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THE
BENZYLATION OF P-CHLORO-O-CRESOL

THESIS FOR THE DEGREE OF M. S.

James B. Milligan

1933

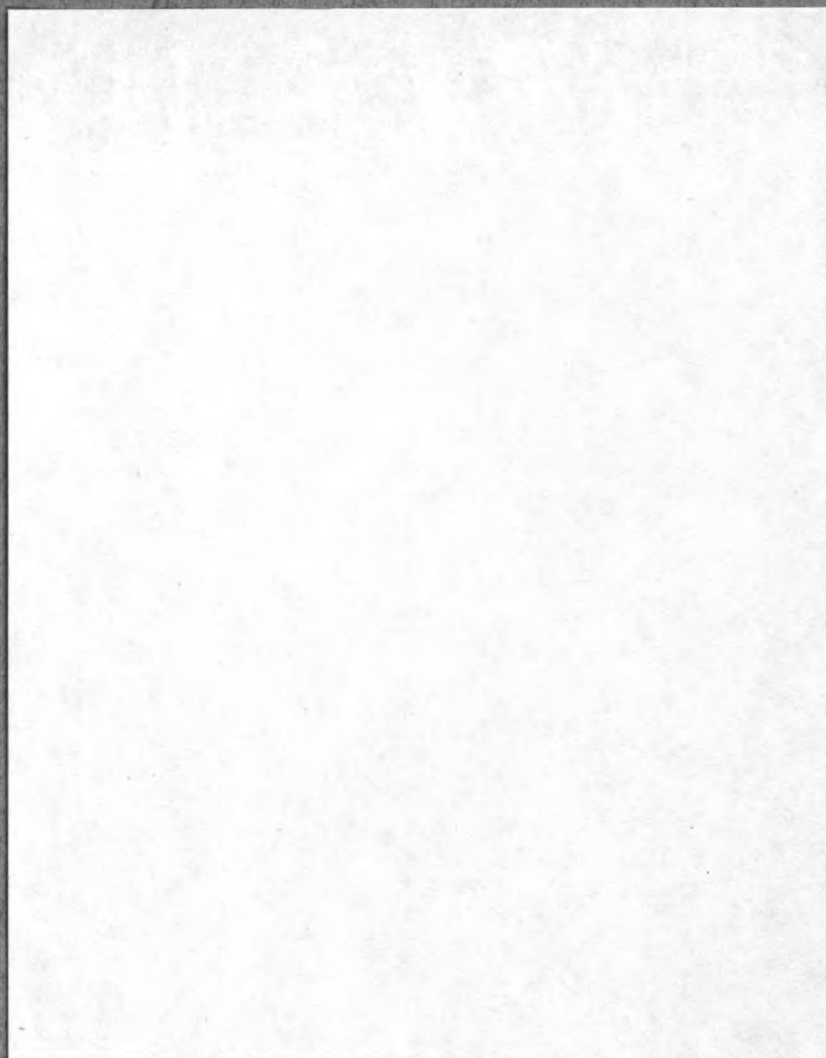
THESIS



C.2.



Chemistry



THE BENZYLATION OF P-CHLORO-O-CRESOL

A Thesis

Submitted to the Faculty of Michigan State
College of Agriculture and Applied Science
in partial fulfillment of the requirements
for the Master of Science Degree.

by

James B. Milligan

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Introduction

Thousands of compounds have been synthesized in the last few years and thousands more are yet to be prepared. The purpose of this work is to add one more link to the long chain of compounds and to describe the method of procedure, preparation of the compounds used and the properties and characteristics of those obtained. The historical portion will deal with work of an analogous nature but since a review of the literature reveals nothing pertaining to these particular compounds few comparisons can be made. On account of the great importance of the reaction by which the experiment was carried out a rather detailed description of it will be made. Other investigators have used the method of procedure for other compounds thus making it possible to draw some conclusions regarding the yields of isomeric compounds.

Historical

Benzylation of phenols.

Some of the early workers in this field were Kollaritz and Mertz (Ztschr. Chem. 1871, 705; Ber. 5, 447; 6, 446) who in 1871-73 synthesized di-phenyl ketone. They stated that they worked according to the principles governing the condensation of aldehydes, ketones and phenols using phosphoric anhydride as a dehydrating agent.

In 1872 E. Paterno (Gazz. Chim. Ital. 2, 1-6) prepared a benzyl phenol by gently heating a mixture of benzyl chloride and phenol in the presence of metallic zinc. This benzyl phenol was soluble in alcohol, ether, benzene, and chloroform and had a melting point of 84°.

Two years later, 1874, Paterno and M. Filetti (Gazz. 3, 121-129; 251-254, 1874) gave a further description of possible derivatives of the benzyl phenol. The action of bromine on benzylated phenol in acetic acid solution gave rise to an unstable oily compound. They also reported a brominated compound, prepared by treating benzyl phenol dissolved in carbon disulfide with excess bromine, with a melting point of 175°. They said it "appeared" to be a dibromide.

In 1876 (Gazz. Chim. Ital. 5, 381-383, 1876) the same two workers, Paterno and Filetti, found that benzyl alcohol with phenol in a mixture of sulfuric and acetic acids yielded

a benzylated phenol, melting at 84° and similar in properties to that prepared from benzyl chloride and phenol in the presence of zinc. They also obtained another oil which they thought to be an isomeric compound.

In 1879 Paterno and Mazzaro (Gazz. 8, 303) condensed p-cresol with benzyl chloride using zinc as a catalyst.

Liebmann (Berr. 14, 1842-44; 15, 152) prepared a benzyl phenol by the use of zinc chloride instead of metallic zinc as was used by Paterno. He raised the question as to whether the zinc was the active catalyst or the zinc chloride formed by the zinc and free hydrochloric acid found in benzyl chloride.

Merz and Weith (Berr. 14, 187 seq.) in 1881 tried to benzylate phenols by the use of both zinc chloride and aluminum chloride. The result was not a benzyl phenol but a diphenyl ether. This work is important only since it marks the beginning of aluminum chloride as a catalyst or dehydrating agent in reactions concerning phenols and analogous compounds.

In 1882 Rennie (J. Chem. Soc. 41, 220, 1882) proved the benzylated compound melting at 84° to be para benzyl phenol and in 1886 (J. Chem. Soc. 49, 406, 1886) he isolated and proved the structure of ortho benzyl phenol which was formed in Paterno and Filetti's experiment.

In 1909 Khotinsky and Patziwitch (Ber. 42, 3104) called attention to the fact that aromatic tertiary carbinols, many

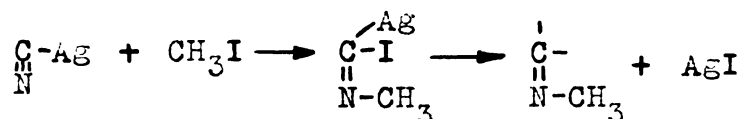
be easily condensed with many compounds including phenol by the aid of acetic acid to which a small quantity of sulfuric acid or zinc chloride has been added.

Powell and Adams in 1920 (J. Chem. Soc. 42, 646-58, 1920) prepared p-bromo-phenyl benzyl ether by refluxing benzyl chloride, p-bromo phenol and potassium carbonate in acetone solution.

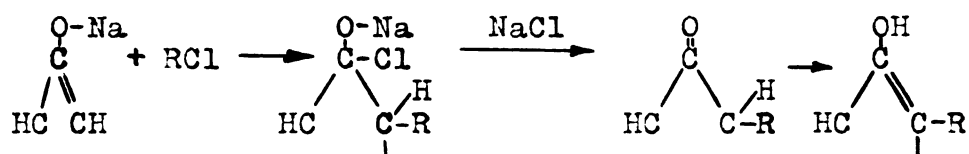
The Work of Claisen.

In 1923 L. Claisen published a paper on the carbon alkylation of phenols in the ring. (Z. Angew. Chem. 36, 478-9, 1923) He states that oxygen alkylation of monophenols is accompanied by carbon alkylation. The phenyl alkyl ethers under the conditions of formation do not rearrange to the alkyl phenols. Therefore, the carbon alkylation in the ring must be a direct reaction. Unsaturated alkyls affect carbon alkylation to a greater extent than when saturated. The use of the halide of the unsaturated alkyl permits the carbon alkylation of phenols that could not otherwise be alkylated. The most important single factor is the solvent medium used. When a dissociating medium such as methyl or ethyl alcohol or acetone is used more oxygen alkylation generally results; but if a non-dissociating medium such as benzene or toluene is used more carbon alkylation is produced. This has been confirmed by other investigators.

Claisen further states that the substituent enters the ring in the position ortho to the hydroxyl provided this position is unsubstituted. He explains this by Michael's theory (J. Pr. 31, 486; 46, 189) of the reaction between silver cyanide and methyl iodide. This can be illustrated as follows:



According to this scheme a shift in valence bonds occurs, CH_3I separates, one part going to the nitrogen and the other to the carbon and AgI splits off from the same carbon atom. If this principle be applied to alkyl halides and a metal derivative of an unsaturated organic compound it may be illustrated as follows:



Again it is seen that the metallic halide is split off and as a result leaves a double bonded oxygen atom. At this point there occurs a shifting of the hydrogen from the adjacent carbon atom to the oxygen atom thus accomplishing the more stable enol form. The double bond between the carbon and oxygen disappears and reappears between the same carbon atom and the alkylated or benzylated carbon atom.

Why the hydrogen shifts from the carbon to the oxygen and why the substituents enter as they do are difficult questions to answer. Nevertheless by this method we are reasonably certain of obtaining products with the OH group and the entering substituent occupying positions adjacent to each other in the ring.

Claisen's enumeration of the factors which affect the course of his anomalous reactions and the proportions of the various products formed is worthy of mention. He says they are as follows:

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

Few comments need be made regarding these points except as they have a direct bearing on this work. Complicated and differently substituted phenols would of course, give different results. In regard to the second point Claisen worked mostly with alcohols indicating that they were best suited to his purpose. He stated that the looser the bond between the halogen and the alkyl radical the more smoothly the reaction progressed. Points three, four and five are

self evident. Point six is a very important one. Claisen found that the influence of the medium was unexpectedly great, especially upon the proportions of the ether and the alkylated or benzylated compound formed. Dissociating mediums seem to favor the formation of ether while non-dissociating mediums favor substitution on the carbon atom. While the exact reason for this is not known it seems probable that the kind of medium affects the condition of the valence bonds between the halogen and the alkyl or benzyl radical and also the bond between the metal and the oxygen.

Source of Material and Preparation.

The p-chloro-o-cresol was prepared by direct chlorination of the o-cresol. One hundred grams of freshly distilled o-cresol was dissolved in three hundred grams of glacial acetic acid in a 500 ml. three necked flask fitted with a mechanical stirrer, aspirator and thermometer. The flask was then placed in an ice bath. When the temperature reached five degrees above zero the stirrer was started and chlorine from a chlorine tank was allowed to bubble through the solution. The chlorine was washed with sulfuric acid. When the theoretical amount (by weight) of chlorine was added the acetic acid was removed by distillation at atmospheric pressure and the remainder fractionated under reduced pressure. The p-chloro-o-cresol came over at 106-109° at 14 mm. pressure. The chlorinated product was then recrystallized from petroleum ether and came down in the form of long white needles.. This compound had a melting point of 47.5-48.5° as compared with 48-49° given in Richter's Lexicon and 47° as given by Datta and Miter (J. Chem. Soc. 42, 435). The yield never at any time exceeded 30%, usually much lower, and was accompanied by the formation of tar. Ferric chloride was sometimes used as a catalyst but seemed to have very little influence.

The p-chloro-toluene was prepared from p-toluidine according to the method of Marvel and McElvain (Gilman

Org. Syn. Vol. I, p. 163) The diazonium salt consisted of a mixture of p-toluidine, hydrochloric acid and sodium nitrite. This solution was added to a cold solution of CuCl (cuprous chloride) with continuous stirring, resulting in the formation of an oily layer on the surface of the solution. This was then steam distilled and the distillate washed with sulfuric acid and dried over calcium chloride.

The p-chloro-benzyl chloride was prepared from the p-chloro-toluene by passing chlorine into the p-chloro-toluene heated in an oil bath to 155° C until the theoretical amount of chlorine was added. Phosphorous penta-chloride was used as a catalyst. The chlorinated compound was then distilled and the fraction boiling at 213-214° was saved.

The o-chloro-benzyl chloride was prepared in exactly the same manner except the source was o-toluidine instead of p-toluidine.

Statement of Problem.

This problem may be briefly stated as follows:

1. To benzylate p-chloro-o-cresol with benzyl Chloride and its p-chloro and o-chloro isomers.
2. To determine properties and characteristics of the compounds formed.
3. To compare the amounts of the compounds formed.

Experimental

Claisen's method.

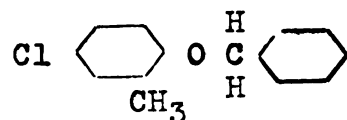
One quarter mole of sodium was suspended in 100 ml. of toluene in a 500 ml. three necked flask fitted with a mechanical stirrer and a reflux condenser. The sodium was melted by heating in an oil bath at 140° C (thermometer in the oil bath) and reduced to bird shot size by vigorous stirring. To the hot solution one-fourth mole of p-chloro-o-cresol dissolved in 50 ml. of toluene was added very slowly through a separatory funnel. During the addition of the p-chloro-o-cresol the flame was extinguished to eliminate the danger of fire since hydrogen was given off through the reflux condenser. The reaction began immediately with the evolution of heat and hydrogen. After the p-chloro-o-cresol was added the mixture was heated in the oil bath for two hours at 150° . At the end of this time the reaction appeared to be complete and one-fourth mole of benzyl chloride was added through the separatory funnel. There was at first no apparent reaction but the mixture was refluxed for eight hours at $155-160^{\circ}$ with continuous stirring. Gradually the white cheesy mass of sodium cresolate changed to a soft brown color with a precipitate of sodium chloride. When the reaction was complete it was allowed to come to room temperature and the sodium chloride removed by washing three (later increased

to five) times with water in a separatory funnel. The toluene was removed by distillation, the temperature being carried to 125° C. When cool the residue was treated with 150 ml. of Claisen's reagent (350 g. KOH, 400 ml. H₂O diluted to one liter with methyl alcohol). The purpose of this treatment was to form the soluble potassium salt of the substituted cresol. The ether was then extracted with 100 ml. of petroleum ether in 25 ml. portions. (It was found better to use 50 ml. or more for the first extraction followed by smaller portions). The petroleum ether was removed by distillation and the reddish brown oil was fractionated three times finally yielding 7 g. of yellow oil coming over at 180-182° at 14 mm. pressure.

Results (Petroleum ether extract)

A. up to 175(14)	9.7 g. (water and benzyl chloride)
B. 175 - 200(14)	10.7 g.
Residue	3.2 g.

The following formula was assigned to this compound:



2 methyl-4 chloro-phenyl benzyl ether. It failed to crystallize after remaining in the refrigerator for several days. It being an ether no further study was made of it except for analysis.

Results of analysis:

Substance	Wt. of Chlorine	% chlorine found	% chlorine Calculated
.1584	.02409	15.21	15.26
.1823	.02760	15.14	15.26

The substituted cresol was reformed by treating the soluble potassium salt with 1 : 1 HCl and ice until it was distinctly acid. This was then extracted with 100 ml. of ethyl ether in portions and fractionally distilled after removing the ether.

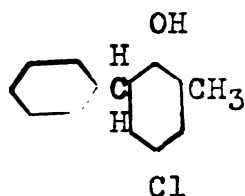
Results (ethyl ether extract)

A. up to 120 ₍₁₄₎	8.7 g.
B. 120 - 185 ₍₁₄₎	2.4 g.
C. 185- 200 ₍₁₄₎	14.3 g.
Residue	3 g.

Fractions B and C were refractionated and on the fourth fractionation yield 12.2 g. of a yellow oil which boiled at 190-192° at 14 mm. pressure. The oil crystallized when cooled with ice. After recrystallizing several times from petroleum ether a constant melting point of 54.5-55.5° was obtained. The substance when recrystallized appeared to form a compact white mass.

Two other benzylations were made but in no case was the yield increased. The three fractions were combined and

redistilled, boiling at 190-192° at 14 mm. pressure. This compound was given the formula:



4 chloro-6 benzyl-o-cresol.

Results of analysis

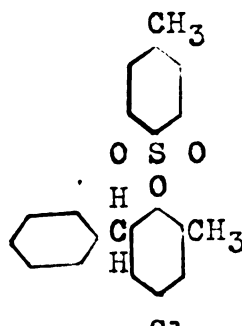
Substance	Wt. of Chlorine	% chlorine found	% chlorine Calculated
.1670	.02535	15.18	15.26
.1598	.02428	15.20	15.26

One crystalline ester was prepared from this compound. It was made from p-toluene sulfonyl chloride. The ester had a melting point of 102-103°.

When analyzed it showed a halogen content according to the following:

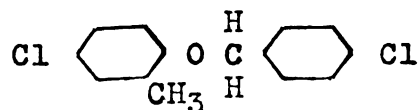
Substance	Wt. of Chlorine	% chlorine found	% chlorine Calculated
.1508	.01409	9.34	9.17
.1348	.01231	9.13	9.17

Its formula may be written in the following manner:



In order to attempt to prove the structure of the benzylated p-chloro-o-cresol some ordinary o-cresol was benzylated by Claisen's method. After separating it from the ether and distilling, an attempt was made to chlorinate it. This yielded a very small quantity of the chlorinated product and a small portion of the original compound was recovered. The remainder was tar. The substance which was thought to be the chlorinated product was purified and its melting point was found to be 53-54°. This decrease in melting point was probably due to an impurity as purification was very difficult due to so small a quantity.

The next task was to benzylate p-chloro-o-cresol with p-chloro-benzyl chloride. This was accomplished in exactly the same manner as the preceding procedure. It will be necessary then to discuss only the results. The petroleum ether extract yielded 3.8 g. of an amber colored oil boiling at 207-208° at 14 mm. pressure. The product crystallized in the receiver. After recrystallizing several times from alcohol it was found to have a melting point of 93.5-94.5°. The formula for the compound is:



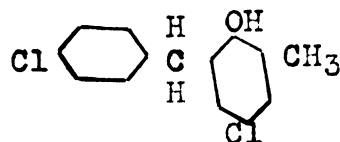
2 methyl 4, 4' dichloro-phenyl benzyl ether

The analysis of the ether gave the following results:

Substance	Wt. of Chlorine	% chlorine found	% chlorine Calculated
.1148	.03037	26.46	26.57
.1324	.03494	26.39	26.57

The ethyl ether extract after distilling three times yielded 18.2 g. of oil boiling at 220-223° at 14 mm. pressure. This oil crystallized when cooled and after recrystallizing many times from petroleum ether the melting point was found to be 40-41°.

This compound was assumed to have the following formula:



4, 4' dichloro-6 benzyl-o-cresol

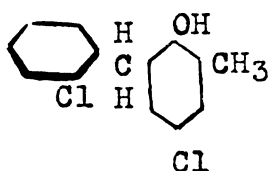
Analysis:

Substance	Wt. of Chlorine	% chlorine found	% chlorine Calculated
.1138	.02998	26.35	26.57
.0956	.02526	26.42	26.57

Two attempts were made to prepare crystalline esters but was unsuccessful in both trials.

The last portion of the problem was to benzylate p-chloro-o-cresol with o-chloro-benzyl chloride. Since this is an isomer of the preceding benzylating agent and

differs only in its structure we might expect somewhat similar results. However, this was not the case. The same procedure of benzylation was followed and the product with substitution on the carbon atom was isolated. The oil boiled at 209-211° at 14 mm. pressure. It was left exposed to the air for an hour and at the end of that time had changed to a purple color. It was redistilled and again a yellow oil was obtained at the same boiling point. It was set in the refrigerator to crystallize and during the night the same change in color occurred. It was distilled again and yielded the yellow oil. The total loss was about 50%. This reaction of the compound appeared to be either decomposition or oxidation. No attempt was made to determine the exact cause of the discoloration, but when the oil was not exposed to air no color change took place. It also failed to crystallize. The following formula was assigned to it:

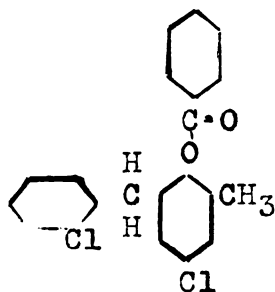


4, 2' dichloro-6 benzyl-o-cresol

Analysis

Substance	Wt. of Chlorine	% chlorine found	% chlorine Calculated
.1036	.02739	26.44	26.57
.1428	.03786	26.51	26.57

An ester of the compound was prepared from benzoyl chloride. The formula assigned to it is:



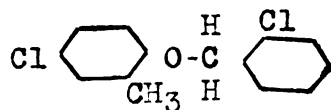
Analysis:

Substance	Wt. of Chlorine	% chlorine found	% chlorine Calculated
.1542	.02964	19.32	19.12
.1634	.03114	19.06	19.12

This ester crystallized from alcohol in small white needles and had a melting point of 99.5-100.5°.

The original yield of the oil was 16 g., this being less than the yield of 2-methyl 4, 4' dichloro-6 benzyl phenol but more than the 2-methyl-4 chloro-6 benzyl phenol.

The petroleum ether extract yielded 11.2 g. of oil which boiled at 143-145° at 14 mm. pressure. This compound was assumed to be an ether. It crystallized and had a melting point 59.5-60.5°. The structure was assumed to be as follows:



2-methyl 4, 2' dichloro phenyl benzyl ether

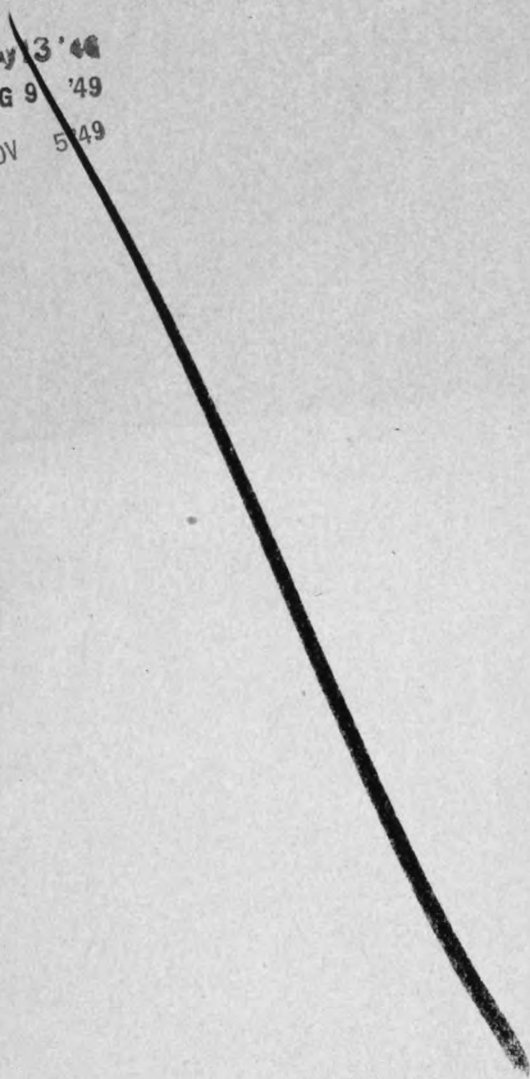
Analysis

Substance	Wt. of Chlorine	% chlorine Found	% chlorine Calculated
.1838	.04866	26.47	26.57
.1566	.04131	26.28	26.57

Conclusion

In conclusion it may be well to state that substitution in the position ortho to the hydroxyl does take place by Claisen's method. There were no evidences of compounds other than those expected in the method of benzylation. Much difficulty was met in the chlorination of o-cresol on account of ortho and para substitution. The greatest yield of benzylated cresol and the smallest yield of ether was obtained when the substituted halogen was in the para position.

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