BENZYLATION OF THYMOL

THESIS FOR THE DEGREE OF M. S.

Harold B. Evans

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BENZYLATION OF THYMOL

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Harold K. Evans

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PREVIOUS WORK AND GENERAL PRINCIPLES

Introduction

Among the thousands of organic syntheses which have been effected during the past decade, not the least interesting are those in which hydrogens of the benzene ring have been replaced by aliphatic or aromatic radicals. Every case of substitution is preceded by an elementary addition reaction, that in the course of subsequent decomposition forms a new compound. The new group may occupy the position of the atom or group replaced or may assume a different position. In most condensation reactions, especially those of Claisen either an acid or salt is split off, and the substituted alkyl or aryl group occupying a different position than that which the metal took before. A satisfactory theoretical explanation for this is still wanted, and new points of view can be expected only from the yield of new experimental facts.

In the benzylation of thymol we have constituents present which exert an influence on the entering group; its final position being determined by the group or atom whose influence predominates. Holleman quotes Beilstein's rule: "If a substituent C enters into a compound C_6H_4AB, both A and B exert an influence; but the group whose influence predominates directs C to the place it will occupy." He then lists the groups which direct to para and ortho positions in order of their diminishing velocities. $OH > NH_2 > I > Br > Cl > CH_3$ and $CooH > So_3H > NO_2$ for meta substitution.

Catalysts used in Organic Condensations

Organic condensations have always been of great historical interest, and such condensations have been effected since 1870. There are numerous types of condensations, likewise, numerous catalysts have been used to effect such condensations. Some of these catalysts are sulphuric and acetic acid, phosphoric anhydride, zinc chloride, hydrochloric acid and aluminum chloride. In most condensations either a halogen acid or water is split off. It is, therefore, easy to see why dehydrating agents or catalysts have often proved necessary in effecting such syntheses.

A mixture of sulphuric and acetic acids was used in 1873 by Meyer & Wuster (Ber. 6, 963) in condensing benzyl alcohol with benzene to form diphenylmethane. Two years later the same catalytic mixture was used by Paterno & Fileti (Gazz. Chim. Ital. 5,381) in condensing benzyl alcohol with phenol to form a benzyl phenol.

In 1881 Liebman (Ber. 14, 1842) prepared p- benzyl phenol from benzyl alcohol and phenol by using zinc chloride as catalyst. He also prepared butyl phenol condensing isobutyl alcohol and phenol with molten Zn Cl$_2$. Propyl and amyl phenols were similarly prepared. Other condensations using Zn Cl$_2$ were performed by Merz & Weith (Ber. 14, 187 seq;) Auer (Ber. 17, 669); Dennstedt (Ber. 23, 2569) and by Baur (Ber. 27, 1614).

Phosphoric anhydride was used in 1886 by Hemilian (Ber. 16, 2360) in forming diphenyl -p- xylylmethone from benzhydrol and p- xylene.

Hydrochloric acid was used in condensing phenols with camphorquinone, by Dey and Sen Gupsta (Proc. Chem. Soc. 29, 155). It was also used by Dionin (J. Russ. Ch. Soc. 46, 1310; 1914) in condensing phenols with unsaturated ketones, such as mesityl oxide.

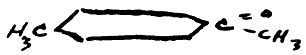
Stannic chloride was used by Bistrzyeki (Ber. 37, 659; 1904) in condensing benzhydrol with toluene to form diphenyl -p- tolylmethane.

Small quantities of iodine were used as catalyst by Knoll & Co., (Ger. 250, 236, Apr. 23, 1911) in condensing organic compounds with alcohols or ketones. It was found to act as a dehydrating agent.

Magnesium chloride was shown by Mazzara (Gazz. 12, 505; 1882) to have a catalytic effect in condensing M- cresol with proply alcohol.

Alkylation of Phenols

In 1889-90 Gatterman, Ehrhardt and Maish (Ber. 22, 1199) prepared condensation products of anisol, phenetol, etc., by treating them with various acyl chlorides and with benzoyl chloride in the presence of $AlCl_3$. They expressed their belief that the constitution of the condensation product of anisol and acetyl chloride is:



Their proof is the fact that the oxidation of this compound gives anisic acid, or p- methoxy benzoic acid. The other condensation products which they prepared gave analogous oxidation products, and on these grounds they repeatedly stated (Ber. 23, 1203, 1205, 1208, 1210) that the acyl or benzoyl groups regularly entered the ring in the p- position.

In 1881 Liebman (Ber. 14, 1842) prepared a butyl phenol by condensing phenol and isobutyl alcohol with the aid of molten Zn Cl . He also prepared propyl phenol and amyl phenol by the same method. The next year Mazzara (Gazz. 12, 505) condensed propyl alcohol and M- cresol with $Mg\ Cl_2$, and a year later (Ber. 16, 242) he used the same catalyst in preparing methyl butyl phenol.

In 1891 Lenkowski (Ber. 24, 2974) reported that he had succeeded in alkylating aniline and some other aromatic compounds. He stated that in such reactions the new substituent always takes the p- position, and that the same is true of the higher homologues of phenol, which are prepared by treating a mixture of phenol and the appropriate alcohol with Zn Cl_2. He thus extended and confirmed the theory that was suggested by Gatterman and his helpers.

In 1894 Bauer (Ber. 27, 1614) condensed isobutyl alcohol and O- cresol with the aid of Zn Cl_2 and heat preparatory to the synthesis of nitrated isobutyl O- cresol. In 1895 Anschutz and Beckerhoff (Ber. 28, 408) prepared amyl phenol by condensing both isoamyl alcohol and tertiary amyl alcohol with phenol. The concluded that the two products were the same, citing similarity of melting points, of boiling points, and of benzoyl derivatives as proof of identity.

In 1904 Clemmenson (Ber. 37, 54 Seq.) prepared ethyl resorcinol, ethyl hydroquinone, ethyl pyrocatechol, and both mono-ethyl and di-ethyl pyrogallol by reducing the appropriate ketones with zinc amalgam and 1:1 or 1:2 HCL. In 1907 Herzig and Wenzel (Monatsch 27, 781) stated that they had methylated phenols by treating them with methyl iodide in alkaline solution. In 1913 Johnson and Hodges (J. Am. Ch. Soc. 35, 1014) used Clemmenson's general method to prepare a few alkyl phenols. They worked with ethers as well as ketones. The next year Johnson and Kohman (J. Am. Ch. Soc. 36, 1259) continued this line of research and succeeded in preparing alkyl phenols with long aliphatic side chains.

Benzylation of Phenols

Some of the earliest work which has a bearing on the benzylation of phenols was done by Kollaritz and Mertz from 1871-73. (Ztschr. Chem. 1871, 705; Ber. 5,447; 6, 446) They succeeded in synthesizing diphenyl ketone, and they stated that they had worked according to principles governing the condensation of aldehydes, ketones, and phenols, using phosphoric anhydride as a dehydrating agent.

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

The uncombined benzyl chloride and phenol were distilled off below 260 . The remaining mass was distilled at 6 mm. The main fraction came over at 180 - 190 . This benzyl phenol was soluable in alkaline solutions, but was reprecipitated by acids. It was insoluable in ammonia. When treated with nitric acid it would form substitution products. When treated with sulphuric acid it produced a sulphonic acid with the phenol, the barium salt which was soluable in water.

They also found that benzylated anisole treated with hydroiodic acid, and boiled for 8 hours at 170 gave methyl iodide, and the same benzyl phenol as just described.

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

In 1880 O. Fisher (Ann. 206, 113) condensed benzyl alcohol and dimethyl aniline with Zn Cl_2 , also benzhydrol and dimethyl aniline. He found that he could used either Zn Cl_2 or phosphoric anhydride to assist in the reaction. While this was not a case of benzylating a phenol, it is of interest because of the constitutional analogy between aniline and phenol.

Liebman (Ber. 14, 1844, 15, 152) prepared a benzyl phenol. Incidentally the question was raised as to whether the zinc used by Paterno was the active catalyst; or whether it was Zn Cl_2 formed from zinc and free HCL always found in benzyl chloride. He referred to some of his own experimental observations as evidence that a very small quanity of Zn Cl_2 could catalyze the reaction.

In 1881 Merz and Weith (Ber. 14, 187 seq.) tried the effect of both Zn Cl and AlCl on phenol. The result was not a benzyl phenol, but a diphenyl ether. Their work is of interest, for it marks one of the first uses of AlCl as a catalyst or dehydrating agent in reactions concerning phenol, being either years in advance of the work of Gatterman and his associates, who used this catalyst in effect the syntheses already mentioned in connection with their names.

In 1909 Khotinsky and Patzewitch (Ber. 42, 3104) called attention to the fact that aromatic teritary carbinols may be easily condensed with many substances, including phenol, by the aid of acetic acid to which a little H_2SO_4 or $Zn Cl_2$ has been added.

The Work of Claisen and His Followers.

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

He further noted that the unsaturated alkyls effect the carbon alkylation to a greater extent than do saturated alkyls. The use of the halide of the unsaturated alkyl permits the carbon alkylation of phenols that could not otherwise be alkylated. The tendency toward carbon alkylation is still further increased if alkyl phenols be used. The substituent enters into ortho position to the hydroxyl, provided this is unsubstituted. Since the work of Claisen is of great importance in connection with this problem, I will give a rather comprehensive review of his work in (Ann. 441-442; 210-245).

"Among the irregular reactions, i.e., those which run contrary to the theory and analogous cases, the irregular metal substitutions claim especial interest. Thus those cases when an organic halide reacts in such a way with an inorganic or organic metal compound, the alkyl or acyl takes a different position than that which the metal took before. The interest concerning this process may be explained on the one hand by the important roll which they have played, and which will further play in the history of tautomerism, and on the other hand that a generally approved theoretical explanation for it is still wanted. It can not be predicted when it occurs or indicated with any certainty the mechanism by which it takes place. Attempting to explain is not necessary since there were brought together and discussed a short time ago without results. (Wislienus) One has the feeling that all that can be said on the basis of previous material facts has been said and that new points of view can be expected only from the yield of new facts.

In the case of phenols, we have as exceptions rescorcinol, orcin, phloroglucinol, anthranol and oxy-anthranol from which we receive instead of the expected phenol ether the isomer C-alkylphenol.

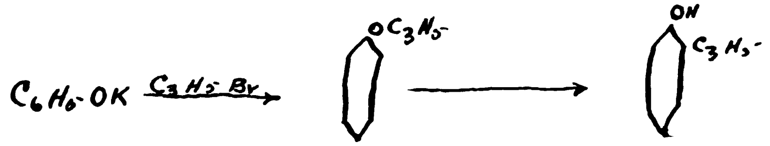
The deviating behavior of the above mentioned phenols can be explained without trouble by tautomeriem appearing in these cases. The double nature of these compounds (half phenol and half ketol) appears also in the alkali salts and causes these to form by reaction with alkyl halides both kinds of alkyl derivatives at the same time since they resemble at the same time the alkyl phenolate and the Na ketones.

All other phenols, however, especially phenols of benzene and napthylene series were supposed to react in the normal way for sure, thus constantly and exclusively giving the O-alkyl derivatives. When this work was begun not a single contradictory case was known. However, this material, as extensive as it is, has yet its deficiency.

At first people considered, in the fewer cases when alkyl phenol ether was produced as a step in the production of the alkali phenolates; especially the possibility of simultaneous resulting of kernal-derivatives. However, where this happens the investigation being specially directed to determine in the case of a phenol, the possibility of forming the C-alkyl derivatives, we have as a rule only employed methylation and alkylation and other alkylations only rarely. We assumed, as a matter of course that the deficit of the reactions depend mainly on the kind of phenol and much less on the kind of alkyl. However, already the works of Hertzig and Zeisel, referring to the above mentioned phenols, show that there, even between so nearly related substances as methyl and its higher homologues, significant differences. Kaufter who likewise has worked on this subject, summarized it in this way:-- that the tendency to enter the nucleus decreases constantly with increasing size and branching of aliphatic alkyls. In the case of benzyl it is said by the same author, not to exist at all. It is strange that the hurt thus given has remained unobserved. If there are alkyls, in the thought we are considering, one would have to believe that there must be among the great number of alkyls, especially among those poor in H_2 , some that exceed the methyl in their tendency to penetrate the nucleus.

There are also other conditions to be considered. If we put together all the factors that are favorable to a transformation of influence, we have the following, including those already mentioned:-- (1) the kind of phenol (2) the kind of alkyl (3) the kind of halogen or other component to which the alkyl is bound (for example SO_4) (4) the kind of metal in the corresponding metal phenolate, particularly light and heavy metal (5) the medium in which the transformation is being attempted (6) temperature. Although there has been many interesting and important points in former researches along this line, especially those of Herzig and Zeisel and their pupils, nevertheless the actual, systematic procedure, step for step, to prove each separate one of the above mentioned influences is not to be had (or is not given). How profoundly these latter factors, in some very as yet uncontrollable way effect the result is seen in Herzigs remark:-- "That the slightest change in the concentration and temperature is of the greatest importance in regard to the nature of the bodies being formed, in spite of the greatest care to preserve identical conditions, not one experiment turned out like any other one." That the medium is of very great consequence appear from the fact, established by Herzig and Erthol, that in an aqueous solution (made strongly alkaline) the nuclear alkylization is more strongly stimulated than in an alcoholic solution. Many other observations of the same kind can be made, but they do not enable us to form a clear idea of the dependence of the transformation upon the conditions. A complete understanding of the whole matter can only be acquired by a careful and minute research into the above mentioned facts.

An excuse for our closer examination of this matter exists in previous studies in the rearrangement of the phenolallylather, by Claisen, and Claisen & Eisleb, which are also a question of nuclear alkylization, but that here, in contradiction from Herzig & Zeisel reactions, it is accomplished not directly, but in two separate steps:--

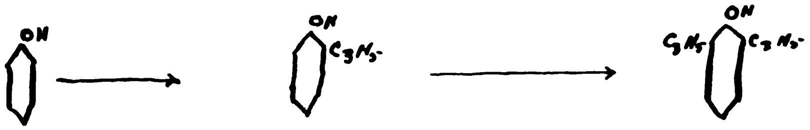


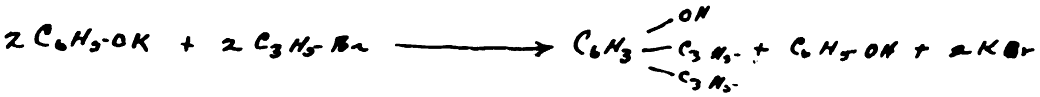
Now it was observed even then that in the first of these steps, in the productions of the phenolallylather according to the Claisen-Eisleb method, by boiling the phenols in acetone solution with alkyl bromide and K_2CO_3, almost always formed some of the corresponding allylphenol. At first it was assumed that this allyl phenol was due to an insufficient rearrangement. However, when it appeared that the phenol ether did not change in the smallest particular after boiling in an acetone solution, not even if one added to the solution those substances with which the ether is in contact with, one could avoid the idea that there was taking place here a direct nuclear alkylization.

$$C_6H_5\text{-}OK + C_3H_5\text{-}Br \longrightarrow C_6H_4 <^{OH}_{C_3H_5} + KBr$$

If this is so, we have won a very fundamental significance, because it shows also that the non-tautomeric phenol at least in solution with the alkyl halogens, are capable of a metal replacement.

In the hope of being able to raise this low percent of alkyl phenol the reaction conditions were altered in many ways. Instead of mixture of phenol and $CaCO_3$, a readily soluble K phenolate or Na phenolate was taken and heated in an acetone solution as well as in alcohol solution with allyl bromide to various temperatures but without desired results. After many attempts it appeared that the solvent is of great importance for the production of this substitution. When instead of the dissociating (used up to the present) media, non dissociating media (benzol and toluene) were used the amount of nuclear alkyl derivative increased from the former 1-3% to 60-70%. The amount of allyl ether sank from 95 to 30%. In this way the former secondary reaction therefore became the principal reaction. An investigation of the phenol portion indicated that it consisted principally of O-allyl phenol and partly of o - o diallyl phenol. Therefore the allylization has proceeded as follows:--





$$2\,C_6H_5\text{-}OK + 2\,C_3H_5\text{-}Br \longrightarrow C_6H_3\begin{array}{l}\diagup OH\\ - C_3H_5\\ \diagdown C_3H_5\end{array} + C_6H_5OH + 2KBr$$

Accordingly there are two ways of arriving at the allyl phenol. The indirect over the phenyl allyl ether and the direct by transformation of the alkali phenolates with allyl bromide. With both the allyl occured in the O- position.[1]

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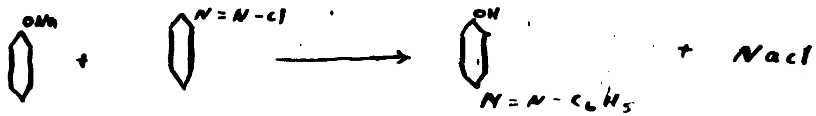
[1] Because by unusual transformation of alkali phenolates, the residue occurs mostly in the para-position.

For example in the benzol azolation:



In the present simpliest case one would naturally prefer the first procedure, because it proceeds completely quantitatively and gives only the mono-allyl derivative. While with the second method the separation of the diallyl phenol, that always arrives, gives some difficulty. On the contrary in many other cases where the rearrangement goes on more smoothly, the latter method is a very welcome one.

The particular tendency of the allyl bromide to unusual metal exchange in this rearrangement which we are discussing, is obviously connected with the fact that the halogen in it is very loosely held, much more loosely than in the halogenids of the saturated alkyl. The great difference was recognized first in 1890 by Conrad, Hecht, and Buchner in connection with their exhaustive researches on the reactivity of organic halogenids and were laid down with the following numbers which show that the allyl bromide in its readiness to exchange is surpassed only by benzyl bromide.

	Propyl	Ethyl	Allyl	Benzyl
Bromid	1	3.24	61.34	120.1

The cause of this loose connection of the Br is naturally the double bond contained in allyl[5], $[Br(CH_2-CH=CH_2]$ or as we express it more recently the strong attraction of the $BrCH_2-$ by the connected vinyl, which takes away so much of the bonding power from the neighboring carbon atom that very little power remains for its connection with the bromine. Why now the looseness of the halogen connection should act in just this direction, that is in the increased tendency to formation of the nuclear alkyl derivative is not at present clear. It might express itself simply in an increased rapidity of transformation to the O- alkyl derivative. Perhaps for the reason that in this way the halide (in the sense of the Michaelson Addition hypothesis) is rendered capable of an easier connection with -CH=C(O Me). Even though the reason for this reaction or relationship is not clear at present, we are sure the relationship exists. It shows itself plainly in the fact that with halides of allyl, methyl, ethyl and ethyl homologues, the tendency to the formation of nuclear derivatives lowers in proportion as the firmness of the connection of the halides rises.

If this is the case then the halides in which the halogen is less firmly fixed than in allyl bromide must be even more inclined to nuclear alkylation. A bromide of this

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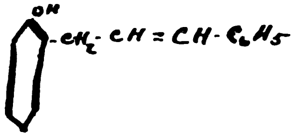
[5] No important difference is to be expected between alkyl with a remote position of double bond and the saturated alkyl. For example:--

$$-CH_2-CH_2-CH=CH_2$$

$Br-CH_2-CH=CH(CH_3)_2$-YY dimethyl allyl bromide in which as before mentioned, the bromine is so loosely held that when shaken with water it is replaced several hundred times more quickly than the bromine in allyl bromide with hydroxy. Correspondingly this bromide unites with alkali phenolates even in a dissociating medium (acetone) quite readily, according to conditions, up to from 30%-50%. Also the A-Y dimethyl allyl bromide out of which one gets in an acetone solution at the most 40% of an O-alkyl derivative, while the residue appears in the form of nuclear alkylation products.

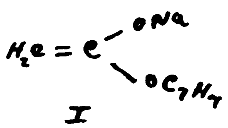
Between these highly unstable homo-allyl bromides and the comparatively stable allyl bromide is the cinamyl bromide from which therefore we might expect that the influence of the different solvents would be most plainly discernible. This is also the case in an alcohol or acetone solution, there is almost no pure O-alkylation to phenol cinamyl ether and in benzol solution almost pure nuclear alkylation to O-cinamyl phenol.



The nature of the resulting product as an ortho-derivative can as in all similar cases be easily recognized by the fact that with treatment with acids it goes over into an alkali insoluable isomer. It is of interest to note the activity of the benzyl chloride as compared to the previous mentioned halides.

	Propyl	Allyl	Benzyl
Chloride	1	65-70	126.5

Kaufler found that out of the phlorglucin so greatly disposed to nuclear alkylization only benzyl ether was obtained but no C-benzyl derivative. However, many reactions show that the effort of benzyl when brought in connection with oxygen and carbon to unite with latter is very great, much greater than that of the saturated alkyl. From this point of view, it is to be understood that the effect of Na upon acetic benzyl ester is different than upon the acetic ethyl ester, in the latter case as the chief reaction the formation of Na acetic ester side by side with $CH_2=C(OC_2H_5)_2$; in the first case on the contrary carbon benzylation of the benzyl ester with contem-paraneons formation of sodium acetate. Assuming that the O-sodium acetate benzyl ester arises as the primary product of the reaction, then with regard to the further transformation of this ester with the still unexhausted benzyl acetate these three reactions have the same two possibilities as with the effect of benzyl chloride upon alkaline phenolates i.e., either O-benzylation to keten dibenzyl acetate II or C benzalation to benzyl acetic benzyl ester III.



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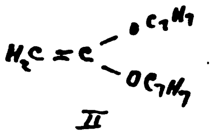

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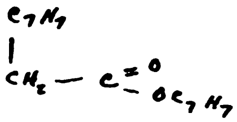
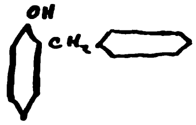


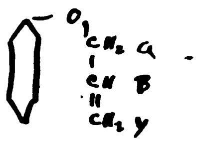
III

As a matter of fact the latter is the case, to support this we have the auto benzylation of the N-benzyl phenyl methyl pyrozolons observed by Jacobson & Jost in which under the influence of alcoholic KOH the benzyl passes from N to C. Additional researches in regard to benzylation of phenol therefore seemed to be necessary.

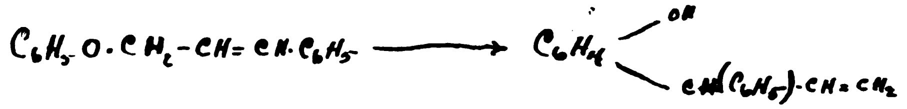
They have indicated that with benzyl chloride the conditions are the same as with allyl bromide i.e., in benzol or toluene solution it transforms itself with the alkali phenolates into nuclear benzyl phenol, and in alcoholic and acetone solution on the contrary, chiefly to phenol benzyl ether. There is here an agreement that the benzyl enters into the O-position so that the O-benzyl phenol from which up to now only one representative, O-Benzyl B- napthol was known are now easily obtained. It is of interest to observe that the O-benzyl derivative of the ordinary phenol  occurs in two different forms Mp. 21° and Mp. 52°, which change easily into each other are therefore probably only physical isomers.

The tendency to unite with the C is even stronger with the diphenyl methyl $-CH(C_6H_5)_2$ than with benzyl whose bromide transforms itself with Na phenolate in a benzol suspension even at room temperature to diphenyl methyl phenol $(C_6H_5)_2-CH-C_6H_5-OH$. Even in alcoholic suspension according to Von Busch the transformation takes place principally in this way; the O- deriviative, C_6H_5 O. $Ch(C_6H_5)_2$. According to some authors it can be obtained only by shutting out of all solvents and melting together the dry materials. In an aqueous alkali it is completely insoluable. It can be removed from benzene solution only by K O H of Claisen, but cannot be removed from ether solution at all.

One difference remains between benzyl and allyl i.e., the phenol allyl ethers do rearrange themselves with heat but phenol benzyl ethers do not. Therefore while one has two ways to nuclear alkylation of an allyl bromide;- the direct method described here and the indirect with the consequent of phenyl allyl ether and the transformation of them to o-allyl phenol, one has with benzyl chloride only one. It is noticeable that when as we formerly assumed the rearrangement of the allyl ether depends entirely upon looseness of bond between allyl and oxygen. Then this transformation might be obtained also with benzyl ether. The difference might be explained if one assumed that with the rearrangement of phenol allyl ether the allyl united not with a carbon atom but with B carbon atom in nucleus. As example:--



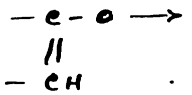
This assumption has recently been published by Claisen & Tietze and is supported by proof that with phenol cinamyl ether the arrangement takes place like this:--



$$C_6H_5O\cdot CH_2-CH=CH\cdot C_6H_5 \longrightarrow C_6H_4\begin{smallmatrix} OH \\ CH(C_6H_5)\cdot CH=CH_2 \end{smallmatrix}$$

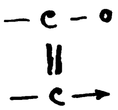
It is plain that a similar process is not possible with phenyl benzyl ether or at least that it can not lead to an o-benzyl phenol. It ought to be discussed whether the explanation up to present for the mechanism for the anomalous exchange agree with facts. These explanations may be divided into two groups. Those which only refer to the one reaction component the metallic connection, and those that refer to two components the metallic and alkyl halide. As an example of first group the view is offered which W. Wislicenus considers the most probable. He assumed that removal of metal by halogen an union of alkyl with oxygen and carbon are not contemporaneous processes. During the short intervals the residue No. 1 arising from removal of metal can remain consistent and will then take up the alkyl with the oxygen valence.

I



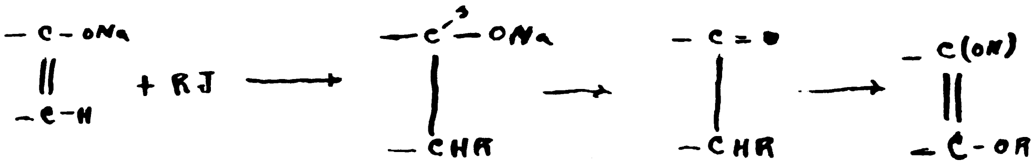
$$\begin{array}{c} -C-O\longrightarrow \\ \| \\ -CH \end{array}$$

II

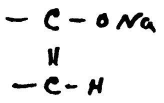


$$\begin{array}{c} -C-OH \\ \| \\ -C\rightarrow \end{array}$$

It can however immediately rearrange itself in II. The alkyl will then enter the carbon, in either case whatever happens depends upon nature of the combination under discussion, which as Wislicenus expresses it depends upon constituent influence and partly upon environmental conditions. (Tempt. solvent and dilution) At the same time, however, this is also true of all explanations of the first method. The destiny of the outcome of the reaction is transferred entirely into the one reaction component and the alkyl halide is left out of consideration. Of course one understands according to this view that of two different phenols, both treated with same alkyl halide that one forms a predominately o-alkyl derivative and the other a carbon, but it is not to be understood why one and the same phenol when treated with two different alkyl halides under exactly the same conditions sometimes produces the O- and sometimes the C alkylation. This and many similar facts are explained only by the explanation of Mecheal which assumes as a primary process a union of alkyl halide with double bond obtained in metal derivative.



Here both factors are taken into consideration the optimum for the occurance of analomous transformation must be obtained on the one hand from a metal derivative whose double bond reanders such a union very easy, and on the other hand if an alkyl halide which on account of very loose union of its halogen is particularly inclined to just such a union. The confirmation of this latter statement by the present work must in fact be considered as a strong argument in favor of Micheal theory. (K. H. Meyer confirms) At all events the C alkylation is a process in itself and does not stand in any casual relation with the o-alkylation that often takes place at the same time. Therefore in no case must a carbon alkyl derivative be assumed as necessarily following an o-alkyl derivative.

In sodium phenolate, we find the group 

$\begin{matrix}-C-ONa\\ \|\\ -C-H\end{matrix}$

and benzyl chloride is analogous to an alkyl halide. We should expect then just such a shift of bonds, a splitting of benzyl chloride into parts which attach themselve to different carbon atoms, the elimination of Na Cl, and the final formation of a compound with OH restored and benzyl radical attached to carbon atom of ring. Probably such a shift could come about only in the case of two adjacent carbon atoms which would direct the benzyl group to a position o- to the OH group. Thus we are reasonably certain of obtaining a condensation product with the OH group and entering constituent adjacent to each other. We also notice that pure p- compounds are not to be expected as Catterman and others seem to think, but are likely to produce mixtures of O and P compounds, as might be expected from Holleman's discussion of general principles governing substitution in benzene ring. (Chem. Rev. July 1924-187 seq.)

It was established of a number of sodium phenolates (phenol, p cresol, A-B napthal, quaicol) in checking over the data on hand that the conversion with chloride in methyl and ethyl alcohol solution produces almost exclusively the benzyl ethers and a very little or none of nuclear banzyl derivatives. Phenyl benzyl ether is entirely undecomposed in spite of high B. p 286° - 288°, that is it is distillable without rearrangement. The distillate does not leave any alkali hydroxide.

Nuclear Benzylation

"The experiments were performed upon five above mentioned phenols and all were capable of nuclear benzylation. It could be proved for phenol and A and B napthol that the benzyl occured in ortho position. (This is a matter of course in p- cresol, but there is no proof in regards to quaicol). The ortho derivative (phenol) up to time of our researches was not known in pure state. According to statement by Remmie it arises as a by-product of the condensation of phenol and benzyl chloride by means of zinc, but could not be separated completely from the p- derivative occuring as chief product. Not until a short time ago did the dye manufacturers F. Byer & Co., succeed in separating the O- benzyl phenol from the oil absorbed in crystalline P- compound in the following manner:-- The oil is boiled with $Ba(OH)_2$. The P derivative is ppte. partly while still hot and completely upon cooling as a Ba salt. From the filtrate the O- derivative separates in pure state by addition of acid.

The sodium phenolate was suspended in 1 liter of toluene, and benzyl chloride was added and allowed to stand over night. There was evidence of a vigorous reaction, the stopper was found blown out the next morning. It was then heated on an oil bath at 168° for five hours. Using aqueous alkali - get mono benzyl and very little or no dibenzyl compound. After separating and redistilling at 171°-13 mm. the oil crystallized, which after pressing

out oil proved to be a pure mono-benzyl phenol. $C_{13}H_{12}O$. By treatment with $Ba(OH)_2$ it was established that there was no trace of an isomer. The phenol boiled in the H_2CO_3 decomposed at 312°. The m.p. 21° - F.p. 19°. The m.p. and b.p. of p. compound was 84° and 325 - 320° respectively. The methyl ether obtained by a 24 hr. heating of phenol in acetone with CH_3I and $CaCo_3$ in a tube to 100° boils at 159-160° at 12 m.m.

After the m.p. of our product A. has been determined to be 21° C. we were surprised to hear that the m.p. of the product B obtained at Edler Field dye works by the other method was found to be much higher. (52°) There was no question of an impurity in our compounds so we asked for a sample of B and were able to determine very readily that it was merely a question of two forms of same substance which readily change into each other. Form A is more energetic and therefore a modification arising immediately in the melted state, which as soon as the change is once started, spontaneously and exothermically goes over to final form B which is of lower energy potenial. Outwardly B presented the appearance of beautifully glittering crystals more than 1 cm. in size melting quite sharply at 52°. When a little piece of it was put into our form A which has remained unchanged for a year, there began a transformation proceeding from of contact and exothermic, but without any liquidation of substance this change began from A to B involving finally the entire amount. The progress of the change was easily recognized by a dunming of crystalline mass something like an efflorescence. If stable form B is on hand then it is not difficult to get unstable form A since smallest portion of B will initiate change. While formerly as long as we did not possess B only A was obtained from melted masa there crystallized now in laboratory traces of B on cooling to about 70 .

In general one has the impression that we have here a chemical isomer.

Only we have here not a chemical isomer out only a physical crystallographic isomer, somewhat like the cinamic acids, the benzophenone and the amino krotoacid esters. No case of this latter kind has been observed among phenols up to present. In connection with benzylation of phenol an effort was made to obtain the corresponding transformation with N-benzyl halides, but this was impossible. By treating p. Nitro benzyl chloride with Na phenolate a change to resin occured, with the effect of N-nitro benzyl bromide almost nothing was obtained from an alkaline solution. The chief product (80%) was a thick yellow oil 219-221 -13 mm. whose insolubility in alkali we first ascribed to covering up of its phenol like characters. Since this oil was completely insoluable, not only in Claisen KOH but even in absolute methyl alcohol KOH, and since further it did not unite with diazo salts it could only of been probably phenol N-nitro benzyl ether

$C_6H_5O\ CH_2.C_6H_4.NO_2$. It seems therefore that the nitro group present in benzyl rendered very difficult or entirely prevents the entrance of the residue into nucleus."*

M. Busch in 1925 working on alkylation of phenols published a very interesting item in Z. Angew. Chem. 38, 1145-1146). He stated that the tendency of benzyl radicals toward carbon alkylation of phenols increased with the increasing substitution of the methane carbon. It was possible to obtain ethers with benzyl chloride in non-dissociating media, but diphenylmethyl chloride yielded only the carbon derivatives. Busch had found that diphenyl brom methane with phenol, with or without a solvent, in the presence of heat gave para hydroxy triphenyl methane and with sodium phenolate it gave the ortho-hydroxy triphenylmethane isomer.

M. Busch and Knoll (Ber. 60B. 2243,2257) have been able to isolate some of these long sought for addition products; claiming the reaction between C_6H_5OH RX (x=chlorine) to proceed as follows:

$$C_6H_5\ OH + RX \rightarrow p\text{-}\ RC_6H_4OH + RX$$

with C_6H_5ONa :

$$C_6H_5ONa + RX \rightarrow o\text{-}\ RC_6H_4OH + RX$$

In dissociating solvents partly according to the latter scheme and partly according to the scheme:

$$C_6H_5O\ Na + RX \rightarrow C_6H_5OR + NaX$$

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* (Ann. 441-442, 210-245)

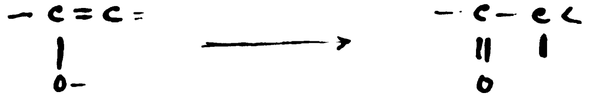
They also reported that the accumulation of alkyl groups, especially those of high molecular weight, on the phenol nucleus materially diminished the ether formation.

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

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

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

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



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

and with the slight reactivity of the alkyl group partial or complete rearrangement of the enol to keto radical, and finally union of the radicals." (Wislicenus) Some recent investigations have shown that the course of the alkylization of a keto-enol depends upon its character and upon the alkylization agent.

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

The third hypothesis stated, that the oxygen derivative should be formed with allyl and with benzyl radicals because of their great reactivity, but this is not the case.

However, the formation of radicals and the isomerization of enol to keto radicals is necessary to explain the reactions. We can assume that the greater reactivity indicates a large requirement for valence, and visa versa, since allyl and benzyl radicals are distinguished by their slight valence requirements and therefore hold oxygen only loosely, they show a preference for combining with carbon to form stable combinations. Claisen has confirmed these views as already noted (Ann. 441-442), when he stated that unsaturation results in a comparatively loosely held halogen, and furthermore the reaction medium, such as toluene and benzene exert a loosening effect on valence bonds between the alkyl or benzyl radical and the halogen.

W. F. Short reported (J. Chem. Soc. I, 528 (1928) that when benzyl phenyl ether is heated to 225° in the presence of $ZnCl_2$, or to 180° in a stream of HCl, a vigorous reaction occured. The product, on distillation under reduced pressure, yielded phenol, o-hydroxdiphenylmethane M.P. 54°; phenylurethane M.P. 180° ; also p-hydroxydiphenylmethane M.P. 84°-84.5°. The para compound was identified by conversion in p- methoxy benzophenone, M.P. 61° - 62°. Since phenol was formed, it is probable that the reaction followed a course similar to the Hofmann rearrangement of alkyl-anilines, benzyl chloride being formed as an intermediate.

G. Vavon and N. Zaharia (Compt. Rend. 187, 346-48) recommended that petroleum ether be used for extracting of oxygen derivatives and that an excess of alkali be employed.

Phenols may be partially extracted from their alkali solutions by means of ethyl ether. The proportion extracted depends on the structure of the phenol. With the introduction of radicals into phenol, the proportion extracted increases, and is greater for ortho-substituted phenols than for the meta- or para- isomers.

The Work of Friedel and Craft

Friedel and Crafts (Compt. rend. 84-1392-1395) in 1876 discovered a new synthetical method of producing hydrocarbons. They noted when amyl chloride was treated with small quantities of aluminum chloride there occured a brisk disengagement of hydrochloric acid gas, accompanied by hydrocarbons which are not absorbed by bromine. When this reaction was made to take place in the presence of a hydrocarbon, it was easy to obtain a combination of the radicle of the organic chloride with the hydrocarbon, less the hydrogen replaced. Thus they were able to condense amyl chloride with an excess of benzene, and having added aluminum chloride by small quantities at a time they obtained by fractionation, a liquid boiling at 185° - 190° and having the composition and properties of amyl benzene $C_6H_5C_5H_{11}$. The other halogen salts of aluminum gave reactions analogous to those of the chloride. They stated (J. Chem. Soc. 41, 115-116) "we found in general that compounds containing the group OH or OR i.e., alcohols, phenols, acids and their esters undergo decomposition with aluminum chloride.

For further references concerning this reaction see articles by J. Boeseken: (Rec. Trav. Chim. 19, 19-26; 20, 102-106; 22, 301-304; 22, 315-317; 23, 98 (1904). Boeseken stated, (Rec. Trav. Chim. 19, 19-26 (1900) that in the synthesis of aromatic ketones and sulphones by means of Friedel and Crafts' reaction, the condensation takes place in three stages:—

(1) $R.\ CoCl \times Alcl_3 \longrightarrow R - CoCl,\ AlCl_3$

(2) $R.\ CoCl,\ Alcl_3 + HR \longrightarrow R - COR,\ AlCl_3 + Hcl$

(3) $R.\ COR,\ AlCl_3 + nH_2O \longrightarrow R\ COR \neq AlCl_3, nH_2O$

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

Analogous additive compounds can be isolated when ferric chloride is used instead of aluminum chloride which has been shown by M. Nenek1 (Ber. 30, 1766-1768; 32, 2414-2419) Boeseken admitted the similarity in (Rev. Trav. Chim. 22, 315-317).

J. Boeseken (Rev. Trav. Chem. 30, 148-150) stated that in the case of a typical Friedel and Crafts' reaction, in every case the initial reaction is the simple addition of two molecules. Three molecules must be present:

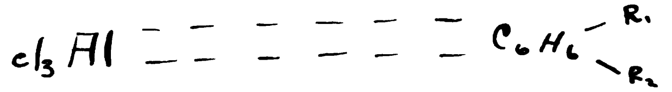
(a) an unsaturated molecule

(b) a molecule which can be so activated that it can combine with the unsaturated molecule.

(c) a catalyst which activates the molecules (a) and (b).

The possibility of the reaction is determined by the loss of free energy. The initial reaction is due to the encounter of the two molecules with a catalyst; in the case of benzene and other unsaturated cyclic systems the initial additive product, a derivative of dihydrobenzene, etc., cannot be isolated, because by elimination of hydrogen chloride or the like it is converted into a system containing less free energy.

Schaarschmidt (2. Angew. Chem. 37, 286-288) based his theory of the mechanism of Friedel and Crafts reaction on the fact that the aromatic hydrocarbon was activated by aluminum chloride or ferric chloride which he claimed appeared possible in producing a simultaneous "loosening" of the bonds of the organic halogen compound. A primary complex was formed, consisting of metallic chloride, hydrocarbon, and addend, in which the metallic chloride was held by auxillary valencies and the addend by ordinary valencies, thus



$$Cl_3Al - - - - - - - - C_6H_4{<}^{R_1}_{R_2}$$

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

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

In 1914, Frankforter and helpers (J. Am. Chem. Soc. 36, 1511-1529; 37, 385) condensed chloral, chloral hydrate, bromal and trioxymethylene with various organic compounds, with the elimination of water. He believed that aluminum chloride, while a catalyst, acts at the same time as a dehydrating agent, a theory which is now generally accepted.

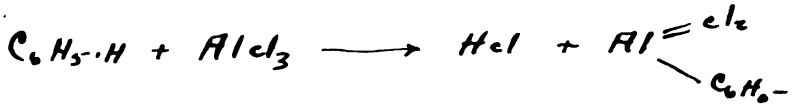
The Theory of the Action of Aluminum Chloride.

Friedel & Crafts reaction is connected more particularly with the union of aromatic hydrocarbons and their derivatives with a variety of other organic compounds, such as alkyl halides, acid chlorides, etc., (Org. Chem.-Cohen I, 224). Cohen stated (Organ. Chem.-Cohen I, 3470 that the results are best explained by assuming the formation of a compound between one or both of the reacting substances and the aluminum chloride, and by the removal of the latter from the system in combination with the ketone formed. It may be observed that the union between molecules or parts of a molecule is nearly always determined by unsaturation and by a consequent tendency for the unsaturated to saturate themselves. Thus Cohen (Org. Chem. - Cohen, I, 196) divided the condensation processes roughly into two groups:

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

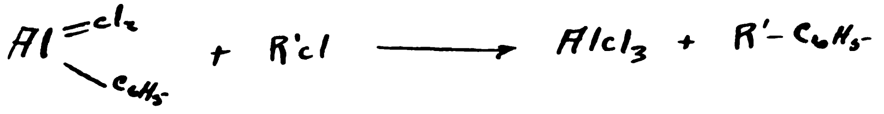
(2) Those which, being already unsaturated, combine either spontaneously or with the help of a reagent or catalyst.

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



$$C_6H_5{\cdot}H + AlCl_3 \longrightarrow HCl + Al\begin{smallmatrix}=Cl_2\\ \diagdown C_6H_5-\end{smallmatrix}$$

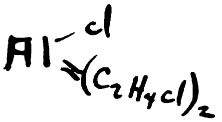
The latter compound would react immediately on the halogen derivative present and we would have:--



$$Al\begin{smallmatrix}=Cl_2\\ \diagdown C_6H_5-\end{smallmatrix} + R'Cl \longrightarrow AlCl_3 + R'-C_6H_5-$$

The regenerated aluminum chloride would react again with the hydrocarbon and the same reaction would be repeated. The reality of the formation of addition products of the aluminum chloride with the organic compounds has been established by Gustavson (Ber. II, 2151 (1878) who has been able to isolate an addition product with benzene, an organic colored oil, $AlCl_3-3C_6H_6$, decomposable by water, and in the case of the mixture of benzene and ethyl chloride,

$AlCl_3(C_2H_4)_2-3C_6H_6$, which heat dissociates into benzene and



$Al\begin{matrix}-Cl\\-(C_2H_4Cl)_2\end{matrix}$

which is stable and serves as a catalyst for the transformation of the mixture. (Compt. rend. 136, 1065 (1903; 140, 940 (1908).

The Works of Huston

Huston & Friedmann (J. Am. Chem. Soc. 38, 2527) published the first of a series of papers on the supposed dehydrating effect of $AlCl_3$ on aromatic alcohols and aromatic compounds. The experiment was performed on benzene and benzyl alcohol in the presence of $AlCl_3$, giving mostly diphenyl-methane. Their work showed the formation of an intermediate product which resembles that formed in Friedel & Crafts' reaction. A large portion of $AlCl_3$ is necessary for the production of a good yield of diphenylmethane. (also excess benzene) Primary alcohols were the principal ones used here.

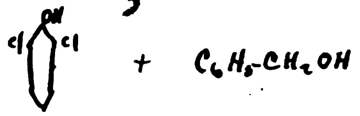
Huston & Friedmann (J. Am. Chem. Soc. 40, 785). In this paper works are described using secondary alcohol, benzene and $AlCl_3$. Three alcohols were used namely methylphenyl carbinol, ethylphenyl carbinol, and a true aromatic secondary alcohol, benzhydrol, the others being mixed aromatic-aliphatic alcohols. The ethyl and methyl groups were shown to interfere to some extent with condensation of alcohols and benzene; the retarding effect of the ethyl group being greater. The presence of the second phenyl group on the other hand from experimental evidence appears to accelerate the reaction. An excess of benzene and a low temperature (below 10) giving from 65%-70% of triphenylmethane.

Huston & Sager on the effect of unsaturation on the activity of alcoholic hydroxyl, (J. Am. Chem. Soc. 48, 1955) found that of the alcoholic derivatives of aromatic hydrocarbons, only those in which the hydroxyl is on the carbon atom adjacent to ring condense with benzene in the presence of $AlCl_3$. The saturated aliphatic alcohols up to and including amyl alcohol do not react with benzene in the presence of $AlCl_3$ to form alkylbenzene. Allyl alcohol ($CH_2=CH-CHOH$) reacts with benzene to give a fair yield of allylbenzene. (16%). As compared to 67% for benzyl alcohol. The hydroxyl in C adjacent to ring, were only aromatic alcohols found to react.

Huston, Lewis & Grotemut (J. Am. Chem. Soc. 49, 1365) worked on condensation of methylphenyl carbinol, ethyl phenyl carbinol and benzhydrol with phenol and $AlCl_3$. They give additional proof of the effect of unsaturation of the alpha C on the reactivity of alcoholic hydroxyl group. Benzhydrol in which both alpha carbon are members of the unsaturated benzene ring gave a much larger yield of the condensation product. There was also shown the strong tendency of the entering group to be directed para to the hydroxyl. The o- compound was not precluded, however, the amounts formed were too small for isolation.

R. C. Huston & E. F. Eldridge, (J. A. C. S. 53, 2260) printed the first paper dealing with chlorination and the chlorine derivatives of the benzylated phenols. Sentinis made a chlorobenzylphenol by treating (Peratoner & Vitsei Gazz. Chem. Ital. 28, 197) benzyl phenol with SO_2Cl_2. Investigator stated chlorine probably entered in ortho position but gave no proof of structure.

An attempt by Huston to substitute more than two chlorine into ortho and para benzyl phenols proved unsuccessful. The $AlCl_3$ condensation of



gave the ether as well as the benzylated phenol. This being of considerable interest--the first time an ether has been isolated from $AlCl_3$ condensation.

Huston & Lewis (J. Am. Chem. Soc. 53, 2379), condensed Para cresol and benzyl alcohol by both Claisen and AlCl methods. An increase in proportion used (phenol) was found to increase mono-benzylated product.

The Problem Stated

There are two general methods by which benzylated thymol may be prepared. Claisen's method should give an o- product, which might properly be called 1-methyl, 2-benzyl, 3-oxy, 4-isopropyl benzol. The product of the $AlCl_3$ condensation, according to Gatterman and others will be a p- product, but if Claisen and Hollemann are right, it should be a mixture of p and o compounds.

Our problem, therefore, has been to benzylate thymol by two methods mentioned above, and determine products formed by proper means of identification.

Condensation by the Claisen Method

In the first trial the following portions were used:—

Toluene............	250 cc.
Thymol.............	150 gm.
Benzyl Chloride....	126.5 gm.
Metallic Na........	23 gm.

Into a one liter 3-way ballon flask fitted with a reflux condenser and an appropirate mercury seal were placed toluene and small pieces of sodium. This mixture was heated, and before the toluene began to boil the stirrer was started in order to bead the sodium. Thymol was added over a period of one hour, and stirring continued over a moderately warm oil bath. Benzyl chloride was added to a warm solution (cautiously), and heated over an oil bath at 150-160C for 8 hours. The temperature was brought to the desired point very slowly. It was thought that the addition of the benzyl chloride to a hot solution would decrease the amount of residue, however, little variation was noticed. Yet my results can not be considered as conclusive, because of the varying factors. The salt was washed out, and toluene and water were distilled off. I then added 350cc. of Claisen's reagent. (Ann. 442, 224) Any derivatives with a free phenolic hydroxyl group would dissolve leaving the ether free to be extracted with petroleum ether. The salt was then acidified with 1:1 HCL to liberate the benzylated thymol.

During this reaction KCL was precipitated. The benzylated compound was extracted with ethyl ether using 50 cc. portions.

From the ethyl ether extract the following fractions were obtained at 4mm. --

80° - 95°	25 gm.
120° - 130°	25.2 gm.
130° - 160°	61.7 gm.
160° - 175°	4.3 gm.
residue..	36 gm.

The fraction 80°-95° crystallized upon distilling over, and upon re-crystallization was found to be thymol.

Fractions 120°-130° and 130°-160° also crystallized upon distilling over. After recrystallization it came down in white, needle like crystals having a melting point of 56.5° - 57.5° and boiling at 157° at 4mm. (189° at 14mm.) Boiling point was determined also at atmospheric pressure (740mm.), and found to be 333°-336°. (without decomposition). This compound was assumed to be the benzylated product, and upon analysis this assumption was verified.

Analysis: $(C_{17}H_{20}O)$

.2223 gms. gave .6932 gms. CO and .1665 gms. H O
.2195 " " .6803 " " " .1625 " "

Calc.	C........ 85%	H.......... 8.33%
Found	C........ 85.02	H.......... 8.29
"	C........ 84.88	H.......... 8.34

The yield of ortho product was 36% of theory. The amount of oil recovered from crystals was very small, but was ~~found to~~ found to increase with increased time of heating.

From the petroleum ether extract the following fractions were obtained at 4mm.

80° - 89°	1 gm.
120° - 130°	9 "
130° - 160°	4 "

Fraction 120°-130° was found to be the benzyl thymyl ether, as proven by running a Claisen in methyl alcohol. The boiling point was found to be 127° at 4mm. Solonina prepared this ether by the action of benzyl chloride on thymol in the presence of sodium ethoxide, and the boiling point was 221°-223° at 35mm. This pressure was duplicated as near as possible, however, the boiling point was much lower than that given by Solonina, being 205°-208° at 36mm.
(Solonina Jr. Russ. Chem. Soc. 1907, 39)

II The same portions were used as in preceding experiment. Benzyl chloride was added to a cold solution and allowed to stand over night before placing on oil bath. The following fractions were collected at 3mm.

Ethyl Ether Extract

80° - 120°	30 gm.
120° - 145°	26.6 "
145° - 160°	73.5 "
160° - 185°	22.7 "
residue.....	34 "

Petroleum Ether Extract (3mm.)

100° - 124°	3	gm.
124° - 130°	12.3	"
130° - 140°	4	"
160° - 185°	6.4	"

Yield of ortho compound was 39% of theory. There was an increase of ortho compound, while the residue remained about the same whether the benzyl chloride was added to a hot or cold solution. The petroleum ether fractions were markedly larger.

III The same portions were used as in preceding experiment. 100 cc. of toluene was used. Thymol was added over a 2 hr. period. The mixture was heated on oil bath at 150°-160° C. for ten hours. The following fractions were collected at 14mm. from the ethyl ether extract.

100° - 130°	25	gm.
130° - 170°	5	"
180° - 195°	30	"
185° - 195°	34	"
195° - 210°	15	"
210° - 240°	11	"
residue...	35	"

Fraction 195°-210° did not crystallize upon standing in refrigerator, and had a boiling point much higher than ortho or para benzyl thymol. It was therefore assumed to be the dibenzyl product.

The test with $FeCl_3$ further confirmed this belief, however, this is not conclusive for even mintue quantities of the ortho or para compound would give a positive test. A benzoyl ester was prepared with a melting point of 122-122.5°. (suggesting benzoic acid) A combustion was run on this sample with the following results.

		C	H
	Cal.	85.71	6.96
	Found	70.0	7.1
(Benzoic acid)	Cal.	68.85	4.95

It will be seen that hydrogen checks with the calculated amount for dibenzyl compound, but the carbon checks very close with that of benzoic acid. The ester was soluable in dilute NaOH. This test for solubility was made before running combustion, however, the melting point for the ester was higher than that for benzoic acid, and the combustion was made for further confirmation.

Petroleum Ether Extract (14mm.)

180° - 190°	29 gm.
200° - 240°	11 "
residue....	9 "

Note:— It will be noticed that most of my benzoyl esters turned out to be benzoic acid. However, Parr Bomb and in some cases combustions were made to further prove the solubility test and in some cases $FeCl_3$ test.

It will be noticed that petroleum ether extracts were larger. Upon crystallizing the ortho compound a considerable amount of oil was noticed after evaporating the petroleum ether. This oil was found to weigh 40 gm. The ortho compound (after being crystallized) weighed 48 gm. This oil was refractioned and found to have a boiling point of 194 at 14 mm.; a boiling point which corresponds very closely to what is supposed to be the para benzyl thymol. (195° at 13mm.) The yield of ortho compound was cut down to 20%. Attempts have been made to prepare esters of this oil and compare with para compound, however, some difficulty was encountered in crystallization. (They have not crystallized, as yet.)

The ortho compound is soluable in petroleum ether, ethyl ether, alkali, and sparingly soluable in ethyl alcohol.

Solonina's test for benzyl thymol ether was tried and found to be positive.

Ethyl and Methyl Ethers of O- compound.

The ethyl and methyl ethers were prepared as follows:-- Using 1/24 mol. quantities. The sodium was dissolved in ethyl alcohol and benzyl thymol added slowly. After it has been added ethyl iodide is added from a separatory funnel with stirring. (An adequate mechanical stirrer and reflux condenser are used throughout, with a 500 cc. 3-neck ballon flask.) Temperature 75°C.

The ethyl benzyl ether was a straw colored liquid boiling at 185°-186° 14mm.

The methyl benzyl ether is a liquid boiling at 186-187° 14mm.

The methyl thymyl ether was prepared by Paterno (Gazz. 5-15) from thymol and methyl iodide. Behal and Tiffinean (Bl. 43, 732) prepared this ether by the reduction of thymol with Na and alcohol. Boiling point was not given in Beilstein.

The ethyl ether was prepared from thymol, C_2H_5I and alcoholic KOH. (Bamburger B. 19, 1820)

Claisen's Ether

Using Claisen's method the thymyl benzyl ether was prepared using methyl alcohol as the dissociating medium. Same apparatus used as in preceding experiments where Claisen's reaction was made use of. 1/10 mol. quantities used. Temperature 85°-90° C. Heated 7 hours.

125°-130° .... 15 gm. 3mm.
residue.... 3 "

II Same quantities as above. Temperature 95°-100° C. Heated for 5 hours.

120°-130° .... 12 gm. 3mm.
residue. 2 "

Preparation of 4 Brom Thymol

For further proof of the ortho compound, it was brominated and then 4-Brom thymol was condensed with benzyl chloride. By such a procedure it was hoped to procure the same compounds, namely 2 Benzyl, 4-Brom thymol.

The 4-Brom thymol was prepared by Mazzara's method. (Cazz. 18, 516) taken from Beilstein's Handbuch 7, 540 series 499-608. The temperature was kept around 0° C. during the bromination. Upon the addition of brominated mixture to a saturated solution of $(NH_4)_2CO_3$, there was formed a heavy reddish-brown oil which sinks to bottom of container. Yield about 80% of theory. Boiling point was 117°C. at 4mm. An oil was obtained from crystals probably 2-4 dibrom thymol.

Condensation of 4-Brom Thymol and Benzyl Chloride.
(Claisen Method)

A Claisen reaction was now tried using 1/5 mol. quantities.

61.8 gm.	4-Brom Thymol
25.3 "	Benzyl chloride
4.6 "	Metallic Na
85 cc.	Toluene

Brom thymol was added over an hour period, and stirring continured for 2 hours. Benzyl chloride was added to a hot solution and the mixture was heated on an oil bath for 7 hours at 145°-150° C.

Petroleum Ether Extract (3mm.)

155° - 165° .... 5.7 gm.

Ethyl Ether Extract (3mm.)

90° - 125°	19.6 gm.
140° - 160°	25.4 "

The fraction 140°-160° of the ethyl ether extract does not crystallize upon standing or upon placing in refrigerator. The third fractionation gave the following results at 3mm.

90° - 125°	19.6 gm.
145° - 160°	7 "
160° - 170°	16.5 "

Fraction 160°-170° came over mostly at 166°, and corresponds to the product given by bromination of the ortho compound. It refractionated at 14mm. and found to have a boiling point of 221°-223° C.

The petroleum ether extract crystallized upon being placed in refrigerator, and was found to have a melting point of 48.5°-49°. A Parr Bomb determination for bromine was made on this ether with the following results.

Sample .2019

Calc..............	25.05
Found.............	24.73
"	24.69

This 4-Brom benzyl thymyl ether was also prepared in a dissociating medium (alcohol), using Claisen's method. The same compound was obtained. Temperature was kept around 90°-100° C., and was heated on oil bath for only 3 hrs. It boiled mostly at 157°. (3mm.)

Bromination of o- Compound

The ortho compound was now brominated using the method of Mazzara. Results probably would have been more accurate using a calculated amount of bromine instead of adhering to Mazzara's method for preparation of 4-brom thymol, which undoubtedly was figured out on the basis of thymol. The following are the results of the second bromination of the ortho compound.

25 gm. of ortho compound was dissolved in 50 gm. of glacial acetic acid and placed in a 500 cc. round bottom 3-neck ballon flask fitted with an adequate mechanical stirrer. To this mixture was added 26 gm. bromine in 26 gm. glacical acetic acid. The temperature was maintained aroung 0° C. The mixture was poured in a saturated solution of $(NH_4)_2CO_3$, extracted with ethyl ether and fractioned at 3mm.

Ethyl Ether Extract

140° - 160°	3.2 gm.
160° - 170°	19 "

Fraction 160°-170° came over mostly at 167° - 3mm. At 13mm. the boiling point was 223°-225°, corresponding very closely to the compound obtained by condensation of 4-brom thymol and benzyl chloride, which boiled at 221°-223° at 14mm. This compound was somewhat darker in appearance suggesting excess bromine.

The P- tolyl sulfonyl ester was made of these compounds which resulted from condensation and bromination namely, 4-Brom, 2-benzyl thymol. They both had a melting point of

126°-126.5°C. Parr Bomb determinations for Br gave the following results.

Calc.......	16.93
Found......	16.68

Preparation of 4-Chloro-Thymol

It was then decided to attack this problem from a different angle, namely by chlorination. 4-Chloro-thymol was made by method given in J.C.S. 74:641. Bocchi (G. 26 II 403) gives m.p. 58°-60°. Condorelli gives a m.p. 62°-64°. I found it to be 59.5°-60° C. Better yields were obtained at a temperature of 80°-85° C. As in the case of the preparation of 4-Brom thymol an oil was obtained. No work was done on this oil in either case. It was probably the di or tri substitution product. A 500 cc. roung bottom 3-neck ballon flask was used fitted with a mechanical stirrer, mercury seal, separatory funnel and a trap to catch SO_2 evolved. After SO_2CL_2 has been added water was added and product was extracted with ethyl ether.

Benzylation of 4-Chloro-Thymol**

The same apparatus used as in preceding Claisen's reactions. One-fourth mol quantities used. Heated for 6 hrs. at 150°-160° C.

Ethyl Ether Extract (3rd Fractionation)

105° - 145°..............	6 gm.	4mm.
145° - 170°..............	26 "	"
170° - 195°..............	6 "	"

Fraction 145°-170° boiled mostly at 165° - 4mm. It refractioned at 14mm. and the largest fraction (200°-210°) came over mostly at 205°-206° (14mm.). It did not crystillize.

Chlorination of O- Benzyl Thymol

One-tenth mol quantities used. The temperature was kept around 80°-90° C. A very copious evolution of SO_2 was noticed.

Ethyl Ether Extract (15mm.)

190° - 200° .... 3 gm.
200° - 215° .... 18.7 "

Fraction 200°-215° came over mostly at 206°-208° 15mm.

Benzoyl esters were prepared of 4-chloro, 2-benzyl thymol, and upon analysis was found to be benzoic acid, however, the P- tolyl esters had a melting point of 118-118.8. Parr Bomb determinations confirmed content of chlorine.

Benzoyl, P-tolyl sulfonyl, and benzene sulfonyl esters were prepared of ortho benzyl thymol. The P-tolyl ester melted at 118°-118.8°, the benzoyl ester turned out to be benzoic acid; the benzene sulfonyl ester did not crystallize.

Aluminum Chloride Condensation

The following quantities were used:--

33.3 gm. $AlCl_3$ .... ¼ mol

150.1 gm. Thymol........... 1 "

300 cc. Petroleum Ether

63.2 gm. Benzyl Chloride -½ mol

A 500 cc. condensation jar fitted with a mechanical stirrer was used. The thymol was suspended in the petroleum ether, and to this suspension is added the benzyl chloride followed by $AlCl_3$. Upon the addition of $AlCl_3$ the solution quickly changed in appearance to a dark brown color followed by free evoltuion of HCL gas.* $AlCl_3$ was added over an hour period, and stirring continued for 3 hrs. It was then allowed to stand for 3 days. The temperature during the addition of $AlCl_3$ was maintained at 18°-23° C.

The complex molecule was then poured with stirring into a mixture of 500 gm. ice and 500 cc. conc. HCL to accomplish decomposition, after which it was extracted with ethyl ether. The ethyl ether was distilled off and 350 cc. of Claisen's reagent was added to the residue. Extract with petroleum ether to remove any ethers formed; the mixture is then treated with 1:1 HCL until neutral and extracted with ethyl ether. Both extractions were distilled under reduced pressure when ether was removed.

Ethyl Ether Extract (3mm.)

85° - 105°............	97.6 gm.
130° - 155°............	28.7 "
155° - 165°............	12.7 "
residue....	15 "

Fraction 130°-155° came over mostly at 145°, and was thought to be the para benzyl thymol. It has a boiling point of 196° at 13mm. The boiling point could not be taken at atmospheric pressure, being higher than the thermometer available.

From fractions 130°-155° and 155°-165° was isolated a crystalline compound, which upon recrystallization was found to have a melting point corresponding to the ortho compound. They were also similar in crystalline structure. Upon final fractionation of these fractions, it came over mostly at 196° at 13mm. The ortho compound was isolated from all condensations using $AlCl_3$ in a very small quantity.

The benzoyl, and P-tolyl ester were prepared of the para compound, but have not crystallized as yet. In making the benzoyl ester the first time benzoic acid was obtained.

Petroleum Ether Extract... 3 gm.

It does not crystallize.

II The following quantities were used for the second condensation:

112 gm. thymol......... ¾ mol

38 " $AlCl_3$............ 1/3.5 mol

63.2 " Benzyl chloride. ½mol

300 cc. Petroleum ether

**Note:-- The petroleum ether extract obtained from this condensation was too small to work with. As will be noticed there is a marked parallelism between the boiling points of product obtained by two methods.

Note:-- All esters were prepared by method given in Porter-Stewart-Branch Methods of Organic Chemistry. (P. 181) Calculated amounts of reagent used for esterification.

*During the addition of $AlCl_3$ to the condensation mixture a solid mass was formed of unknown composition insoluable in ethyl ether, petroleum ether, acid and alkali.

Temperature was maintained from 25°-30° C. $AlCl_3$ was added over a 1¾ hour period.

Ethyl Ether Extract (3mm.)

90° - 105°	63 gm.
115° - 145°	6.7 "
160° - 175°	22 "
residue....	24 "

As before a gumy mass was formed. Fraction 160°-175° was refractioned at 14mm. and found to have a boiling point corresponding to the para compound in the preceding condensation. I have no plausible reason why it should come over at a higher temperature using the same pressure (3mm.) unless it was super-heated. The lower boiling fractions in both cases, namely 85°-105° and 90°-105°, were found to be thymol. The structure of para compound was proven by bromination. Mazzara probably obtained a different compound than para benzyl thymol by his method using zinc filings. He obtained a product boiling at 255 8mm. (Beilstein Handbuch 7, 690)

Preparation of 2-Bromothymol

2-Brom thymol was made using method of Englehardt and Lotschinoff (J.C.S. 60, 899) with some deviation from their procedure.

The following quantities were used:--

2 mol	KOH
1 "	Thymol
1¼ "	(conc.) H_2SO_4
1 "	Bromine

Sulfuric acid was added to thymol and allowed to stand on water bath for 2½ hrs. One mol KOH was added and allowed to stand on the water bath for 6 hrs. Another mol of KOH was added to make alkaline before brominating. Bromine was added to the mixture keeping the temperature around -5°C. This mixture was allowed to stand until next morning and then steam distilled over an oil bath up to 175°C. 300 cc. of conc. H_2SO_4 was then added and temperature was taken up to 190° during distillation. More acid was added and distillation continued. Not much more was recovered upon addition of more acid.

(1) Before adding acid.. .... 33 gm oil

(2) After adding acid............. 166 " "

Fractionation (1)

$110^\circ \overset{(116)}{-} 120^\circ$ .... 3mm. 24 gm.

Fractionation (2)

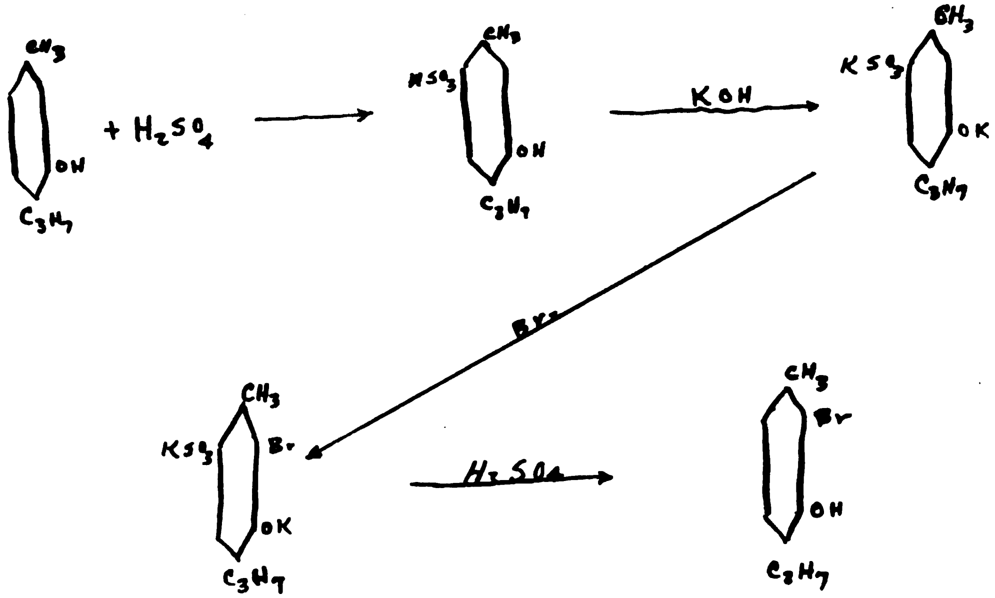
$95^\circ \overset{(107)}{-} 115^\circ$ .... 3 mm. 79 gm.

$120^\circ \overset{(143)}{-} 145^\circ$ .... " " 76 "

After refraction, and Parr Bomb determinations the brominated products were as follows:--

Thymol...........	28.5 gm.
Dibrom "	77.7 "
Mono-brom thymol........	65 "

The reaction may be represented as follows:



The dibrom product was found to have a boiling point of 186°-187° at 34mm. Corresponding very closely to the boiling point given by Clans-Krause (J. Pr. 2 43, 345) which was 187°-188° 34mm. The product distilled over before making acid was found to be dibrom thymol.

AlCl$_3$ Condensation of 2-Brom Thymol

This 2-brom thymol was condensed with benzyl chloride using Huston's method. The following quantities were used:--

1/5 mol	2-Brom Thymol
1/8 "	Benzyl chloride
1/12 "	AlCl$_3$

The reaction approaches violence with much HCL given off.

Petroleum ether extract was very small.

Ethyl Ether Extract (14mm.)

115° - 135°	17.6 gm.
135° - 170°	9 "
170° - 205°	6 "

Fraction 170°-205° was assumed to be desired product, for para compound itself has a boiling point above 190° at the same pressure used here.

Bromination of p- benzyl Thymol

25 gm.	p- benzyl thymol
10.6 "	Bromine

Glacial acetic acid used as a medium.

Fractionation (13mm.)

170° - 200°	3 gm.
200° - 210°	22 "

The fraction 200°-210° was assumed to be desired product. This fraction and fraction 170°-205° of preceding condensation were used to make esters. The benzoyl esters were made but turned out to be benzoic acid in both cases no product was left to permit the making of this ester again.

Summary

1. Thymol was condensed with benzyl chloride by the Huston method, forming an ortho and para mono benzylated product. The structure of the ortho compound being definitely proven. Although the para isomer is the expected predominating product to be isolated from this condensation, I have cited no conclusive evidence for this fact. However, test for phenolic groups were positive. Esters have not crystallized as yet.

2. Thymol was condensed with benzyl chloride by the Claisen method, forming ortho and para mono benzylated products. The para compound being favored by longer heating and less vigorous stirring. Although giving a test with $FeCl_3$ and having a boiling point similar to the para isomer obtained from Huston condensation, evidence is not of such a nature as to establish or assign definitely the para structure to this oil. Those esters prepared turned out to be benzoic acid, others have not crystallized as yet.

3. The "Claisen Ether" was isolated in small amounts using a non dissociating medium, but in much larger amounts using a dissociating medium. (CH_3OH) A small amount of ether was isolated from Huston condensation, however, to small to conveniently handle.

4. In the condensation of 4-Bromothymol and benzyl chloride by the Claisen method an ether was isolated which proved to be the 4-Bromobenzyl thymyl ether. This ether

was produced also by Claisen's method using a dissociating medium. Although not mentioned in the course of the thesis, an attempt was made to brominate Claisen's benzyl thymol ether in an effort to obtain 4-brom-benzyl thymol ether. The ether was evidently split, for the presence of benzyl bromide was obvious. Because of obnoxious odor this experiment was abandoned.