THE PREPARATION AND CHARACTERIZATION OF THE DIPHENYLMETHANES PREPARED FROM MONOCHLOROBENZYL CHLORIDE AND ORTHO AND PARA CRESOL

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THE PREPARATION AND CHARACTERIZATION OF THE DIPHENYLMETHANES PREPARED FROM MONOCHLOROBENZYL CHLORIDE AND ORTHO AND PARA CRESOL

By

Kenneth Robert Robinson

A THESIS

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THESIS ABSTRACT

THE PREPARATION AND CHARACTERIZATION OF THE DIPHENYLMETHANES PREPARED FROM MONOCHLOROBENZYL CHLORIDE AND ORTHO AND PARA CRESOL

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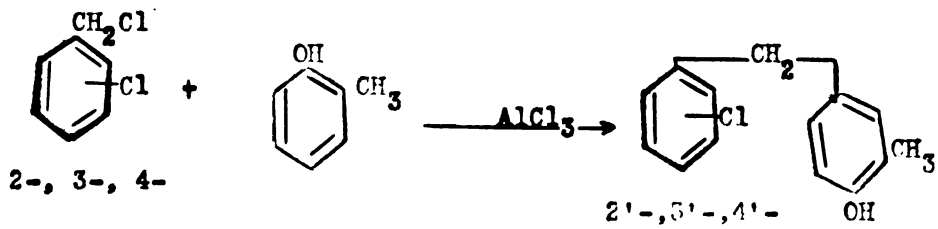
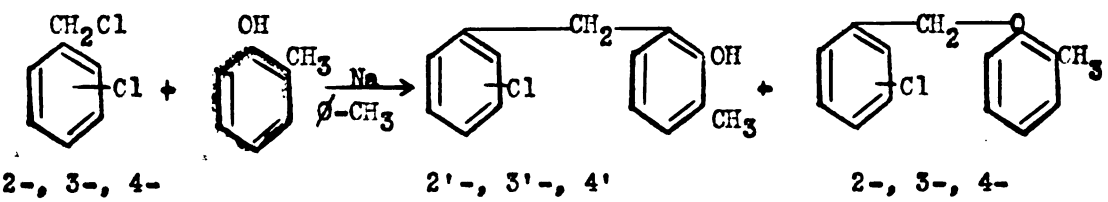
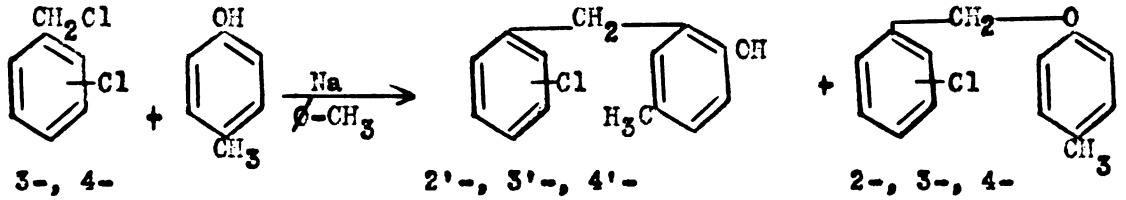
This investigation was undertaken in order to extend a series of diphenylmethanes prepared in this laboratory. The preparation of nine hydroxy-methyl-chloro'-diphenylmethanes is described.

Two methods of direct alkylation of o- and p-cresol were used. When the condensation was carried out using acidic conditions (aluminum chloride), p-alkylation of o-cresol took place.



However, if basic conditions were used in a "non-dissociating" solvent, only o-alkylation occured. [L. Claisen and E. Tietze, Ber., 58B, 275 (1925); Ber., 59B, 2344 (1926)]. The corresponding ethers were also produced as side-products in this reaction.



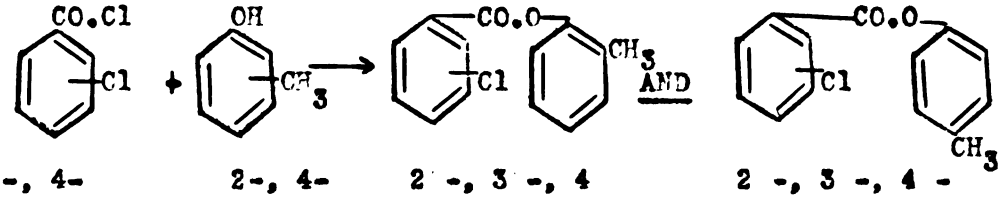


2-, 3-, 4- 2'-, 3'-, 4'- 2-, 3-, 4-

The ethers produced in the above reactions were also synthesized by allowing the appropriate chlorobenzyl chloride to react with o- or p-cresol in a sodium hydroxide-ethyl alcohol medium.

It was found that if xylene was used as the solvent as suggested by W. B. Wheatley et al. [J. Am. Chem. Soc., 71, 64 (1949)], instead of the lower boiling toluene, the yields of both the diphenylmethanes and ethers were substantially increased in many cases.

In an indirect method of preparation of these hydroxy-methyl-chloro'-diphenylmethanes, the following series of reactions were used:



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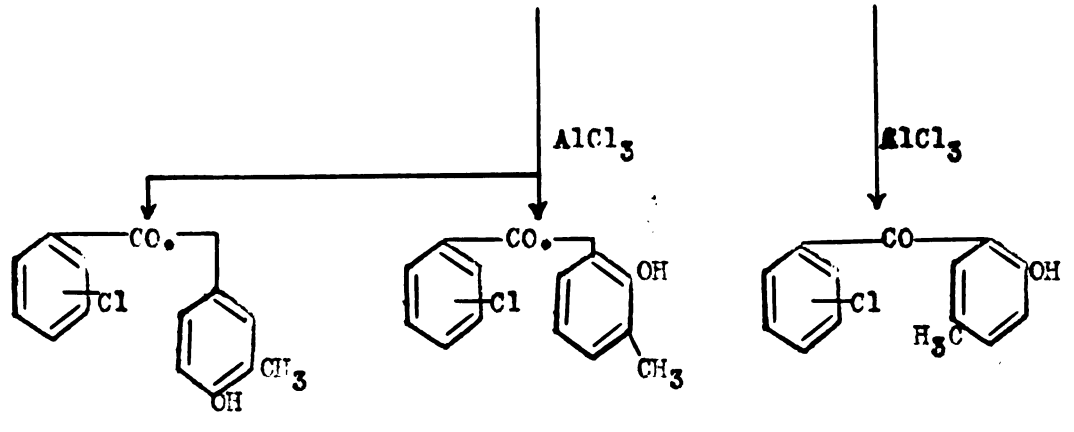

2'-, 3'-, 4'- 2'-, 3'-, 4'- 2'-, 3'-, 4'

ACKNOWLEDGMENT

The candidate wishes to thank Dr. R. C. Huston, for his guidance and suggestions throughout the course of this investigation.

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CONTENTS

INTRODUCTION

There have been a large series of hydroxydiphenylmethanes prepared in this laboratory under the direction of Dr. R. C. Huston (1).

Of this series, the chloro and bromo derivatives of o- and p-benzylated phenols and recently (2) the o- and p-monobromobenzylated o- and p-cresols have been shown to possess specific bactericidal activity.

This investigation was undertaken in order to extend the series to include the o- and p-monochlorobenzylated o- and p-cresols as well as the evaluation of activity of the methylphenyl-chlorobenzyl ethers and the hydroxy-methyl-chloro'-benzophenones prepared as biproducts and intermediates, respectively.

HISTORICAL

The preparation of diphenylmethanes can be accomplished by a number of different methods. The parent compound itself was first isolated by Jena (3) in 1870. His method of preparation involved heating diphenylacetic acid with sodium carbonate.

The first hydroxydiphenylmethane was prepared by Paterno (4) in 1872. This benzylphenol was prepared by heating a mixture of phenol and benzyl chloride in the presence of zinc dust.

In 1875 Paterno (5) isolated the same compound and an oil from the reaction products of phenol and benzyl alcohol condensed by a mixture of sulfuric and acetic acids. It was later shown by Rennie (6) that the crystalline compound was the p-benzylphenol while the oil was the ortho isomer. The latter compound, when sufficiently pure, is a solid at room temperature. Rennie prepared these benzylphenols by condensing benzyl chloride with phenol using zinc chloride as the catalyst. The two isomers thus formed were separated by precipitating the o-isomer as the barium salt. Rennie also states that aluminum chloride and ferric chloride will function as condensing catalysts. The credit, however, for suggesting that zinc chloride and not zinc was the catalyst for condensations involving benzyl chloride, must go to Leibmann (7). His suggestion was fully justified when he found that benzyl alcohol would condense with phenol in the presence of zinc chloride to give p-benzylphenol.

The use of aluminum chloride as a condensing agent will be discussed in detail in a later part of this section.

More recent acidic condensing agents that have been employed with varying degrees of success on compounds of this type are boron trifluoride (8), hydrogen fluoride (9), and sulfonic acid esters (10).

In 1905 Auwers (11) heated, in the absence of a catalyst, equimolar quantities of 3,5-dibromo-4-hydroxybenzyl bromide and a phenol to 100-150° until there was no further evolution of hydrogen bromide. This reaction yielded o- and p-derivatives in the cases of phenol and o-cresol as well as the dibenzylated products of p-cresol.

FRIES REARRANGEMENT

Diphenylmethane and its derivatives can frequently be made by reduction of the corresponding benzophenone.

There are a number of methods available for the preparation of these ketones. One of the earliest methods used to prepare benzophenone itself was the condensation of benzoic acid with benzene (12). The condensing agent used was phosphorus pentoxide.

Nencki (13) prepared hydroxy ketones by condensing fatty acids with phenol in the presence of zinc chloride. This method was later utilized by Johnson (14) and by Dohme et al. (15), to prepare a series of acyl derivatives of resorcinol. The reaction is adaptable to aromatic acids in some cases as indicated by the successful preparation of benzoylresorcinol (16).

Another method that is particularly adaptable for the preparation of polyhydroxy benzophenones is the Hoesch reaction (17). Klarmann (18) has used this reaction very extensively in his work on alkylated resorcinols.

The Friedel-Crafts reaction, in which a phenol or an aromatic ether is condensed with an acid chloride or acid anhydride in the presence of aluminum chloride, is a widely used method of preparation of hydroxybenzophenones.

However, according to Blatt (19) the best method of preparation of aromatic hydroxyketones is to rearrange the phenyl esters with aluminum chloride. This is known as the Fries reaction (20).

The benzoyl esters of o- and p-cresol have been rearranged to give over 90 percent yields of the ketones (21). Rosenmund and Schnurr have also rearranged the o-chlorobenzoate, the o-bromobenzoate, and the p-bromobenzoate of p-cresol in practically quantitative yields.

This reaction is discussed in great detail in "Organic Reactions" (19) and so a more comprehensive survey will not be taken up in this thesis.

WOLFF-KISHNER REDUCTION

There are three main methods available for the reduction of ketones to their corresponding hydrocarbons.

The Clemmensen (22) method of reduction is useful in reducing many aliphatic, alicyclic, and aliphatic-aromatic ketones but is generally unsatisfactory for aromatic-aromatic ketones (23). There are some exceptions to this statement. For example, Klarmann (18) was able to reduce 4'-chloro-2,4-dihydroxybenzophenone to the corresponding diphenylmethane in 33 percent yield.

Bradlow and Vanderwerf (24) found that if the ortho positions of benzophenone are substituted the yields of the corresponding diphenylmethanes are fairly good.

The second main method of reducing ketones to hydrocarbons involves catalytic hydrogenation. This method suffers from the defect that other unsaturated points of the molecule may be attacked. In addition the carbonyl group must be conjugated with an aromatic system (25). However hydrogenation with palladium-charcoal catalyst at normal temperature and pressure has been found to be an effective means for the complete reduction of the conjugated carbonyl group (26).

The final common method of reducing ketones is by the use of the Wolff-Kishner reaction (27). In this method the carbonyl group is converted to a hydrazone or semicarbazone and this is then decomposed by using a strong base such as sodium ethoxide.

Cook et al. (28) have been able to reduce camphor to camphane in yields of 84 percent.

The method is equally as good for aromatic aliphatic ketones in that Lock and Stach (29) were able to reduce 4-methylacetophenone to 4-ethyltoluene in an 80 percent yield.

Recently the method has been revised so that large amounts of material could be used. Thus a charge of 168 grams of 5-keto-8-methylnonanoic acid was reduced in 48 hours to isodecanoic acid in a 92 percent yield by Soffer et al. (30).

Huang-Minlon (31) further modified the method and was able to reduce a charge of 500 grams of β-(p-phenoxybenzoyl)-propionic acid in approximately 6 hours. Yield amounted to 95 percent.

A discussion of the Wolff-Kishner reduction can be found in "Organic Reactions" (32) and a more detailed review of the reactions seems unnecessary at this point.

ALKYLATION USING ACIDIC CONDITIONS

The general method of alkylation using acidic catalysts, known as the Friedel-Crafts Synthesis, is completely covered in the literature (33). In addition the condensation as applied to aromatic compounds has been covered in a very elegant manner by Gyorgy (2). Therefore, only those references which are pertinent to the benzylation of phenols using aluminum chloride will be cited.

Huston and coworkers (1) have extensively studied this benzylation of phenols. The alkylation of phenol using aluminum chloride and benzyl alcohol was first reported by Huston in 1920 (34). When one mole of benzyl alcohol and 1.1 moles of the phenol were treated with 0.5 mole of aluminum chloride at 20-30°, a 45 percent yield of p-benzylphenol was obtained. Petroleum ether was used as the solvent. Later it was found that when o-cresol was treated with benzyl alcohol and aluminum chloride under approximately the same conditions the main product was 2-methyl-4-benzylphenol but that some of the o-benzylated and di-benzylated compounds could be isolated (35).

This method of preparing benzylated phenols was extended to benzyl chlorides and o-cresol and finally to the chloro and bromobenzyl chlorides and phenol (1). Recently the para monobromobenzylated o-cresols were synthesized (2).

The best conditions for carrying out this reaction were worked out by Huston et al. (1). They found that the maximum yields could be obtained when three moles of the phenol and one mole of the benzyl chloride, catalyzed by one-half mole of aluminum chloride, were allowed to react at 20-35°. They used petroleum ether as the solvent.

ALKYLATION USING BASIC CONDITIONS

As has been seen from the previous discussion all the reactions involving the direct alkylation of phenols have produced predominately the para substituted compound unless that position was already occupied. This difficulty was solved by Claisen in 1923 (36).

The results of his investigations showed that when the sodium salt of a phenol is treated with an active halide of the alkyl or benzyl type in a "non-dissociating" medium such as toluene, carbon alkylation takes place exclusively in the ortho position. Some oxygen alkylation, however, does occur. On the other hand, if the reaction is carried out in a "dissociating" medium such as methyl alcohol, alkylation takes place almost exclusively on the oxygen.

Several other investigators (37) had noticed this carbon alkylation in basic solution and had mentioned it in their papers but they did not further investigate the matter.

The first extensive work by Claisen was carried out using allyl halides but later was extended to the benzyl halides (38).

Huston and coworkers (1) have used this reaction to prepare the orthobenzylated compounds of phenol, o-cresol, and p-cresol. The field was then extended to chloro and bromobenzylated phenol as well as benzylated chloro and bromophenols and cresols. Recently the series was further extended when the bromobenzylated o- and p-cresols were prepared (2).

DISCUSSION

The purpose of this investigation was to extend a series of diphenylmethanes that have been prepared in this laboratory. The nine ortho and para monochlorobenzylated o- and p-cresols were successfully prepared.

Eight of these substituted diphenylmethanes were synthesized by a three step synthesis which involved the preparation of the methylphenyl chlorobenzoates, rearranging these esters with aluminum chloride (20) (Fries rearrangement) to form hydroxy-methyl-chloro'-benzophenones, and finally reducing these ketones by means of the Wolff-Kishner reaction to the corresponding hydroxy-methyl-chloro'-diphenylmethanes. The six esters and nine ketones thus produced were also isolated and characterized.

By using the Friedel-Crafts method to prepare the para chlorobenzylated o-cresols and the Claisen method of C-alkylation to prepare the ortho chlorobenzylated o- and p-cresols, it was possible to make all nine of the desired hydroxy-methyl-chloro'-diphenylmethanes by a one step synthesis.

The six methylphenyl-chlorobenzyl ethers, produced as side products in the Claisen (36) method of C-alkylation, were also isolated and characterized. The structure of these ethers was further established by a second method of synthesis.

Finally, the product, isolated when 2-hydroxy-5-methyl-2'-chlorobenzophenone was subjected to the Huang-Minlon (31) modification of the Wolff-Kishner reduction (27), was identified as 2-methylxanthene. This xanthene was also prepared by hydrogenating the known compound, 2-methylxanthone.

The six methylphenyl chlorobenzoates were readily prepared from o-, m-, p-chlorobenzoyl chloride and the necessary o- or p-cresol. The method of preparation used was essentially the same as that described by Ralston (39).

There was little difficulty encountered in the purification of the products, the details of which are found in the experimental section. The yields of these reactions ranged from 79.0-90.8 percent.

The rearrangement of these esters to the corresponding hydroxymethyl-chloro'-benzophenones was accomplished by using aluminum chloride. There are various methods available for carrying out this Fries rearrangement. The merits of each of these methods are discussed in "Organic Reactions" (19). The procedure used, because it is recommended for benzoyl type compounds, consisted of treating the ester with aluminum chloride at 130-180° for 45 minutes for the o-cresyl esters, and 140-160° for 10 minutes for the p-cresyl esters, without the aid of a solvent. The aluminum chloride complex was then decomposed, using dilute hydrochloric acid, and the resulting solid distilled at reduced pressure.

The rearrangement of the o-cresyl esters always gave two ketones with the p-hydroxybenzophenone isomers predominating. The latter were readily separated from the o-hydroxy isomers by the judicious use of solvents, the ortho isomer being more soluble. After separating the two isomers they were purified by recrystallization from appropriate solvents.

The o-hydroxybenzophenone always had a lower melting point than the p-hydroxybenzophenone and was always yellow whereas the p-isomer was white. This color is reported being due to chelation (40).

The three hydroxy-methyl-chloro'-benzophenones obtained from the three p-methylphenyl chlorobenzoates always contained a small amount of the corresponding chlorobenzoic acid. This is probably due to incomplete rearrangement of the ester which was then hydrolyzed when the aluminum chloride complex was decomposed with dilute hydrochloric acid. These acids were readily removed by a sodium bicarbonate wash preceding purification by recrystallization.

When the mother liquors of these recrystallizations were concentrated, they always yielded a small amount of oil, but never enough to purify and identify.

The three benzophenones prepared by rearrangement of the p-cresyl esters were also yellow in color thus indicating a hydroxy group in the ortho position (40).

The yields of ketones obtained from the o-methylphenyl chlorobenzoates amounted to 35.3 to 55.7 percent for the p-hydroxy isomers and 11.8 to 17.3 percent for the o-isomers. Those obtained by the rearrangement of the p-methylphenyl chlorobenzoates varied from 45.1 to 71.3 percent.

Several different methods of reduction were attempted on the above hydroxy-methyl-chloro'-benzophenones. The Bradlow procedure (24) of the Clemmensen method was found to be unsatisfactory in that only the original ketone and a small amount of heavy oil could be isolated. The reduction was attempted on 2-hydroxy-5-methyl-2'-chlorobenzophenone.

The second method attempted involved treating 2-hydroxy-5-methyl-2'-chlorobenzophenone with hydriodic acid and phosphorus. The only material isolated here was a viscous oil and this only in small yields.

The most successful method and the one used for all the reductions to the diphenylmethanes was the Huang-Minlon (31) modification of the Wolff-Kishner reaction (27). This reaction involved treating the ketone with 85 percent hydrazine hydrate and sodium hydroxide. Because high temperatures are needed to decompose the hydrazone formed, diethylene glycol was used as the solvent. To form the hydrazone the reaction mixture was refluxed for 1.5 hours. To decompose this hydrazone the reflux condenser was removed and the temperature allowed to rise to 195-200°. At this point the reflux condenser was replaced and the heating continued for 4 hours.

After cooling, the reaction mixture was acidified, and the organic layer extracted with ethyl ether. The oil thus removed was distilled and finally recrystallized.

The only difficulty encountered in this procedure was due to small amounts of diethylene glycol in the ether extract. This material was relatively insoluble in the solvents used to recrystallize the diphenylmethanes and tended to coat the crystals as they were formed.

This reduction of the 3'-chloro and 4'-chlorobenzophenones was quite satisfactory and yields ranging from 41.0 to 71.8 percent were obtained.

However, the reduction of the 2'-chlorobenzophenones was less satisfactory. The reduction of 4-hydroxy-3-methyl-2'-chlorobenzophenone and 2-hydroxy-3-methyl-2'-chlorobenzophenone was accomplished although the yields were small. In the case of 2-hydroxy-5-methyl-2'-chlorobenzophenone only 2-methylxanthene was isolated, rather than the expected product, namely, 2-hydroxy-5-methyl-2'-chlorodiphenylmethane.

Evidently the labile chlorine atom was replaced by a hydroxyl group, followed by the removal of a molecule of water. The latter step is very characteristic of 2-2'-dihydroxybenzophenones or diphenylmethanes.

The reaction mixture obtained from the first two 2'-chlorobenzophenones mentioned above gave a goodly amount of higher boiling material, and it may well be that they contained some 2'-4-dihydroxy-3-methyl-diphenylmethane and 3-methylxanthene respectively.

It is possible that either compound, that is, the one on which the chlorine atom remains intact or the one on which the chlorine atom has been replaced by a hydroxy group, can be obtained in predominance by the judicious use of reaction conditions.

The Friedel-Crafts synthesis of the hydroxy-methyl-chloro'-diphenylmethanes was accomplished by condensing o-, m-, p-chlorobenxyl chlorides and o-cresol with aluminum chloride using petroleum ether as the solvent. The reaction was carried out at room temperature over a period of three days. The mixture thus obtained was treated with hydrochloric acid to decompose the aluminum chloride complex. The organic layer was taken up in strong alcoholic potassium hydroxide and any ethers present were extracted. This ether extraction always yielded a small amount of oil, but there was never enough to purify and identify.

The desired diphenylmethanes were then obtained from the basic solution by acidification and extraction. The oil thus obtained was readily purified by distillation and recrystallization in the cases of 4-hydroxy-3-methyl-2'-chlorodiphenylmethane and 4-hydroxy-3-methyl-4'-chlorediphenylmethane. Concentration of the mother liquors of

the former compound yielded a small amount of unidentified oil.

In the case of 4-hydroxy-3-methyl-2'-chlorodiphenylmethane there was a considerable mount of oil obtained thus making it extremely difficult to purify this compound. Undoubtedly, there was more of the compound produced in the reaction than the 12.4 percent yield indicates but it could not be isolated in the pure form. The reduction method therefore, is much superior to the Friedel-Crafts method for the preparation of this compound.

The Claisen C-alkylation method of preparing o-benzylated phenols is excellent in that it is a one step process and gives only the one C-alkylated isomer. However, it suffers from the disadvantage that the purification process of isolating the desired compound from the reaction mixture is long and tedious. In addition to this, the reaction yields are generally rather low.

The Claisen C-alkylation reaction is carried out by placing sodium in a "non-dissociating" solvent such as toluene and heating it to reflux temperature. The necessary o- or p-cresol and the desired o-, m-, or p-chlorobenzyl chloride, in this order, were then added.

After refluxing and stirring this mixture for 36 hours it was acidified with dilute hydrochloric acid and the resulting organic layer taken up in alcoholic potassium hydroxide. The ethers formed in the reaction were removed by extraction with petroleum ether. The basic solution was acidified and the desired hydroxy-methyl-chloro'-diphenylmethanes removed by extraction.

It was proved that a higher boiling solvent increases the yields of both the diphenylmethane and the ether. This is true of course

only if all of the starting materials did not completely react. Thus, the benzylation of o-cresol with o-chlorobenzyl chloride gave only a 9.5 percent yield of the diphenylmethane using toluene as the solvent. Recovered o-chlorobenzyl chloride amounted to 49.7 percent.

When the same reactants were used under exactly the same conditions, except that the higher boiling xylene was substituted for the toluene, the yield of 2-hydroxy-5-methyl-2'-chlorodiphenylmethane amounted to 29.9 percent. Only 0.5 percent of unreacted o-chlorobenzyl chloride was found to be present in this case. The idea of using a higher boiling solvent was suggested by Wheatley (41).

In this work on the Claisen method of preparation there were many high boiling residues encountered. Usually there was no attempt made to identify these fractions.

The ethers produced as side-products by the Claisen method were also synthesized in a sodium hydroxide-ethyl alcohol medium. This well known method of preparing ethers is described by Lyman (42).

The necessary o- or p-cresol was dissolved in an alcoholic sodium hydroxide solution and then the o-, m-, or p-chlorobenzyl chloride was added. After refluxing for three hours the solution was diluted with water, cooled to 0° C., and the oil or solid removed and purified. The ethers thus prepared proved to be the same as those isolated from the Claisen reaction.

There was little difficulty encountered in the preparation and purification of these compounds.

As has been pointed out elsewhere in this thesis the Huang-Minlon (31) modification of the Wolff-Kishner (27) reduction did not give

the corresponding substituted diphenylmethane when applied to 2-hydroxy-5-methyl-2'-chlorobenzophenone. The product isolated contained no halogen, was insoluble in Claisen's solution (43) and melted at a much higher temperature (96.4-97.4°) than would be expected for 2-hydroxy-5-methyl-2'-chlorodiphenylmethane.

This evidence coupled with the nature of the reaction used, indicated that the compound which had been isolated was either 2-methylxanthene or 2-methylxanthone. Since the xanthone has been reported in the literature as melting at 125.5° (44), the compound was probably 2-methylxanthene.

Therefore, a small quantity of 2-methylxanthone was prepared by heating 2-hydroxy-5-methyl-2'-chlorobenzophenone with sodium hydroxide in diethylene glycol (44). The 2-methylxanthone was then reduced by catalytic hydrogenation to 2-methylxanthene following approximately the same procedure that Ipatieff (45) used in reducing xanthone itself to xanthene.

The compound thus prepared was identical with that isolated from the Wolff-Kishner reduction of 2-hydroxy-5-methyl-2'-chlorobenzophenone. A mixed melting point of the two compounds showed no depression.

CHEMICALS USED

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

Benzoyl Peroxide E.K. 713

Chlorine Chio Chemical Company

o-Chlorobenzoyl Chloride Heyden Chemical Co.

p-Chlorobenzoyl Chloride Heyden Chemical Corp.

o-Chlorobenzyl Chloride E.K. 1059

p-Chlorobenzyl Chloride E.K. P1103

m-Chlorotoluene E.K. 2449

o-Cresol E.K. P81 (Redistilled)

p-Cresol E.K. P449 (Redistilled)

β - β -Dihydroxyethyl ether E.K. P2401

Drierite Hammond Drierite Company

Ethyl Alcohol 95 percent, Commercial Solvents

Ethyl Ether Merck 71633

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

Methanol CP E. & A. A-412

m-Nitrobenzaldehyde E.K. 182

Petroleum Ether (30-75°) CP Baker

Pyridine E.K. P216 (Distilled from BaO)

Raney Catalyst Powder No. 23020B

Sodium Merck

Sodium Peroxide CP Baker

Sulfuryl Chloride E.C. P322

PREPARATION OF INTERMEDIATES

PREPARATION OF m-CHLOROBENZALDEHYDE

There are two common methods available for the preparation of m-chlorobenzaldehyde. The first, direct chlorination of benzaldehyde, however, will give some of the ortho and para isomers and since it is very difficult to eliminate these isomers by any known procedure, this method was discarded.

The second method utilizes m-nitrobenzaldehyde as the starting material. It can be reduced to m-aminobenzaldehyde with stannous chloride. This amine can be diazotized and treated with a hydrochloric acid--cuprous chloride solution to give m-chlorobenzaldehyde without isolating the m-aminobenzaldehyde. The directions for this reduction and replacement reactions as given in "Organic Syntheses"(46) were followed.

The average yield of m-chlorobenzaldehyde based on five reactions was 56.5 percent.

PREPARATION OF m-CHLOROBENZOYL CHLORIDE

It was possible to synthesize this acid chloride from the m-chlorobenzaldehyde prepared above by the direct chlorination at a high temperature. Nearly the same procedure and apparatus as described in "Organic Syntheses" (47) for the direct chlorination of o-chlorobenzaldehyde was used. The reaction mixture was distilled at reduced pressure and the fraction boiling from 98-99°/10 mm. represented a 77.0 percent yield.

PREPARATION OF m-CHLOROBENZYL CHLORIDE

There are several methods available for preparing benzyl chlorides. One method is the chloromethylation reaction (48). The main disadvantage of this method is that chloromethylation of chlorobenzene gives mostly the ortho and para substituted chlorobenzyl chlorides and even here the yields are small.

A much better method of preparation of m-chlorobenzyl chloride is the direct chlorination of m-chlorotoluene. Here the main problem is regulation of conditions so that only one hydrogen of the methyl group is substituted. This can be accomplished by using a large ratio of hydrocarbon to chlorine but if this is done the excess hydrocarbon must be separated from the chlorinated compound. This separation is relatively easy but still the process is tedious and more important, a large quantity of the relatively expensive m-chlorotoluene is required.

Probably the best laboratory method for the preparation of this compound is the direct chlorination of m-chlorotoluene using sulfuryl chloride and benzoylperoxide as described by Kharash (49). He found that one chlorine could be substituted into the side chain very easily while the second chlorine could be introduced only with difficulty and a third could not be added.

The peroxide-catalyzed reaction proceeds rapidly in the dark, whereas the light-promoted reaction with sulfuryl chloride is much slower. The general reaction is as follows:

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

Reactants:

2.0 moles m-chlorotoluene (253 g.)

1.0 mole sulfuryl chloride (135 g.)

1.0 mole carbon tetrachloride

0.004 benzoyl peroxide (1.0 g.)

The reaction was carried out in a three liter, one-neck flask equipped with a bulb reflux condenser and a thermometer so fixed that it would dip into the solution. A means of trapping all acidic gases was also used. Two moles of m-chlorotoluene, one mole of freshly distilled sulfuryl chloride, one mole of carbon tetrachloride and two thousandths of a mole of benzoyl peroxide were added to the flask. It must be pointed out here that all of these products must be pure since any impurities will interfere with the free radical reaction.

The contents of the flask were then heated with an electric mantle. When the temperature had reached 70° a slow evolution of gases started. The temperature was allowed to rise to 85-90° where the gases were evolving at a fairly vigorous rate. After three hours at this temperature an additional 0.5 grams (0.002 mole) of benzoyl peroxide was added.

After nine hours, total time, at 85-90°, the evolution of gases had practically ceased. Therefore, the temperature was raised to 105°. This higher temperature was maintained for one hour following which the mixture was allowed to cool to room temperature.

After the carbon tetrachloride had been removed from the reaction mixture at atmospheric pressure, the remaining liquid was distilled

at diminished pressure. There were 143.0 grams of m-chlorotoluene recovered (B.P. 46-48°/14 mm.). The fraction boiling from 93-95°/14 mm. amounted to 121.9 grams, a 76 percent yield based on the sulfuryl chloride of which none was recovered.

A reaction carried out on twice the amounts of material listed above resulted in a yield of 79 percent.

EXPERIMENTAL

PREPARATION OF METHYLPHENYL CHLOROBENZOATES

Reactants:

1.0 moles chlorobenzoyl chloride (145 g.)

1.25 moles cresol (135.2 g.)

One mole of the chlorobenzoyl chloride was added to a 500 ml. round-bottomed flask which was equipped with a reflux condenser, thermometer, and a trap for the HCl gas. One and one-quarter moles of cresol were then added and the mixture heated to 95-100°. This temperature was maintained for a period of 2.5-5 hours at which time all the HCl gas had evolved. After cooling, the mixture was taken up in benzene or ether and this solution washed with 2 N NaOH to remove the excess cresol. After washing the organic layer with water it was placed over Drierite. The solution was then decanted from the Drierite and the solvent evaporated. The remaining oil or solid was taken up in an appropriate solvent and recrystallized if the ester was a solid at room temperature. If the ester was an oil it was distilled at reduced pressure, using a small modified Claisen flask described in the section dealing with diphenylmethanes. The pressure was determined by means of a McLeod guage. The melting points of the solid esters were determined by the capillary-tube method (50). All yields are based on products having a 1-3° melting point range.

2-METHYLPHENYL 2-CHLOROBENZOATE

o-Chlorobenzoyl chloride and o-cresol were allowed to react in the manner described in the previous section. Evaporation of the

extraction solvent left an oil which could not be induced to crystallize. Therefore it was distilled at reduced pressure. Average yield was 90.8 percent. Physical properties:

B.P.	138-140°/1.0 mm.
n_D^{20}	1.5787
Cl calc'd	14.37 percent
Cl found	14.50, 14.17 percent

2-METHYLPHENYL 3-CHLOROBENZOATE

This ester was prepared in the usual manner except that only 0.36 mole of m-chlorobenzoyl chloride and 0.45 mole of o-cresol were used. It was found that the crude product could be satisfactorily purified by the use of 95 percent ethyl alcohol as the crystallization solvent. The average yield was 80.4 percent. The white granular crystals had the following physical constants:

M.P.	53.2-54.2°
Cl calc'd	14.37 percent
Cl found	14.25, 14.14 percent

2-METHYLPHENYL 4-CHLOROBENZOATE

The reactants in this case were p-chlorobenzoyl chloride and o-cresol. The ester was recrystallized from 95 percent ethyl alcohol to give white granular crystals. Two runs gave an average yield of 86.3 percent. The pure ester has the following physical constants:

M.P.	44.7-45.4°
Cl calc'd	14.37 percent
Cl found	14.34, 14.28 percent

4-METHYLPHENYL 2-CHLOROBENZOATE

This ester was synthesized by Rosemund and Schnurr (51) but they did not list any of its physical properties in their article. However, Auwers (52) lists it as melting from 69-71°.

Two different runs were made using o-chlorobenzoyl chloride and p-cresol. The crude product was recrystallized from methyl alcohol. The average yield of product was 79.0 percent. The crystals were white flat needles which had the following physical constants:

M.P.	68.8-69.8°
Cl calc'd	14.37 percent
Cl found	14.49, 14.14 percent

4-METHYLPHENYL 3-CHLOROBENZOATE

Smaller quantities of m-chlorobenzoyl chloride and p-cresol were used for these runs than the one mole quantities generally used, but the reaction mixture was treated in the same manner. The crude product gave white needles from methyl alcohol. Average yield of product was 90.2 percent.

Physical constants:

M.P.	75.1-76.0°
Cl calc'd	14.37 percent
Cl found	14.37, 14.32 percent

4-METHYLPHENYL 4-CHLOROBENZOATE

This ester was readily prepared from p-chlorobenzoyl chloride and p-cresol. It was found that the ester could be purified by using 90-120° ligroin or methyl alcohol. The ester crystallized in the form

of large white plates and the average yield was 90.8 percent.

Physical constants:

M.P.	97.4-98.3°
Cl calc'd	14.37 percent
Cl found	14.21, 14.34 percent

PREPARATION OF HYDROXY-METHYL-CHLORO'-BENZOPHENONES

Reactants:

1.0 mole ester (246.7 g.)

1.50 moles aluminum chloride for o-cresyl esters (200.0 g.)

1.25 moles aluminum chloride for p-cresyl esters (166.7 g.)

These Fries rearrangements (20) were carried out in the same manner as that described for similar compounds by Adams (19).

The o-Cresyl Esters. These reactions were carried out in a two liter, three-necked flask that was equipped with an air condenser, thermometer, mechanical stirrer, and an HCl gas trap. One mole of the ester was placed in the flask and heated to 130°. One and one-half moles of anhydrous aluminum chloride were then added in small portions at such a rate as to keep the temperature as near 130° as possible. The reactions were quite exothermic and heating was discontinued during this addition. After all of the catalyst had been added, the temperature was raised to 165-180° and maintained there for 45 minutes. The stirring usually had to be discontinued soon after raising the temperature because the reaction mixture became too viscous.

After the mixture had cooled to room temperature the complex was decomposed with 300 ml. of concentrated hydrochloric acid and 500 g. of ice. It was usually necessary to heat the acid mixture on the steam bath in order to speed up the decomposition.

The resulting solid was filtered, washed with water and dried. Distillation of the dry solid, at reduced pressure (15 mm.) in a flask described by Fieser (53) using a flame, gave a product that was quite free from any tarry materials.

It will be noted that there are two possible isomers obtainable from rearrangement of o-cresyl esters. They are, namely, the o-hydroxybenzophenones and the p-hydroxybenzophenones. It was found that these two isomers could be separated by the judicious use of solvents, the o-hydroxy ketone always being more soluble in the solvent than the p-hydroxybenzophenone. It is quite easy to distinguish between the isomers as the o-hydroxy compound is yellow and has a lower melting point. After separating the isomers, purification was accomplished by recrystallization from an appropriate solvent.

The p-Cresyl Esters. The rearrangement of these esters was carried out in the same type of apparatus as described in the foregoing section, except that the mechanical stirrer was omitted. In this case one mole of the ester and one and one-quarter moles of anhydrous aluminum chloride were placed in the flask and thoroughly mixed. This mixture was then heated rapidly by means of an electric mantle until the temperature had reached 120°. At this temperature an exothermic reaction occurred which raised the temperature to 140-160°. The mixture was then maintained at 160° for ten minutes and finally allowed to cool to room temperature.

The orange solid, that resulted from this reaction, was treated with 300 ml. of concentrated hydrochloric acid and 500 g. of ice. In order to decompose the complex completely, it was usually necessary to heat this mixture on the steam bath. The cold mixture was filtered, washed with water, and the dried precipitate distilled at reduced pressure (15 mm.) in the same type of apparatus as described in the above section. The distillate was taken up in ethyl ether and washed

with a saturated solution of sodium bicarbonate in order to remove the chlorobenzoic acid. The solid that remained on evaporation of the ether was recrystallized from an appropriate solvent.

All melting points were taken with a capillary tube. The yields are the average of at least two runs and are based on products having a 1-3° melting point range.

4-HYDROXY-3-METHYL-2'-CHLOROBENZOPHENONE

This white granular compound was prepared from 2-methylphenyl 2-chlorobenzoate by the general procedure described above. It was possible to separate this main isomer from 2-hydroxy-3-methyl-2'-chlorobenzophenone by recrystallizing from benzene, the latter being more soluble, remains in the mother liquor. After isolating the compound in this manner, it was further purified by recrystallizing from 60 percent ethyl alcohol. The yield amounted to 35.3 percent.

Physical constants:

M.P.	167.9-168.6°
Cl calc'd	14.37 percent
Cl found	14.43, 14.30 percent

4-HYDROXY-3-METHYL-3'-CHLOROBENZOPHENONE

The rearrangement of 2-methylphenyl 3-chlorobenzoate gave 2-hydroxy-3-methyl-3'-chlorobenzophenone in addition to the p-isomer above. The 2-hydroxy compound was readily separated from the 4-hydroxy isomer by taking the mixture up in hot toluene and allowing it to cool. The latter compound crystallizes while the o-isomer remains in solution.

The white solid thus obtained was further purified by recrystallizing from toluene. Yield of finely powdered material amounted to 55.7 percent based on three runs.

Physical constants:

M.P.	151.2-151.8°
Cl calc'd	14.37 percent
Cl found	14.12, 14.31 percent

4-HYDROXY-3-METHYL-4'-CHLOROBENZOPHENONE

The separation of this benzophenone from 2-hydroxy-3-methyl-4'-chlorobenzophenone, both produced when 2-methylphenyl 4-chlorobenzoate was rearranged in the manner previously described, was readily accomplished by treating the mixture with ethyl ether which extracted the more soluble o-isomer. The solid that remained after said extraction was recrystallized from 95 percent ethyl alcohol. The average yield of white needles amounted to 52.1 percent.

Physical constants:

M.P.	210.5-211.5°
Cl calc'd	14.37 percent
Cl found	14.33, 14.16 percent

2-HYDROXY-3-METHYL-2'-CHLOROBENZOPHENONE

As was mentioned previously, this benzophenone is also produced by the Fries rearrangement of 2-methylphenyl 2-chlorobenzoate. After separation from 4-hydroxy-3-methyl-2'-chlorobenzophenone, it was recrystallized from methyl alcohol. The average yield from two runs

amounted to 11.8 percent. These coarse yellow rhombic crystals had the following physical constants:

M.P.	72.3-72.8°
Cl calc'd	14.37 percent
Cl found	14.27, 14.38 percent

2-HYDROXY-3-METHYL-3'-CHLOROBENZOPHENONE

This yellow compound was formed by the Fries rearrangement of 2-methylphenyl 3-chlorobenzoate as indicated in the discussion of 4-hydroxy-3-methyl-3'-chlorobenzophenone. After separation from the p-hydroxy isomer it was purified by recrystallization from methyl alcohol. The average yield of three runs amounted to 17.3 percent. These yellow prisms had the following physical constants:

M.P.	69.5-70.3°
Cl calc'd	14.37 percent
Cl found	14.13, 14.23 percent

2-HYDROXY-3-METHYL-4'-CHLOROBENZOPHENONE

When 2-methylphenyl 4-chlorobenzoate was subjected to the conditions of the Fries rearrangement, this ketone was one of two found in the reaction mixture. It was separated from the mixture by extraction with ethyl ether, leaving behind the higher melting isomer, namely, 4-hydroxy-3-methyl-4'-chlorobenzophenone. The yield thus obtained, amounted to 12.6 percent. When the orange-yellow solid, remaining after evaporation of the ether, was taken up in methyl alcohol, flat needles deposited which had the following physical constants:

M.P.	61.5-62.0°
Cl calc'd	14.37 percent
Cl found	14.29, 14.26 percent

2-HYDROXY-5-METHYL-2'-CHLOROBENZOPHENONE

This ketone was prepared by Rosenmund and Schnurr (51) in 1928 from 4-methylphenyl 2-chlorobenzoate by means of the Fries rearrangement. It was listed as being a yellow solid melting at 78°.

The compound was prepared in this laboratory by the same method in yields of 71.3 percent. The product was purified by recrystallization from petroleum ether. It came out of this solvent as very coarse yellow, rhombic crystals.

Physical constants:

M.P.	76.3-77.2°
Cl calc'd	14.37 percent
Cl found	14.25, 14.26 percent

2-HYDROXY-5-METHYL-3'-CHLOROBENZOPHENONE

The yellow granular compound was prepared in the same general way as described above. It was recrystallized from petroleum ether and the average yield was 45.1 percent.

There was some difficulty in the purification of this solid due to the presence of an oil. This accounts for the lower yield of ketone.

The following physical constants of the solid were noted:

M.P.	70.5-71.5°
Cl calc'd	14.37 percent
Cl found	14.19, 14.31 percent

2-HYDROXY-5-METHYL-4'-CHLOROBENZOPHENONE

By treating 4-methylphenyl 4-chlorobenzoate with aluminum chloride in the manner previously described, this yellow ketone was prepared in yields of 50.9 percent.

The compound crystallized from petroleum ether in the form of large prisms. Ethyl alcohol (95 percent) is also a suitable solvent for recrystallization.

The amount of chlorine found in this substance was lower than the theoretical despite repeated recrystallizations and distillations. The melting point indicates that the substance was quite pure but the percentage of halogen was not raised appreciably even after distilling the compound to remove any possible occulded solvent.

Reduction of this substance by the Wolff-Kishner method gave 2-hydroxy-5-methyl-4'-chlorodiphenylmethane and therefore it must contain some 2-hydroxy-5-methyl-4'-chlorobenzophenone.

Physical constants:

M.P.	66.9-67.6°
Cl calc'd	14.37 percent
Cl found	13.43, 13.48 percent

PREPARATION OF HYDROXY-METHYL-CHLORO'-DIPHENYLMETHANES

The main problem of this research was to synthesize nine hydroxy-methyl-chloro'-diphenylmethanes. One method of preparation was the reduction of the previously discussed substituted benzophenones. While this means of preparation was successfully employed for eight of the nine compounds in question, it was found that generally these substituted diphenylmethanes could be synthesized more easily by the following methods of direct alkylation.

Two methods of direct alkylation of o- and p-cresol were used. If the condensation is carried out using an acidic catalyst (aluminum chloride) p-alkylation of o-cresol takes place. However, if basic conditions are used in a non-dissociating solvent all carbon alkylation takes place exclusively in the o-position to the hydroxyl group of the phenol (36). In addition some oxygen alkylation occurs to give the corresponding ethers.

The hydroxy-methyl-chloro'-diphenylmethanes thus prepared by these two direct methods were compared and found to be identical with those prepared by the reduction method, in that mixed melting points gave no appreciable depression.

All the yields are based on products having a 1-3° melting point range. At least two reactions were made in every case that yields are reported unless otherwise noted. All final melting points were taken by the capillary tube method (50) and are uncorrected.

REDUCTION OF HYDROXY-METHYL-CHLORO'-BENZOPHENONES

Reactants:

0.5 mole benzophenone (123.4 g.)

0.87 mole hydrazine hydrate 85 percent (51.5 g.)

1.38 moles sodium hydroxide (55.0 g.)

500 ml. diethylene glycol

As was noted in a previous section it was found that the Wolff-Kishner (27) method of reduction was successful whereas the Clemmensen (22) method and the hydroidic acid plus phosphorus (54) method were not satisfactory.

The Huang-Minlon (31) modification of the Wolff-Kishner reaction was used in carrying out these reductions. The reaction was carried out in a one liter three necked flask equipped with a mechanical stirrer, reflux condenser and a thermometer extending into the liquid. Heating was accomplished by means of an electric mantle. One-half mole of the necessary substituted benzophenone and one and thirty-eight-hundredths mole of sodium hydroxide were added to 500 ml. of diethylene glycol. This mixture was then heated to reflux temperature (140°) and maintained there for one and one-half hours. At the end of this time the reflux condenser was removed and the temperature allowed to rise to 195°. The condenser was then replaced and refluxing continued for four hours after which it was allowed to cool to room temperature. Stirring was continued during the entire heating period.

The viscous mixture was then added to 750 ml. of water and acidified with enough 6 N hydrochloric acid to make the solution distinctly acid and this mixture extracted with three 250 ml. portions of ethyl ether.

The oil, remaining after evaporation of the ethyl ether on a steam bath, was distilled at reduced pressure (2-3 mm.) in order to separate it from any tars, and the distillate recrystallized from an appropriate solvent.

DIRECT ALKYLATIONS

The apparatus for these alkylations consisted of a one-liter, round-bottomed, standard-taper, three-necked (24/40 - 34/45 - 24/40) flask which was equipped with a dropping funnel, reflux condenser, and Hershberg stirrer (55) of nichrome wire. It was found that a glycerine seal was adequate for the stirrer but it is recommended that silicone stopcock grease be used to lubricate the glass joints.

The vacuum distillations were carried out in a 50 ml. or 100 ml. round-bottomed flask attached to a Claisen adapter. This adapter was filled with small glass beads (6 mm. in diameter) and arrangements were made to heat it electrically. The flask was heated to the desired temperature by means of an oil bath. It was possible to collect three fractions without breaking the vacuum by using an inclined rotating receiver (56). The high boiling points and high viscosity of these compounds make the use of more elaborate distillation apparatus untenable.

The final boiling points were taken with a corrected thermometer using material that had a melting point range of 1-2 degrees. The pressure was determined with a McLeod guage. The apparatus here consisted of a 50 ml. Claisen flask containing glass beads (6 mm. in diameter) in the bend of the neck.

Alkylations Using Acidic Conditions

Reactants:

1.5 moles o-cresol (163 g.)

0.5 mole chlorobenzyl chloride (80.5 g.)

400 ml. petroleum ether

0.25 mole aluminum chloride (33.4 g.)

The 400 ml. of petroleum ether, one and one-half moles of o-cresol and one-half mole of chlorobenzyl chloride, in this order, were added to the flask and vigorously stirred. One-quarter mole of powdered anhydrous aluminum chloride was then added to this mixture over a period of two hours. The stirring was continued at room temperature (25-35°) for a period of 72 hours.

At the end of this time the red, oily mixture (two layers) was poured, with stirring, into a mixture of 500 grams of ice and 300 ml. of concentrated hydrochloric acid. This acidic mixture was extracted with four 100 ml. portions of ethyl ether. Evaporation of the ethyl ether left an oil which was dissolved in 250 ml. of Claisen's solution* (18) and extracted with four 100 ml. portions of petroleum ether to remove any ethers that may have been formed during the reaction. There was always a small amount of oil left upon evaporation of the petroleum ether but never enough to purify and identify.

The alkaline fraction was poured over 500 grams of crushed ice and acidified with 6 N hydrochloric acid. Finally, the mixture was

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* 350 g. KOH in 250 g. H_2O, diluted to one liter with methanol. Concentrated aqueous (50 percent) KOH is unsuitable for the salts are insoluble in it. Therefore they form either an oily layer between the petroleum ether and aqueous KOH, or partially dissolve in the ether.

extracted with four 100 ml. portions of ethyl ether and the ether evaporated.

The resulting oil was distilled at reduced pressure and the fractions containing the desired phenolic product recrystallized from an appropriate solvent.

The temperatures of these distillations are given under the respective compounds, but it must be remembered that there is a great tendency of these viscous oils to superheat. In addition, the pressures were observed on a finger manometer (Corning Glass 6950) and it is difficult to read accurately pressures below 3 mm. Correct values are given with the summarized physical constants of the compounds.

4-HYDROXY-3-METHYL-2'-CHLORODIPHENYLMETHANE

This diphenylmethane was isolated from the reduction products of 4-hydroxy-3-methyl-2'-chlorobenzophenone in very small yields. There was a considerable amount of high boiling residue but no definite products could be isolated other than the diphenylmethane. However this compound was produced in yields of 26.8 percent by the Friedel-Crafts condensation of o-chlorobenzyl chloride and o-cresol. After removal of the excess and unreacted o-cresol (94-96 grams) the following fractions were taken:

52-147°/2 mm.	2.7 g.
147-153°/2 mm.	37.2 g.
153-157°/2 mm.	24.5 g.
157-175°/2 mm.	2.1 g.
Residue	28.7 g.

The fractions boiling from 147-157°/2 mm. were taken up in hexane and a solid was obtained by cooling to 0° C. This solid was then further purified by using petroleum ether.

Mixed melting points of the products prepared by the two methods indicated that they were identical.

The compound crystallized from petroleum ether in the form of long, white needles and has the following physical constants:

B.P.	142-145°/0.8 mm.
M.P.	57.8-58.5°
Cl calc'd	15.24 percent
Cl found	15.27, 15.13 percent

4-HYDROXY-3-METHYL-3'-CHLORODIPHENYLMETHANE

The reduction of 4-hydroxy-3-methyl-3'-chlorodiphenylmethane by the Wolff-Kishner method produces the diphenylmethane in yields of 41.0 percent. This method of preparation was superior to the Friedel-Crafts method for this diphenylmethane in that the reaction product was much more easily purified.

The Friedel-Crafts reaction was run in the usual manner (m-chlorobenzyl chloride plus o-cresol) except that only four-tenths mole proportions, based on m-chlorobenzyl chloride, were used. After recovering 80-82 grams of o-cresol the following fractions were obtained:

47-143°/3 mm.	0.3 g.
143-148°/3 mm.	9.2 g.
148-151°/3 mm.	35.0 g.
151-156°/3 mm.	7.5 g.
Residue	19.6 g.

The fractions boiling from 143-156°/3 mm. were redistilled, the distillate taken up in hexane and placed in the freezing compartment of the refrigerator. After remaining there for two weeks the oil had partially crystallized. These crystals were quickly filtered to allow most of the oil to go along with the filtrate. Further recrystallization from hexane gave a 12.4 percent yield of very fine, white, fluffy needles. The product thus isolated proved to be identical with that prepared by the reduction method.

The compound had the following physical constants:

B.P.	143-146°/0.7 mm.
M.P.	39.9-40.4°
Cl calc'd	15.24 percent
Cl found	15.28, 15.20 percent

4-HYDROXY-3-METHYL-4'-CHLORODIPHENYLMETHANE

It was possible to prepare this compound by the reduction of 4-hydroxy-3-methyl-4'-chlorobenzophenone, in yields of 44.9 percent.

However, the acidic condensation of p-chlorobenzyl chloride and o-cresol also gave good results, 35.3 percent, and the reaction product was readily purified. The results of distillation of the oil remaining after recovering 46-52 grams of o-cresol from a one-quarter mole run, based on p-chlorobenzyl chloride, are recorded below:

60-151°/3 mm.	2.4 g.
151-160°/3 mm.	31.4 g.
Residue	11.0 g.

This oil was readily purified by recrystallization from hexane. The white fine needles obtained by this method were the same as those prepared by the other method and they have the following physical constants:

B.P.	145-147°/0.9 mm.
M.P.	74.1-74.8°
Cl calc'd	15.24 percent
Cl found	15.15, 15.07 percent

Alkylations Using Basic Conditions

Reactants:

0.5 mole sodium (11.5 g.)

0.5 mole o- or p-cresol (54.7 g.)

0.5 mole chlorobenzyl chloride (80.5 g.)

500 ml. toluene or xylene (dry)

Four hundred ml. of dry toluene or xylene were placed in a one-liter, three-necked flask fitted as described previously. One-half mole of freshly cut sodium was then placed in the solvent and heat applied by means of an electric mantle until reflux temperature had been reached. The stirrer was then started in order to beat the sodium into small pellets. With continued stirring one-half mole of o-cresol, dissolved in 100 ml. of the solvent, was slowly added and this mixture allowed to stir and reflux for one-half hour. At this point one-half mole of chlorobenzyl chloride was added over a period of one-half hour. Refluxing and stirring of this mixture was then continued for 36 hours.

After cooling, the reaction mixture was acidified with dilute hydrochloric acid and ice. The organic layer was separated and the aqueous

layer extracted with two 100 ml. portions of toluene or xylene, depending on which had been used. The oil that was left after stripping off the solvent was taken up in 250 ml. of Claisen's solution (43). This alkaline mixture was extracted with four 100 ml. portions of petroleum ether to remove any oxygen-benzylated compound. Evaporation of the petroleum ether left an oil which proved to be the ether. The series of ethers thus produced will be discussed in the following section. (Ethyl ether cannot be used for extraction, because of the solubility of the methanolic solution of the phenolates in it.) It is necessary to remove all the solvent in the reaction mixture, otherwise an emulsion is formed which is very difficult to break.

The basic solution was poured over 500 g. of crushed ice and acidified with dilute hydrochloric acid. Following this, the organic layer was separated and the aqueous layer extracted with four 100 ml. portions of ethyl ether. The ether extract and the organic layer were combined and the ether evaporated. The resulting oil was distilled in the same type of apparatus described in the previous section on diphenylmethanes.

The fractions containing the desired diphenylmethanes were recrystallized and physical constants determined as described previously. Again it must be pointed out that accuracy of the original boiling points and pressure readings are open to question due to the ease of superheating. Accurate readings are listed with the physical constants of the compounds.

2-HYDROXY-3-METHYL-2'-CHLORODIPHENYLMETHANE

2-Hydroxy-3-methyl-2'-chlorobenzophenone was reduced by the Wolff-Kishner reaction to produce this diphenylmethane. Here again, as in

the case of other 2-chloro'-benzophenones, the yield was small. However, a sufficient quantity was isolated, so that it could be purified, and was found to be the same compound as that produced by the Claisen condensation of o-chlorobenzyl chloride and o-cresol.

The basic condensation of o-chlorobenzyl chloride and o-cresol was first tried using toluene as the solvent. However, the average yield amounted to but 9.5 percent, based on original charge, with 49.7 percent of the o-chlorobenzyl chloride being recovered. When the higher boiling xylene was used, as suggested by Wheatley (41), the yield of the desired product amounted to 29.9 percent while the unreacted o-chlorobenzyl chloride amounted to less than 0.5 percent.

The following data was obtained from a typical distillation.

-60°/3 mm.	3.5 g.
60-140°/3 mm.	0.1 g.
140-147°/3 mm.	40.9 g.
Residue	12.4 g.

The 140-147°/3 mm. fraction was recrystallized from petroleum ether to give short, white needles having the following physical properties:

B.P.	131-133°/0.7 mm.
M.P.	42.2-42.8°
Cl calc'd	15.24 percent
Cl found	15.26, 15.16 percent

2-HYDROXY-3-METHYL-3'-CHLORODIPHENYLMETHANE

This diphenylmethane was readily prepared from 2-hydroxy-3-methyl--3'-chlorobenzophenone, by reduction, in a 44.5 percent yield based on one reaction.

The yield by the Claisen condensation of m-chlorobenzyl chloride and o-cresol, using xylene as a solvent, amounted to 19.1 percent. The results of a typical distillation are listed below.

-41°/2 mm.	2.7 g.
41-139°/2 mm.	1.2 g.
139-144°/2 mm.	34.0 g.
Residue	8.4 g.

The fraction boiling from 139-144°/2 mm. was recrystallized from petroleum ether. The long, white needles thus obtained were identical with those obtained by the reduction process. The physical constants of this compound are listed below:

B.P.	133-136°/0.7 mm.
M.P.	43.7-44.5°
Cl calc'd	15.24 percent
Cl found	15.12, 15.12 percent

2-HYDROXY-3-METHYL-4'-CHLORODIPHENYLMETHANE

Klarmann et al. (57) prepared this compound in 1932, using the Claisen method. Its melting point (48°) and boiling point (167-172°/4 mm.) were listed but there was no mention made of the yields they obtained.

It was possible to obtain this diphenylmethane by the Wolff-Kishner reduction of 2-hydroxy-3-methyl-4'-chlorobenzophenone. The yield, based on one reaction, was 60.0 percent.

When p-chlorobenzyl chloride and o-cresol were allowed to react in a basic solution with toluene as the solvent, a 33.2 percent yield of this compound was obtained.

Distillation:

-52°/3 mm.	13.5 g.
52-146°/3 mm.	1.0 g.
146-160°/3 mm.	45.1 g.
Residue	4.0 g.

The main fraction was recrystallized from petroleum ether and found to be the same as that produced by the reduction method of preparation. These crystals were in the form of long, white needles.

Physical constants:

B.P.	135-137°/0.7 mm.
M.P.	47.2-47.9°
Cl calc'd	15.24 percent
Cl found	15.24, 15.09 percent

2-HYDROXY-5-METHYL-2'-CHLORODIPHENYLMETHANE

When 2-hydroxy-5-methyl-2'-chlorobenzophenone was reduced by means of the Wolff-Kishner reaction, 2-methylxanthene was isolated instead of the desired substituted diphenylmethane. The characterization and a second method of preparation of this substituted xanthene will be found in a following section.

The Claisen method of preparation using o-chlorobenzyl chloride and p-cresol, with toluene as the solvent, gave the desired compound in yields of 30.3 percent.

Distillation:

-70°/3 mm.	5.5 g.
70-163°/3 mm.	0.2 g.

163-174°/3 mm.	43.8 g.
Residue	23.9 g.

The fraction containing 43.8 grams was recrystallized from petroleum ether to give white needles in 30.3 percent yields.

Physical constants:

B.P.	138-140°/0.7 mm.
M.P.	42.6-43.4°
Cl calc'd	15.24 percent
Cl found	15.03, 15.12 percent

2-HYDROXY-5-METHYL-3'-CHLORODIPHENYLMETHANE

When 2-hydroxy-3-methyl-3'-chlorobenzophenone was reduced in the usual manner, the corresponding diphenylmethane was produced in yields averaging 78.8 percent. The reaction product was purified in the manner described and the distilled oil taken up in petroleum ether. The compound crystallized in the form of short, close-packed, white needles.

The basic condensation of m-chlorobenzyl chloride and p-cresol, using xylene as the solvent, gave a 29.8 percent yield of this diphenylmethane. Typical distillation data are given below.

-58°/3 mm.	5.0 g.
58-153°/3 mm.	2.1 g.
153-158°/3 mm.	45.3 g.
Residue	20.8 g.

Recrystallization of the large fraction from petroleum ether gave a compound that was identical with the one prepared by the reduction method. This fact was determined by utilizing the mixed melting point technique.

PREPARATION OF METHYLPHENYL-CHLOROBENZYL ETHERS

These six ethers were produced as side-products in the Claisen alkylation reaction. They were also prepared from the appropriate chlorobenzyl chloride and cresol in an alcoholic sodium hydroxide medium. Their physical properties were then compared and a mixed melting point taken if the compounds were solids. In all cases the compounds prepared by the two methods were identical.

CLAISEN-C-ALKYLATION METHOD

The ethers were separated from the diphenylmethanes by extracting the strong alkaline solution with petroleum ether as was mentioned in the section on preparation of diphenylmethanes. The petroleum ether was then removed by evaporation on the steam bath and the resulting oil distilled at reduced pressure (2-3 mm.) in the large type of Claisen adapter, as described in the section on the preparation of diphenylmethanes by direct alkylation. The fraction containing the ether was then purified by recrystallization from an appropriate solvent if the substance was a solid or redistilled if the ether could not be induced to crystallize.

The boiling points of these original distillations were taken by using an ordinary thermometer and the pressure determined with a finger type manometer (Corning Glass 6950).

PREPARATION IN A SODIUM HYDROXIDE - ETHYL ALCOHOL MEDIUM

Reactants:

500 ml. ethyl alcohol (95 percent)

0.25 mole sodium hydroxide (10 g.)

0.30 mole ortho or para cresol (32.4 g.)

0.25 mole chlorobenzyl chloride (40.3 g.)

The procedure used was essentially the same as that described by Lyman (42). The apparatus consisted of a three-necked, one liter flask equipped with a mechanical stirrer and a reflux condenser. Five hundred ml. of 95 percent ethyl alcohol was introduced into the flask and brought to its boiling point on the steam bath and one-quarter mole of sodium hydroxide then dissolved in the ethyl alcohol. To this solution was added three tenths mole of the necessary cresol and finally one-quarter mole of the chlorobenzyl chloride. Stirring and refluxing were continued for three hours. In every case a white solid, which was presumedly sodium chloride, was deposited at the bottom of the flask.

This reaction mixture was treated with 450 ml. of water and then placed in the refrigerator. If the oil solidified it was removed by filtration and recrystallized from a suitable solvent. If the oil could not be induced to crystallize it was separated from the water-alcohol layer and distilled in the large Claisen apparatus.

In order to obtain a more accurate boiling point at a definite pressure the crystallized esters were distilled in the small type Claisen apparatus described in the previous section. A calibrated thermometer was used and the pressure determined by a McLeod guage.

2-METHYLPHENYL-2-CHLOROBENZYL ETHER

When toluene was used as the solvent in the Claisen condensation of o-cresol and o-chlorobenzyl chloride, the yield of this ether amounted to only 3.1 percent. However when the higher boiling xylene was used

the yield amounted to 14.9 percent. The increase in yield was at the expense of the unreacted o-chlorobenzyl chloride.

Distillation:

-115°/2 mm.	0.3 g.
115-120°/2 mm.	22.0 g.
Residue	20.5 g.

The desired fraction was recrystallized from methyl alcohol in white granular form.

This same ether was prepared from o-cresol and o-chlorobenzyl chloride in a sodium hydroxide-ethyl alcohol medium by the general procedure described at the beginning of this section. The yield by this method, based on one reaction, was 71.5 percent.

Physical constants:

B.P.	118-119°/0.8 mm.
M.P.	37.9-38.8°
Cl calc'd	15.24 percent
Cl found	15.01, 15.06 percent

2-METHYLPHENYL-3-CHLOROBENZYL ETHER

This condensation of o-cresol and m-chlorobenzyl chloride was carried out in xylene. The yield of ether amounted to 21.0 percent. The compound is a liquid at room temperature, resisting all attempts to crystallize it by common methods.

Distillation:

-133°/2 mm.	0.5 g.
133-140°/2 mm.	20.4 g.

140-145°/2 mm.	2.4 g.
Residue	19.2 g.

The two fractions boiling from 133-145°/2 mm. were redistilled again and analyzed for chlorine.

When o-cresol and m-chlorobenzyl chloride were allowed to react by the second method of preparation the same compound was produced that had been isolated from the Claisen reaction. Proof of this lies in the fact that the refractive indices and boiling points of the two samples were the same. The yield, based on one reaction, amounted to 87.6 percent.

Physical constants:

B.P.	125-127°/1.0 mm.
n_D^{20}	1.5791
Cl calc'd	15.24 percent
Cl found	15.10, 15.22 percent

2-METHYLPHENYL-4-CHLOROBENZYL ETHER

This ether was isolated from the basic condensation of o-cresol and p-chlorobenzyl chloride (toluene as solvent) in yields of 12.5 percent.

Distillation:

50-65°/4 mm.	9.0 g.
65-135°/4 mm.	2.1 g.
135-160°/4 mm.	21.0 g.
Residue	15.5 g.

Recrystallization of the fraction containing the ether from petroleum ether gave white, flat needles.

The compound prepared in this manner is identical with that prepared by the second method in a 84.3 percent yield. This later yield is based on only one reaction of o-cresol and p-chlorobenzyl chloride.

A methyl alcohol - water system can also be used to purify this compound by recrystallization.

Physical constants:

B.P.	125-126°/0.8 mm.
M.P.	61.2-61.7°
Cl calc'd	15.24 percent
Cl found	15.05, 15.24 percent

4-METHYLPHENYL-2-CHLOROBENZYL ETHER

It was possible to isolate this ether in an 8.6 percent yield from the alkaline condensation reaction of p-cresol and o-chlorobenzyl chloride in toluene. This ether would solidify if placed in the refrigerator but the melting point was too low to effectively purify it in this manner.

The distillation results of the crude product are given below:

-66°/3 mm.	0.9 g.
66-146°/3 mm.	0.2 g.
146-156°/3 mm.	13.3 g.
Residue	6.8 g.

The fraction boiling from 146-156°/3 mm. was redistilled and the distillate found to be the same compound as that prepared by the sodium hydroxide-ethyl alcohol method. This second method, in which p-cresol and o-chlorobenzyl chloride were used, gave a yield of 76.8 percent based on one reaction.

The refractive index and boiling point of the product prepared by the first method were the same as those shown by the compound prepared by the second method.

Physical constants:

B.P.	120-123°/0.8 mm.
n_D^{20}	1.5791
Cl calc'd	15.24 percent
Cl found	15.17, 15.02 percent

4-METHYLPHENYL-3-CHLOROBENZYL ETHER

One of the reaction products produced by the alkaline condensation of p-cresol and m-chlorobenzyl chloride, using xylene as the solvent, was this ether. It was prepared in yields amounting to 10.8 percent. The white plates that came out of petroleum ether were obtained by crystallizing the 128-135°/3 mm. fraction of the following distillation:

-128°/3 mm.	0.1 g.
128-135°/3 mm.	17.6 g.
Residue	11.2 g.

A mixed melting point of these crystals and those obtained by the second method of preparation (p-cresol plus m-chlorobenzyl chloride) indicated that they were the same. The latter method gave a 67.8 percent yield of product based on one reaction.

The following physical constants were noted:

B.P.	128-129°/0.9 mm.
M.P.	53.8-54.6°
Cl calc'd	15.24 percent
Cl found	14.98, 15.01 percent

4-METHYLPHENYL-4-CHLOROBENZYL ETHER

The last in this series of ethers was isolated from the basic condensation reaction mixture in yields of 4.9 percent. Toluene was employed as the solvent and the reactants consisted of p-cresol and p-chlorobenzyl chloride. The reaction mixture was handled in the usual manner. However, when the petroleum ether had been evaporated, the oil that remained solidified and therefore it was not distilled, although a corrected boiling point was later taken. This solid was recrystallized from hexane to give a granular product. This ether can also be purified by using an ethyl alcohol-water mixture as the solvent.

The latter method of preparation using p-cresol and p-chlorobenzyl chloride was very satisfactory in that a yield of 88.0 percent was obtained. The ether prepared in this manner was identical with the one prepared by the previous method. It had the following physical constants:

B.P.	127-130°/0.9 mm.
M.P.	91.7-92.6°
Cl calc'd	15.24 percent
Cl found	15.08, 15.08 percent

PREPARATION OF 2-METHYLXANTHENE

As has been pointed out in the discussion section, the reduction of 2-hydroxy-5-methyl-2'-chlorobenzophenone by the Huang-Minlon (31) modification of the Wolff-Kishner (27) reaction did not give the desired 2-hydroxy-5-methyl-2'-chlorodiphenylmethane.

The reaction conditions and apparatus by which this xanthene was prepared are discussed in the experimental section under reduction of Hydroxy-Methyl-Chloro'-benzophenones. The oil obtained, after acidification and extraction of the reaction mixture, solidified upon being distilled. This solid could be recrystallized in the form of small plates, from either hexane or methyl alcohol, the latter being the better solvent. Yield, 34.4 percent.

The second method of preparing this xanthene involved the reduction of 2-methylxanthone. This ketone was readily prepared by adding 0.1 mole (24.68 g.) of 2-hydroxy-5-methyl-2'-chlorobenzophenone to 100 ml. of diethylene glycol, which had been placed in a 250 ml. round bottomed flask. The flask was equipped with a reflux condenser and thermometer dipping into the liquid. To this mixture was added 0.28 mole (11.0 g.) of sodium hydroxide and the contents heated to reflux temperature (approximately 180°). This temperature was maintained for 1.5 hours. At the end of this time the temperature was allowed to rise to 195-210°. The refluxing was continued at this temperature for four hours. The heat for this reaction was supplied by a Bunsen burner.

After cooling, the reaction mixture was poured into 150 ml. of water, acidified with 6 N hydrochloric acid and extracted with 300 ml. of benzene. The benzene was then evaporated and the resulting solid

distilled at reduced pressure (approximately 15 mm.). The distillate was taken up in 90-120° ligroin and recrystallized. Finally, it was recrystallized from methyl alcohol.

The compound had a melting point of 123-125°. Yield, 78.0 percent. Meisenheimer et al. (44) lists its melting point as 125.5°.

The reduction of 2-methylxanthone to 2-methylxanthene was accomplished by hydrogenation. The procedure used was similar to that described by Ipatieff (45).

Five grams of 2-methylxanthone were placed in a rocking bomb along with 50 ml. of absolute ethyl alcohol. To this was added 0.5 gram of a copper-chromium oxide catalyst prepared in the manner described by Adkins(59). The initial pressure of hydrogen was 80 atmospheres. After heating the bomb to 185° it was rocked for two hours.

The contents of the bomb were taken in acetone and this solution filtered several times to remove the catalyst. Evaporation of the solvents left a solid which was taken up in hot methyl alcohol and allowed to crystallize. After several recrystallizations a mixed melting point was taken with the compound prepared by the Wolff-Kishner reduction of 2-hydroxy-5-methyl-2'-chlorobenzophenone. There was no depression of the melting point.

Physical constants:

M.P.	96.4-97.4°
C, H calc'd	85.68, 6.14 percent
C, H found	85.79, 6.27 percent

The carbon and hydrogen values were determined by Clark Microanalytical Laboratory (60).

SUMMARY OF YIELDS AND PHYSICAL CONSTANTS

The yields and physical constants of the compounds prepared are listed in the following tables.

The boiling points listed are uncorrected but were obtained by distillation of the pure product under reduced pressure. This pressure was measured using a tilting type McLeod guage. (Scientific Glass Co. N. 10-297).

The melting points were taken on products which had been dried at room temperature. All melting points are uncorrected and were taken by the capillary tube method (50).

The yields are based on the quantity of material having a 1-3° melting point range.

The amount of halogen present in the compounds was determined by the Parr bomb-sodium peroxide fusion method (61). The Volhard method of titration (62) was employed in the last operation of the determination.

METHYLPHENYL CHLOROBENZOATES

COMPOUND	YIELD PERCENT	M.P. °C.	RECRYSTALLIZATION SOLVENT	Cl CALC'D PERCENT	Cl FOUND PERCENT
2-methylphenyl 2-chlorobenzoate	90.8	138-140/10 mm.[a]	-------	14.37	14.59 14.17
2-methylphenyl 3-chlorobenzoate	80.4	53.2-54.2	ethyl alcohol (95)	14.37	14.25 14.41
2-methylphenyl 4-chlorobenzoate	86.3	44.7-45.4	ethyl alcohol (95)	14.37	14.37 14.28
4-methylphenyl 2-chlorobenzoate	79.0	68.8-69.8	methyl alcohol	14.37	14.49 14.14
4-methylphenyl 3-chlorobenzoate	90.2	75.1-76.0	methyl alcohol	14.37	14.37 14.32
4-methylphenyl 4-chlorobenzoate	90.8	97.4-98.3	methyl alcohol or ligroin (90-120°)	14.37	14.21 14.34

(a) Boiling point.

HYDROXY-METHYL-CHLORO'-BENZOPHENONES

COMPOUND	YIELD PERCENT	M.P. °C.	RECRYSTALLIZATION SOLVENT	Cl CALCD PERCENT	Cl FOUND PERCENT
4-hydroxy-3-methyl-2'-chlorobenzophenone	35.3	167.9-168.6	ethyl alcohol (60%)	14.37	14.43 14.30
4-hydroxy-3-nethyl-3'-chlorobenzophenone	55.7	151.2-151.8	toluene	14.37	14.12 14.31
4-hydroxy-3-methyl-4'-chlorobenzophenone	52.1	210.5-211.5	ethyl alcohol(95%)	14.37	14.33 14.16
2-hydroxy-3-methyl-2'-chlorobenzophenone	11.8	72.3-72.8	methyl alcohol	14.37	14.27 14.38
2-hydroxy-3-methyl-3'-chlorobenzophenone	17.3	69.5-70.3	methyl alcohol	14.37	14.13 14.23
2-hydroxy-3-methyl-4'-chlorobenzophenone	12.6	61.5-62.0	methyl alcohol	14.37	14.29 14.26
2-hydroxy-5-methyl-2'-chlorobenzophenone	71.3	76.3-77.2	petroleum ether	14.37	14.25 14.26
2-hydroxy-5-methyl-3'-chlorobenzophenone	45.1	70.5-71.5	petroleum ether	14.37	14.19 14.31
2-hydroxy-5-methyl-4'-chlorobenzophenone	50.9	66.9-67.6	petroleum ether or ethyl alcohol (95%)	14.37	13.43 13.48

HYDROXY-'ETHYL-CHLORO'-DIPHENYL'ETHANES

COMPOUND	REDUCTION YIELD PERCENT	CONDENSATION YIELD PERCENT	B.P. °C.	M.P. °C.	RECRYSTALLIZATION SOLVENT	Cl CALCD PERCENT	Cl FOUND PERCENT
4-hydroxy-3-methyl-2'-chlorodiphenylmethane	(a)	26.8	142-145/ 0.8 mm.	57.8-58.5	petroleum ether	15.24	15.27 15.13
4-hydroxy-3-methyl-3'-chlorodiphenylmethane	41.0	12.4	143-146/ 0.7 mm.	39.9-40.4	hexane	15.24	15.28 15.20
4-hydroxy-3-methyl-4'-chlorodiphenylmethane	44.9	35.3	145-147/ 0.9 mm.	74.1-74.8	hexane	15.24	15.15 15.07
2-hydroxy-3-methyl-2'-chlorodiphenylmethane	(a)	9.5(t) 29.9(x)	131-133/ 0.7 mm.	42.2-42.8	petroleum ether	15.24	15.26 15.16
2-hydroxy-3-methyl-3'-chlorodiphenylmethane	44.5 (b)	19.1(x)	133-136/ 0.7 mm.	43.7-44.5	petroleum ether	15.24	15.12 15.12
2-hydroxy-3-methyl-4'-chlorodiphenylmethane	60.0 (b)	33.2(t)	135-137/ 0.7 mm.	47.2-47.9	petroleum ether	15.24	15.24 15.09
2-hydroxy-5-methyl-2'-chlorodiphenylmethane	(c)	30.3(t)	138-140/ 0.7 mm.	42.6-43.4	petroleum ether	15.24	15.03 15.12
2-hydroxy-5-methyl-3'-chlorodiphenylmethane	78.8	29.8(x)	139-141/ 0.7 mm.	53.2-54.0	petroleum ether	15.24	15.13 15.03
2-hydroxy-5-methyl-4'-chlorodiphenylmethane	42.1	36.9(t)	140-142/ 0.8 mm.	51.4-52.1	petroleum ether	15.24	15.06 15.17

(a) Yield was small and not calculated
(b) Yield based on only one reaction
(c) Only 2-methylxanthene was isolated

(t) Toluene used as the solvent in the condensation
(x) Xylene used as the solvent in the condensation

METHYLPHENYL-CHLOROBENZYL ETHERS

COMPOUND	CONDENSATION YIELD PERCENT	NaOH-EtOH YIELD (a) PERCENT	B.P. °C.	M.P. °C.	RECRYSTALLIZATION SOLVENT	Cl CALC'D PERCENT	Cl FOUND PERCENT
2-methylphenyl-2-chlorobenzyl ether	3.1 (t) 14.9 (x)	71.5	118-119/ 0.8 mm.	37.9- 38.8	methyl alcohol	15.24	15.01 15.06
2-methylphenyl-3-chlorobenzyl ether	21.0 (x)	87.6	125-127/ 1.0 mm.	-----	----------	15.24	15.10 15.22
2-methylphenyl-4-chlorobenzyl ether	12.5 (t)	84.3	125-126/ 0.8 mm.	61.2- 61.7	petroleum ether	15.24	15.05 15.24
4-methylphenyl-2-chlorobenzyl ether	8.6 (t)	76.8	120-123/ 0.8 mm.	-----	----------	15.24	15.17 15.62
4-methylphenyl-3-chlorobenzyl ether	10.8 (x)	67.8	128-129 0.9 mm.	53.8- 54.6	petroleum ether	15.24	14.98 15.01
4-methylphenyl-4-chlorobenzyl ether	4.9 (t)	88.0	127-130/ 0.9 mm.	91.7- 92.6	hexane	15.24	15.08 15.08

(a) These yields are based on only one reaction.
(t) Toluene used as the solvent in the condensation.
(x) Xylene used as the solvent in the condensation.

DERIVATIVES

The p-chlorobenzoates for the nine o- and p-monochlorobenzylated o- and p-cresols were prepared.

Six ml. of anhydrous pyridine, 2 ml. of p-chlorobenzoyl chloride and 2 grams of the phenol were added to a ten inch test tube. This mixture, protected with a drying tube, was heated on the steam bath for one-half hour. At the end of this time it was poured into 20 ml. of water. This mixture was then treated with ethyl ether and the ether layer washed successively with dilute sulfuric, 10 percent sodium carbonate and water. The ether was evaporated and the oil taken up with 95 percent ethyl alcohol. After several recrystallizations from this solvent the white crystals were dried under a vacuum (2-3 mm.) over night at room temperature.

The uncorrected melting points, crystal forms and chlorine content of these derivatives are given in a table on the following page. The melting points were determined by the capillary tube method; the chlorine content by sodium peroxide fusion method.

PARA-CHLOROBENZOATE DERIVATIVES

COMPOUND	M.P.° C.	CRYSTAL STRUCTURE	Cl CALC'D PERCENT	Cl FOUND PERCENT	
4-hydroxy-3-methyl-2'-chlorodiphenylmethane	77.1-77.9	rhombic	19.10	18.90	19.04
4-hydroxy-3-methyl-3'-chlorodiphenylmethane	62.2-62.9	very fine needles	19.10	18.90	19.09
4-hydroxy-3-methyl-4'-chlorodiphenylmethane	50.9-51.6	needles	19.10	18.90	18.91
2-hydroxy-3-methyl-2'-chlorodiphenylmethane	55.5-56.5	rhombic	19.10	18.84	18.91
2-hydroxy-3-methyl-3'-chlorodiphenylmethane	85.5-86.5	small plates	19.10	19.11	18.91
2-hydroxy-3-methyl-4'-chlorodiphenylmethane	81.6-82.3	needles	19.10	19.08	19.18
2-hydroxy-5-methyl-2'-chlorodiphenylmethane	73.2-74.1	granular	19.10	18.93	18.96
2-hydroxy-5-methyl-3'-chlorodiphenylmethane	84.0-85.0	needles	19.10	18.95	18.93
2-hydroxy-5-methyl-4'-chlorodiphenylmethane	78.5-79.1	needles	19.10	18.99	19.02

THE QUANTITATIVE DETERMINATION OF CHLORINE, METHOD

The familiar and rapid sodium peroxide fusion method (61) was used for the quantitative determination of chlorine.

A charge consisting of approximately 10 grams of sodium peroxide, 1.0 to 1.5 grams of potassium nitrate and 0.40 to 0.45 grams of sucrose was placed in a Parr bomb. To this was added 0.20 to 0.25 grams of the sample to be analyzed. The contents of the bomb were thoroughly mixed by shaking.

The charge was then ignited by means of a Bunsen flame by heating for a period of three minutes. The usual precaution of placing the bomb in a shield was taken.

After ignition the bomb was quenched with water, opened and placed in 200 ml. of hot water in a 600 ml. beaker. This solution was allowed to digest for five minutes. At the end of this time the bomb was removed and the solution carefully acidified with concentrated nitric acid. The acid solution was boiled for five minutes and then allowed to cool to room temperature.

At this point the solution was transferred to a 500 ml. Iodine flask and a measured excess of 0.1 N silver nitrate added. Using the procedure of Caldwell and Moyer (14), five ml. of nitrobenzene was added and the contents vigorously shaken. The excess silver nitrate present was determined by the Volhard method (62) using 0.1 N standard potassium thiocyanate with ferric-ammonium sulfate solution as indicator (2 ml./ 100 ml. solution).

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

SUMMARY

The following methylphenyl chlorobenzoates were prepared from o- or p-cresol and o-, m-, or p-chlorobenzoyl chloride:

2-methylphenyl 2-chlorobenzoate

2-methylphenyl 3-chlorobenzoate

2-methylphenyl 4-chlorobenzoate

4-methylphenyl 2-chlorobenzoate

4-methylphenyl 3-chlorobenzoate

4-methylphenyl 4-chlorobenzoate

The following hydroxy-methyl-chloro'-benzophenones were prepared by rearranging the above esters with aluminum chloride:

4-hydroxy-3-methyl-2'-chlorobenzophenone

4-hydroxy-3-methyl-3'-chlorobenzophenone

4-hydroxy-3-methyl-4'-chlorobenzophenone

2-hydroxy-3-methyl-2'-chlorobenzophenone

2-hydroxy-3-methyl-3'-chlorobenzophenone

2-hydroxy-3-methyl-4'-chlorobenzophenone

2-hydroxy-5-methyl-2'-chlorobenzophenone

2-hydroxy-5-methyl-3'-chlorobenzophenone

2-hydroxy-5-methyl-4'-chlorobenzophenone

The following hydroxy-methyl-chloro'-diphenylmethanes were prepared by the Wolff-Kishner reduction of the corresponding above benzophenones and by the Friedel-Crafts synthesis:

4-hydroxy-3-methyl-2'-diphenylmethane

4-hydroxy-3-methyl-3'-diphenylmethane

4-hydroxy-3-methyl-4'-diphenylmethane

The following hydroxy-methyl-chloro'-diphenylmethanes were prepared by the Wolff-Kishner reduction of the corresponding above benzophenones and by the Claisen method of C-alkylation of phenols with but one exception. The reduction of 2-hydroxy-5-methyl-2'-chlorobenzophenone gave 2-methylxanthene.

2-hydroxy-3-methyl-2'-chlorodiphenylmethane

2-hydroxy-3-methyl-3'-chlorodiphenylmethane

2-hydroxy-3-methyl-4'-chlorodiphenylmethane

2-hydroxy-5-methyl-2'-chlorodiphenylmethane

2-hydroxy-5-methyl-3'-chlorodiphenylmethane

2-hydroxy-5-methyl-4'-chlorodiphenylmethane

The methylphenyl-chlorobenzyl ethers corresponding to these compounds were isolated and in addition prepared by another method:

2-methylphenyl-2-chlorobenzyl ether

2-methylphenyl-3-chlorobenzyl ether

2-methylphenyl-4-chlorobenzyl ether

4-methylphenyl-2-chlorobenzyl ether

4-methylphenyl-3-chlorobenzyl ether

4-methylphenyl-4-chlorobenzyl ether

The p-chlorobenzoates of the hydroxy-methyl-chloro'-diphenylmethanes were prepared.

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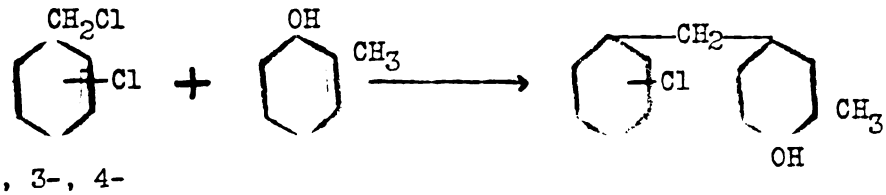
SCHEME OF CONDENSATIONS

DIRECT METHODS

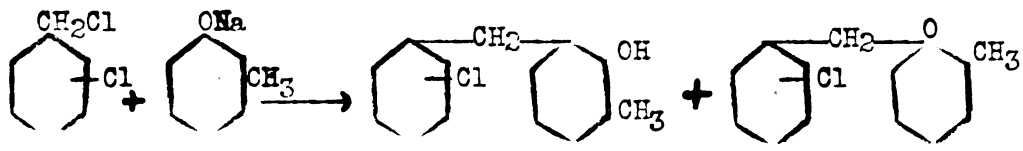
FRIEDEL-CRAFTS METHOD



2-, 3-, 4-

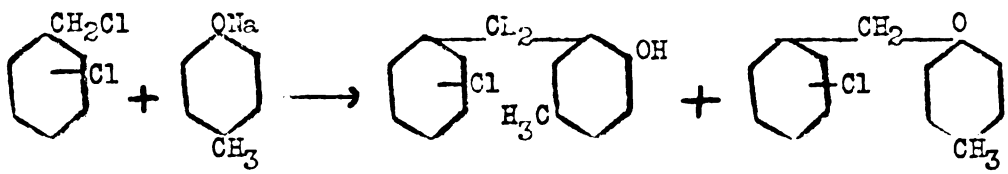
	Chlorine Position		
	2'	3'	4'
M.P. °C	57.8-58.5	39.9-40.4	74.1-74.8
Yield	26.8	12.4	35.5

CLAISEN METHOD



2-, 3-, 4-

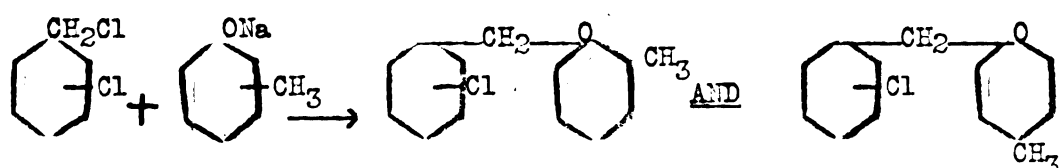
	Chlorine Position			Chlorine Position		
	2'	3'	4'	2	3	4
M.P. °C	42.2-42.8	43.7-44.5	47.2-47.9	37.9-38.8	liquid	61.2-61.7
Yield	29.9	19.1	33.2	14.9	21.0	12.5



2-, 3-, 4-

	Chlorine Position			Chlorine Position		
	2'	3'	4'	2	3	4
M.P. °C	42.6-43.4	53.2-54.0	51.4-52.1	liquid	53.8-54.6	91.7-92.6
Yield	30.3	29.8	36.9	8.6	10.8	4.9

SODIUM HYDROXIDE - ETHYL ALCOHOL METHOD



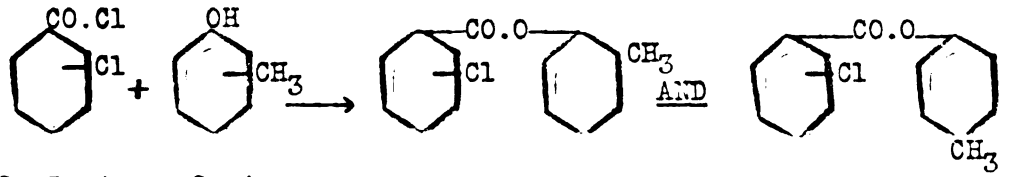
2-,3-,4- 2-,4-

	Chlorine Position			Chlorine Position		
	2	3	4	2	3	4
M.P. °C	37.9-38.8	liquid	61.2-61.7	liquid	53.8-54.6	91.7-92.6
Yield	71.5	87.6	84.3	76.8	67.8	88.0

SCHEME OF CONDENSATIONS

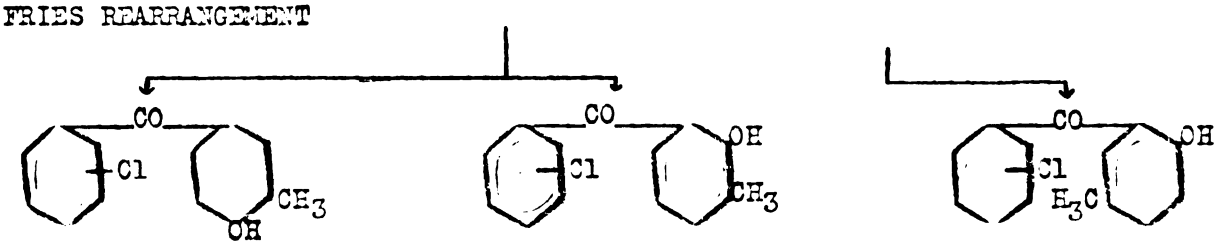
INDIRECT METHODS

ESTERIFICATION



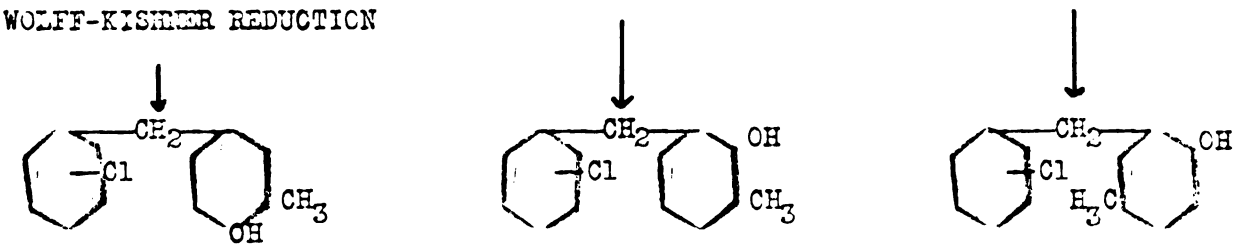
2-,3-,4-	2-,4-	Chlorine Position			Chlorine Position		
		2	3	4	2	3	4
	M.P. °C	liquid	53.2-54.2	44.7-45.4	68.8-69.8	75.1-76.0	97.4-98.3
	Yield	90.8	80.4	86.3	79.0	90.2	90.8

FRIES REARRANGEMENT



	Chlorine Position			Chlorine Position			Chlorine Position		
	2'	3'	4'	2'	3'	4'	2'	3'	4'
M.P. °C	167.9-168.6	151.2-151.8	210.5-211.5	72.3-72.8	69.5-70.3	61.5-62.0	76.3-77.1	70.5-71.5	66.9-67.6
Yield	35.3	55.7	52.1	11.8	17.3	12.6	71.3	45.1	30.9

WOLFF-KISHNER REDUCTION



	Chlorine Position			Chlorine Position			Chlorine Position		
	2'	3'	4'	2'	3'	4'	2'	3'	4'
M.P. °C	57.8-58.5	39.9-40.4	47.1-74.8	42.2-42.8	43.7-44.5	47.2-47.9	(a)	53.2-54.0	51.4-52.1
Yield	Not calc'd	41.0	44.9	Not calc'd	44.5	60.0		78.8	43.1

(a) 2-Methylxanthene isolated, M.P. 96.4-97.4°.

The preparation and characterization of the diphenylmethanes prepared from monochlorobenzyl chloride and ortho and para cresol.