the phenol. This mixture, protected by a drying tube, was heated in the steambath for one-half hour. It was then poured into 10 ml. of water. The benzoate was extracted with ethyl ether. This ether solution was washed with dilute sulfuric acid, 10 percent sodium carbonate solution and water. The ether was evaporated off and replaced by 95 percent ethyl alcohol. The white crystals obtained from the ethyl alcohol on cooling were filtered off and dried at room temperature.

p-TOLUENE SULFONATES

To 2 grams of phenol in 5 ml. of pyridine was added 2 grams of p-toluene sulfonyl chloride. The solution was heated in the steambath for one-half hour. The purification of the p-toluene sulfonate was accomplished as in the case of the benzoate.

ARYLOXYACETIC ACIDS

For the preparation of these derivatives the procedure of Koelsch as given in Shriner and Fuson (206) was used.

3,5-DINITROBENZOATES

These were prepared by the same pyridine method used in the preparation of the benzoates. However, this preparation, and the subsequent crystallization, of this derivative proved to

be so difficult that only a few were attempted.

The 3,5-dinitrobenzoate of 2-hydroxy-3-methyl-4'-bromodiphenylmethane (M.P. 157-158°) was found to contain 15.96 percent Br (Calcd 16.96 percent Br). This was the only 3,5-dinitrobenzoate which could be prepared from the three p-bromobenzylated o- and p-cresols. As can be seen from the bromine determination, this compound is impure. No further attempts were made to prepare these derivatives.

The benzoates for the nine o- and p-monobromobenzylated o- and p-cresols were prepared.

The p-toluene sulfonates were prepared successfully for only seven of the compounds. In the case of 4-hydroxy-3-methyl-3'-bromodiphenylmethane and 2-hydroxy-5-methyl-3'-bromodiphenylmethane these derivatives were isolated as viscous, white oils which could not be crystallized. An attempt to prepare the crystalline alpha naphthylurethanes of these two compounds was likewise unsuccessful.

The uncorrected melting points and the bromine content of the derivatives prepared is given in the table on the following page. The melting points were determined by the capillary-tube method; the bromine content was determined by the sodium peroxide fusion method.

	DERIVATIVES					
	BENZOATE			p-TOLUENE SULFONATE		
COMPOUND	M.P. °C	Br Calcd %	Br Found %	M.P. °C	Br Calcd %	Br Found
4-hydroxy-3-methyl-2'-bromodiphenylmethane	50.0-51.0	20.96	20.97, 21.03	82.4-83.0	18.53	18.56, 18.61
4-hydroxy-3-methyl-3'-bromodiphenylmethane	74.4-75.4	20.96	20.77, 20.91	---------	-----	----------
4-hydroxy-3-methyl-4'-bromodiphenylmethane	74.2-74.8	20.96	20.70, 20.84	58.8-59.2	18.53	18.34, 18.49
2-hydroxy-3-methyl-2'-bromodiphenylmethane	87.3-88.2	20.96	21.06, 20.98	60.2-60.6	18.53	18.71, 18.62
2-hydroxy-3-methyl-3'-bromodiphenylmethane	50.0-50.6	20.96	21.21, 21.10	39.4-40.6	18.53	18.71, 18.64
2-hydroxy-3-methyl-4'-bromodiphenylmethane	50.5-51.2	20.96	20.87, 20.89	63.5-64.5	18.53	18.59, 18.62
2-hydroxy-5-methyl-2'-bromodiphenylmethane	66.8-67.6	20.96	21.18, 21.07	74.0-74.8	18.53	18.67, 18.50
2-hydroxy-5-methyl-3'-bromodiphenylmethane	75.5-75.9	20.96	21.14, 20.80	---------	-----	----------
2-hydroxy-5-methyl-4'-bromodiphenylmethane	63.5-64.0	20.96	21.09, 20.94	69.5-71.0	18.53	18.75, 18.63

THE QUANTITATIVE DETERMINATION OF BROMINE, METHOD

Although the Raney nickel method of Papa and co-workers (205) can be used quantitatively, the more familiar and more rapid sodium peroxide fusion method was used (207).

A charge consisting of approximately 10 grams of sodium peroxide, 1 to 1.5 grams of potassium nitrate and 0.40 to 0.45 grams of cane sugar was placed in a Parr bomb. To this were added 0.20 to 0.25 grams of the sample to be analyzed; and the compounds were mixed thoroughly.

The bomb was placed in a shield, and the charge was ignited over a Bunsen flame. To accomplish this, heating was necessary for up to three minutes.

The melt was cautiously washed into 200 ml. of hot water in a 400 ml. beaker and digested for ten minutes.

An excess of 0.1 N silver nitrate was added to the solution, and the precipitate was coagulated by boiling for 15 minutes.

The solution was then acidified with concentrated nitric acid. To reduce any silver bromate formed in the reaction, hydrazine sulfate was added to the hot acidified solution until no evidence of nitrogen evolution was noted.

The excess silver nitrate present was determined by the Volhard method (206) using standard ammonium thiocyanate (approximately 0.1 N) and ferric-ammonium sulfate solution as indicator (5 ml./200 ml. solution). The addition of 3 ml. of nitrobenzene to the solution before titration removed the

silver halide suspension and made the determination of the orange-red endpoint considerably easier.

The results of these determinations are given under the compounds analyzed.

PHENOL COEFFICIENTS*

In order to determine the germicidal effectiveness of these compounds against standard test organisms it was attempted to ascertain the phenol coefficients of the diphenylmethanes and the ethers prepared by the foregoing reactions.

However, the solubility of these compounds in alcohol concentrations approaching or exceeding the strengths lethal to bacteria made it impossible to get an accurate phenol coefficient. The fact that the compounds begin to precipitate out of the alcohol solution on the addition of the test organism made the results very inconsistent.

Phenol coefficients in the order of from ten to fifteen were obtained; but these were inaccurate because of the difficulty of maintaining a solution, and the contributory germicidal effect of the alcohol. That the high percentage of alcohol (above 37 percent) contributed markedly to the death of the organisms used is indicated by the phenol coefficient of phenol in the concentration of alcohol needed to dissolve most of the compounds. Mixed with 37 percent of alcohol, phenol has a coefficient of ten.

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* The author is indebted to Dr. W.L. Mallmann and Mr. D.P. Roman for these determinations.

DISCUSSION

The nine ortho and para monobromobenzylated o- and p- cresols were made successfully in one-step syntheses, using the Claisen method for C-alkylation of phenols to prepare the ortho bromobenzylated products, and the Friedel-Crafts method for the preparation of the para bromobenzylated o-cresols.

Although the yields, based on the pure product isolated from the reaction mixture, were low in some cases, the simplicity of the one-step syntheses, and the predominance of either the ortho or the para alkylated product, depending on the procedure, made the reactions used for these syntheses quite satisfactory.

A total of fifty-three condensations were run. Thus each reaction was duplicated one or more times; and the yields are reported as an average of two or more of the reactions run. In this manner it was also possible to check the physical constants of the products of one reaction against those of a duplicate reaction.

The difficulties encountered in the isolation and purification of these products caused a considerable loss of yield from the crude to the final pure product. For this reason statements based on the quantitative relationships of the yields of the reaction products must be made with some reserve.

The yields of the bromobenzylated o- and p-cresols,

in practically all cases, were highest when p-bromobenzyl chloride was used in the condensations, and lowest in the case of m-bromobenzyl chloride. The one exception to this was found in the two condensations of p-bromobenzyl chloride and sodium o-cresolate, which were isolated in yields of only 8.7 and 8.8 percent. It is interesting to note that in the sidechain chlorination of the three bromotoluenes (using sulfuryl chloride, and catalyzed by benzoyl peroxide) the yield of p-bromobenzyl chloride is the highest, and that of m-bromobenzyl chloride the lowest, of the three. The initiation temperature necessary for this chlorination was lowest in the case of p-bromotoluene, highest for m-bromotoluene.

It has been stated that in the Friedel-Crafts benzylation of phenol the presence of bromine in the nucleus of benzyl chloride favors the formation of the phenyl bromobenzyl ether (191). This has not been found to be true to any extent in the bromobenzylation of o-cresol, in which only small amounts of oxygen alkylated fractions were isolated. The quantities of these products were insufficient for purification and identification. However, in the case of p-cresol, where the position para to the phenolic hydroxyl is blocked, the aluminum chloride catalyzed condensation with p-bromobenzyl chloride gave an average yield of 24 percent of the 4-methylphenyl-4-bromobenzyl ether and only 4.5 percent of the 2-hydroxy-5-methyl-4'-bromodiphenylmethane.

The fact that the addition of the oxygen benzylated

product to the reaction mixture in the Claisen method benzylations increases the yield of C-benzylated product has been investigated by Guile (128) and Nealey (129). These workers found that the yield of 2-hydroxy-3'-chlorodiphenylmethane, and 2-hydroxy-3'-bromodiphenylmethane could be increased three to five times by the addition of 3-chloro-, or 3-bromobenzylphenyl ether, respectively. The addition of a large amount of this ether was found to increase the yield to only one and one-half times that obtained without addition of the ether. This may be due to a dilution effect.

In the bromobenzylations of o- and p-cresol the addition of the corresponding ethers was carried out in the Claisen method C-bromobenzylations of o-cresol and p-bromobenzyl chloride, p-cresol and p-bromobenzyl chloride, and o-cresol with o-bromobenzyl chloride. In the case of the condensation of o-cresol and p-bromobenzyl chloride the addition of 15 g. of 2-methylphenyl-4-bromobenzyl ether to the reaction mixture (0.5 mole) increased the yield of 2-hydroxy-3-methyl-4'-bromodiphenylmethane from 8.7 percent to 22.8 percent. The addition of 25 g. of the ether increased the yield of the pure product to only 17.0 percent.

When 14 g. of the 4-methylphenyl-4-bromobenzyl ether were mixed with the sodium p-cresolate, before addition of the p-bromobenzyl chloride, the yield of 2-hydroxy-5-methyl-4'-bromodiphenylmethane was little affected (41.9 percent without addition of the ether, 39.7 percent with 14 g. of the ether added).

In the reaction of o-cresol and o-bromobenzyl chloride the addition of 15 g. of 2-methylphenyl-2-bromobenzyl ether caused a decrease in the yield of 2-hydroxy-3-methyl-2'-bromodiphenylmethane from the 13 percent obtained without the addition of this ether, to 4.4 percent; the addition of 21 g. decreased the yield of product to 5.2 percent.

Although this work is insufficient to further explain the role that the addition of phenyl benzyl ether plays in the Claisen method of C-benzylation of phenols, it is shown that addition of the ether does not always cause an increase in the yield of the C-benzylated phenol.

The structures of the compounds prepared were proven by the reductive dehalogenation of the three groups of compounds: ortho bromobenzylated o-cresol, para bromobenzylated o-cresol, and ortho bromobenzylated p-cresol to 2-hydroxy-3-methyldiphenylmethane, 4-hydroxy-3-methyldiphenylmethane, and 2-hydroxy-5-methyldiphenylmethane, respectively. The three compounds in each group (2', 3', or 4' bromobenzylated cresols), which differ considerably in their physical constants (See p. 97) all contain the theoretical percentage of bromine. On removal of this bromine all three give the same product as is obtained by the condensations of benzyl chloride and the respective cresol. These reduced compounds are known; and the physical constants obtained agree with those given in the literature (See p. 96).

As further proof of structure the o-, m-, and p-bromobenzyl ethers of o-cresol, which were obtained as bi-

products in the condensations of the bromobenzyl chlorides and sodium o-cresolate, were rearranged to give the para bromobenzylated o-cresols which were shown to be identical to those obtained by the Friedel-Crafts condensations (See P. 93).

To guard against possible by-products resulting from the chlorination of p-bromotoluene, one reaction was run to condense p-bromobenzyl alcohol and o-cresol in the presence of aluminum chloride. The 4-hydroxy-3-methyl-4'-bromodiphenylmethane obtained was found to be identical to that isolated from the reactions using p-bromobenzyl chloride and o-cresol.

No attempt was made to isolate or purify the many by-products formed in the reactions. Most of these by-products boiled at high temperatures and were fairly easily separated from the lower boiling, desired products, by distillation. The oils obtained from the filtrates of some of the crystallizations from hexane were likewise not identified.

All the compounds prepared, a total of 18, were sent to the Eli Lilly & Co. Research Laboratories for testing.

SUMMARY

The following compounds were prepared by the Friedel-Crafts synthesis:

4-hydroxy-3-methyl-2'-bromodiphenylmethane

4-hydroxy-3-methyl-3'-bromodiphenylmethane

4-hydroxy-3-methyl-4'-bromodiphenylmethane

The following compounds were prepared by the Claisen method of C-alkylation of phenols:

2-hydroxy-3-methyl-2'-bromodiphenylmethane

2-hydroxy-3-methyl-3'-bromodiphenylmethane

2-hydroxy-3-methyl-4'-bromodiphenylmethane

2-hydroxy-5-methyl-2'-bromodiphenylmethane

2-hydroxy-5-methyl-3'-bromodiphenylmethane

2-hydroxy-5-methyl-4'-bromodiphenylmethane

The cresyl bromobenzyl ethers corresponding to these compounds were isolated:

2-methylphenyl-2-bromobenzyl ether

2-methylphenyl-3-bromobenzyl ether

2-methylphenyl-4-bromobenzyl ether

4-methylphenyl-2-bromobenzyl ether

4-methylphenyl-3-bromobenzyl ether

4-methylphenyl-4-bromobenzyl ether

The structures of the C-bromobenzylated cresols were proven by reductive dehalogenation of the correspon-

ding compounds to 4-hydroxy-3-methyldiphenylmethane, 2-hydroxy-3-methyldiphenylmethane, and 2-hydroxy-5-methyldiphenylmethane.

The o-, m-, and p-bromobenzyl ethers of o-cresol were rearranged, in the presence of $ZnCl_2$ and HCl, to give the para bromobenzylated o-cresols identical to those obtained by the Friedel-Crafts synthesis.

The benzoates and p-toluene sulfonates of all the phenolic compounds were prepared. The p-toluene sulfonates of 4-hydroxy-3-methyl-3'-bromodiphenylmethane and 2-hydroxy-5-methyl-3'-bromodiphenylmethane could not be crystallized.

The role of the addition of the corresponding phenyl benzyl ethers to the Claisen method reaction mixture has been further investigated.

Attempts to obtain the phenol coefficients of these compounds were not successful, due to their low solubility.

All compounds prepared have been tested by the Eli Lilly & Co. Research Laboratories for specific bactericidal activity.

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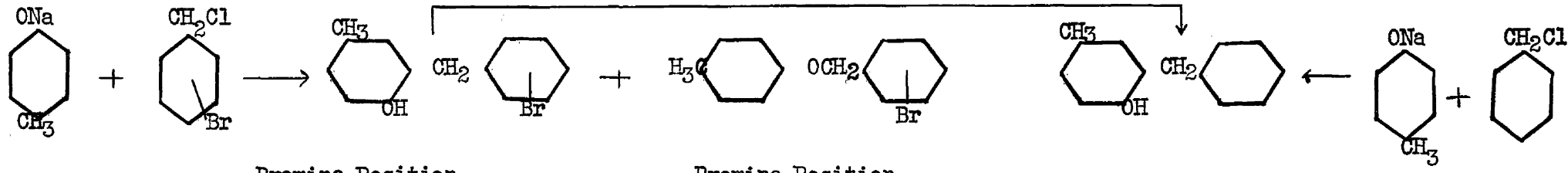
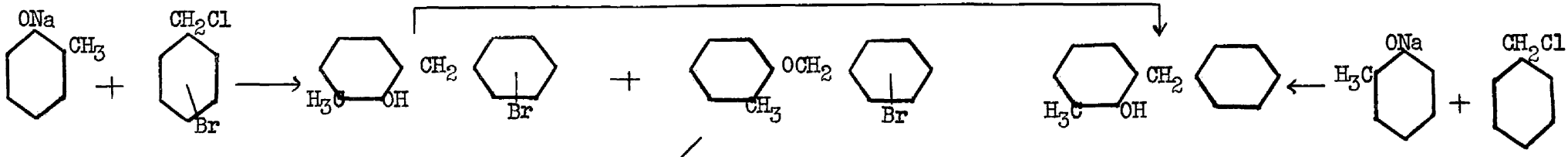
SCHEMA OF CONDENSATIONS

CLAISEN METHOD



Bromine Position	2'	3'	4'	Bromine Position	2'	3'	4'	
M.P.	47.5-48.0	58.8-59.2	61.6-62.2		25.0-26.0	53.0-53.6	101.5-102.0	M.P. 36.2-36.8
Yield	20.0%	16.0%	41.9%		14.0%	10.6%	10.0%	



Bromine Position	2'	3'	4'	Bromine Position	2'	3'	4'	
M.P.	41.4-42.0	48.8-49.4	50.6-51.0		46.6-47.2	liquid	70.8-71.2	M.P. 50.2-50.6
Yield	13.0%	12.0%	8.7%		18.0%	18.0%	18.0%	

FRIEDEL-CRAFTS

Bromine Position	2'	3'	4'	
M.P.	65.4-65.8	46.4-46.8	75.4-76.0	M.P. 49.6-50.2
Yield	21.0%	5.4%	30.4%	

Suggestions for further Investigation

A. CLAISEN METHOD

1. Carry out identical Claisen method C-alkylations of phenols in benzene, toluene, p-xylene, hexamethylbenzene, naphthalene, and anthracene to determine possible increase in yield by increase in temperature of reaction.

2. Does the Claisen method give ANY alkylation para to the phenolic hydroxy group?

3. Further investigation of the effect of adding the corresponding ethers to the Claisen reaction mixtures. Why does the ether of o-bromobenzyl chloride and o-cresol decrease the yield of C-benzylated product?

4. Can the o-alkylated product be prepared by the reaction of o-chloromercuriphenol and benzyl chloride? If so, in better yield than by Claisen Method?

5. Use Ag salts of phenol in the Claisen method alkylation and compare yields to runs using Na salts.

B. FRIEDEL-CRAFTS CONDENSATION

6. Can the Friedel-Crafts method yield be bettered by using $ZnCl_2$ - HCl rearrangement of the phenyl benzyl ether rather than the direct $AlCl_3$ alkylation? This may avoid the by-products caused by the action of the catalyst of benzyl chloride.

7. Purification of phenolic fractions into o- and p-alkylated fractions may better be accomplished by Ba salts. The o-alkylated are water soluble, the p-alkylated insoluble, in water. This may not always work, but may be an improvement on the separation by distillation.

8. What is the red gas given off when the sulfuryl chloride-peroxide catalyzed chlorination is used with bromotoluenes? (Bromine?) What are the low B.p. by-products? Is Br removed or is it replaced by Cl?

9. Brominate the nine diphenylmethanes prepared (in the phenolic ring) and retest their pharmacological activity.

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