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BENZYLATION OF O-CRESOL

THESIS FOR DEGREE OF M. S.

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R.C. Houston.

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BENZYLATION OF O- CRESOL

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H. O. Swartout

FOREWORD

The experienced chemist will doubtless find many statements in the following pages that betray the work and the type of observation of a childish dabbler, rather than a mature scientific investigator. I have written, however, more for the sake of those who will follow in my footsteps; and it may be that some of them will appreciate the details of technique and observation that would be tiresome to a person of more experience. If I have told too much, let me plead in extenuation the fresh interest of a man with a new task,- his first essay in the line of research.

H. O. Swartout

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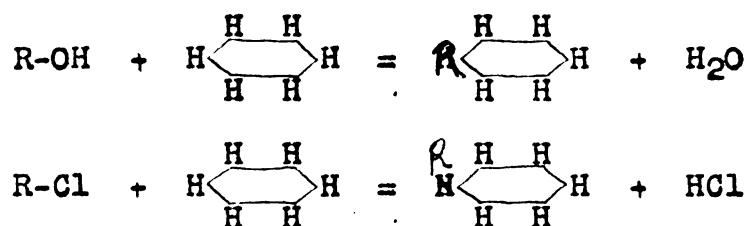
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! BENZYLATION OF O-CRESOL . !

PREVIOUS WORK AND GENERAL PRINCIPLES

Introduction

Among the thousands of organic syntheses which have been effected during the past few decades, not the least interesting are those in which hydrogen atoms belonging to simple or substituted benzene rings have been replaced by aliphatic or aromatic radicles. Compounds that in a general way may be classed as alcohols or esters theoretically could be, and in fact have been, used to bring about these reactions; and water or acids have consequently been eliminated in the process. It is easy, therefore, to see why dehydrating agents or catalysts have usually proved helpful,- often necessary,- in effecting such syntheses, the simplest scheme of which is as follows:



If one or more substituents are already present, it is but reasonable to suppose that they will exert an influence upon further substitution. Thus reactions concerning o-cresol, the results of certain investigations of which compound have occasioned this report, depend partly upon the OH and CH₃ groups originally attached to the ring. Perhaps

Holleman (Chem. Rev., July, 1924, 187 seq.) has best summed up present views which bear on this point. He quotes Beilstein's rule: "If a substituent C enters 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." Then he lists the common groups which direct to p- or o-positions, in the order of the speed of the reactions which they produce, which of course determines their comparative directing influence: $OH > NH_2 > I > Br > Cl > CH_3$. From this series it is clear that in o-cresol the influence of the OH group is greatly predominant, and that it will direct further substituents to positions p- or o- to its own.

These facts lead to the idea that the OH group, which is characteristic of phenols, should cause all of them to react in an analogous manner, except in cases where further complications exist. Possible complications are, of course, not few; but to discuss them in detail would add very little to the elucidation of our subject, and it would lead us too far afield. Because of the analogy among phenols, however, it will be worth while to note some of the work that has been done in alkylating or benzylating them, as an introduction to the problems connected with the benzylation of o-cresol.

Alkylation of Phenols

In 1881 Liebmann (Ber. 14, 1842) prepared a butyl phenol by condensing phenol and isobutyl alcohol with the aid

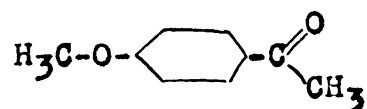
of molten ZnCl_2 . He also prepared propyl phenol and amyl phenol by the same method. The next year Mazzara (Gazz. 12, 505) condensed propyl alcohol and m-cresol with MgCl_2 , and a year later (Ber. 16, 242) he used the same catalyst in preparing methyl butyl phenol. In 1884 Auer (Ber. 17, 669) obtained an ethyl phenol by condensing absolute alcohol and phenol with ZnCl_2 . Six years later Dennstedt (Ber. 23, 2569) prepared the same compound, but he used zinc dust instead of ZnCl_2 , and he considered that his compound was a mixture of two of the three possible isomeric ethyl phenols.

In 1894 Bauer (Ber. 27, 1614) condensed isobutyl alcohol and o-cresol with the aid of ZnCl_2 and heat, preparatory to the synthesis of a 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. They concluded that the two products were the same, citing similarity of melting points, of boiling points, and of benzoyl derivatives as proof of the 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 CH_3I 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 chains.

In 1889-'90 Gattermann, Ehrhardt, and Maisch (Ber. 22, 1129; 23, 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, as it may as properly be called. The other condensation products which they prepared gave analogous oxidation products, and on these grounds they repeatedly stated (Ber. 23, 1203, 1204, 1205, 1208, 1210) that the acyl or benzoyl groups regularly entered the ring in the p-position.

In 1891 Senkowski (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 ZnCl_2 . He thus extended and confirmed the theory that was suggested by the work of Gattermann and his helpers.

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 Paterno (Gazz. 2, 20) prepared benzyl phenol by treating phenol with benzyl alcohol or with benzyl chloride in the presence of zinc turnings. He also benzylated anisol. This work was repeated in 1875 by Paterno and Filetti, (Gazz. 5, 381) using a mixture of acetic and sulfuric acids instead of zinc turnings. Three years later Paterno and Mazzara, (Gazz. 8, 303) again using zinc as a catalyst, condensed cresol with benzyl chloride.

In 1880 O. Fischer (Ann. 206, 113) condensed benzyl alcohol and dimethyl aniline with ZnCl_2 , also benzhydrol and dimethyl aniline. He found that he could use either ZnCl_2 or phosphoric anhydride to assist in the reaction. While this was not a case of benzylating a phenol, yet it is of interest because of the constitutional analogy between aniline and phenol.

As already noted, Liebmann prepared several alkyl phenols, using ZnCl_2 as a catalyst; but he also prepared a benzyl phenol. (Ber. 14, 1844; 15, 152) Incidentally he raised the question as to whether the zinc used by Paterno was the

active catalyst, or whether it was ZnCl_2 formed from the zinc and the free HCl always found in benzyl chloride. He referred to some of his own experimental observations as an evidence that a very small quantity of ZnCl_2 could catalyze the reaction.

In 1881 Merz and Weith (Ber. 14, 187 seq.) tried the effect of both ZnCl_2 and AlCl_3 on phenol. The result was not a benzyl phenol, but a diphenyl ether. Their work is of interest in connection with our subject, however, for it marks one of the first uses of AlCl_3 as a catalyst or dehydrating agent in reactions concerning phenol, being eight years in advance of the work of Gattermann and his associates, who used this catalyst in effecting the syntheses already mentioned in connection with their names.

In 1909 Khotinsky and Patzewitch (Ber. 42, 3104) called attention to the fact that aromatic tertiary carbinols may easily be condensed with many substances, including phenol, by the aid of acetic acid to which a little H_2SO_4 or ZnCl_2 has been added.

But the condensation of aliphatic, or aromatic, or mixed aliphatic and aromatic alcohols with aromatic compounds, using AlCl_3 as a catalyst or dehydrating agent, - its exact office is not yet fully known, - has, so far as I can learn, not been reported by any investigators except Dr. Huston and his helpers at Michigan State College. Reports of their work have appeared from time to time since

1916. (J. Am. Ch. Soc. 38, 2527; 40, 785; 46, 2775; 48, 1955) Only the 1924 report, however, dealt with phenols. Condensations of benzyl alcohol with phenol, with anisol, and with phenetol, also of benzyl chloride with phenol, were effected, AlCl_3 being used to aid in the reactions. The opinion was expressed that the benzyl phenols thus prepared were p- compounds, in agreement with the theory of Gattermann, Senkowski, and others, as previously noted.

Claisen's Work and Method

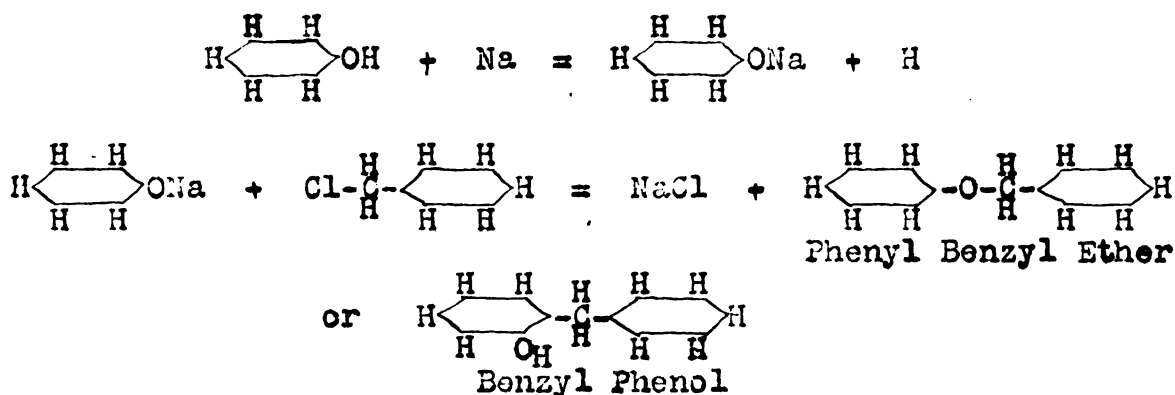
The work of Claisen deserves particular notice. He has prepared both alkylated and benzylated phenols by a method which is fundamentally different from any that have thus far been mentioned, and his discussions throw much light upon the question as to whether his products are identical with, or isomeric with, those prepared by ordinary condensation methods. I shall refer only to his 1924 report, (Ann. 442, 212 seq.) as that is sufficient for our present purpose.

Claisen generally uses an alkali metal salt of a phenol, dissolved or suspended in a suitable medium, and treats it with an alkyl or benzyl halide. The result is usually a mixture, containing a mono- alkyl or benzyl phenol, an ether which may be removed by extracting with ligroin, and a small proportion of a di- alkyl or benzyl phenol. When suitable precautions are taken the chief product is the mono- alkyl or benzyl compound. A brief consideration of

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• *Chlorophyll a* (Chl *a*) is the primary photosynthetic pigment in all photosynthetic organisms. It is a green pigment that absorbs light energy in the blue and red regions of the visible spectrum. Chl *a* is the most abundant pigment in the chloroplasts of green plants and algae.

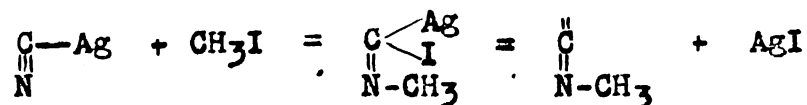
the main reactions involved will make Claisen's discussions more intelligible:



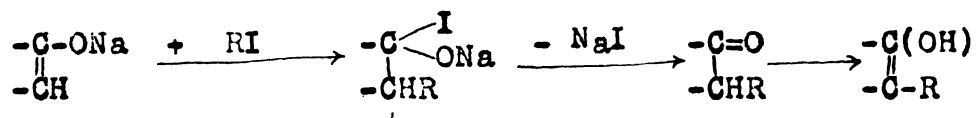
A brief inspection of these equations shows why Claisen said that the ether is the product one would expect to be formed, and that the benzyl phenol is the result of "anomalous metal substitution", or, as he otherwise expresses it, the result of ring alkylation, when one would naturally think that the benzyl group should take the place of the metal atom that is displaced. Why in the course of the reaction a hydrogen atom from the ring should give up its place to the benzyl group, and why the OH group should be re-formed in the process, are somewhat difficult questions to answer; but it is evident from the fact that a considerable quantity of the mono- benzyl compound is regularly formed that this is exactly what occurs.

Claisen's discussion of this point, in the course of which he stated his belief that the substituent group in these cases always takes a position o- to the OH, was based on Michael's theory of the reaction between silver cyanide and methyl iodide. (J. pr. 37, 486; 46, 189) The following

reaction scheme will help to make this theory clear:



It can be seen that a shift in valence bonds occurs, that the CH_3I separates, one part going to the carbon and one to the nitrogen, and that AgI is finally split off, leaving the CH_3 attached to the nitrogen, instead of to the carbon as we might expect. Claisen applies this principle to the reaction between an alkyl iodide and a metal derivative of an unsaturated organic compound, as follows:



In sodium phenolate, used above to illustrate Claisen's general theory, we find the group $\begin{array}{c} -\text{C}-\text{ONa} \\ \parallel \\ -\text{CH} \end{array}$; and benzyl chloride is analogous to an alkyl iodide. We should expect, then, just such a shift of bonds, a splitting of benzyl chloride into parts which attach themselves to different carbon atoms, the elimination of NaCl , and the final formation of a compound with the OH group restored and the benzyl radicle attached to a carbon atom in the ring, instead of to the oxygen atom. Probably such a shift of bonds 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, through Claisen's method of preparing alkyl or benzyl phenols, we are reasonably sure of obtaining products with the OH group and the new substituent occupying

positions adjacent to each other in the ring. And, in this connection, we should give attention to his opinion that ordinary condensation methods are not sure to give pure p-products, as Gattermann and others seem to think, but are likely to produce mixtures of p- and o- compounds, as might be predicted from Holleman's discussion of the general principles governing substitution in the benzene ring.

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

1. The kind of phenol.
2. The kind of alcohol,- whether 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 occurs.

It is not necessary to discuss these factors at any length; but they have a bearing upon the present problem, because Claisen's method is one way of benzylating o- cresol, so a few comments will be made. Naturally a complex phenol would introduce more complications than a simple phenol. As to the second point, Claisen worked mostly with unsaturated alcohols, indicating that he found them best suited to his purpose. He stated that the looser the bond between the halogen and the alkyl radicle the more smoothly

the reaction progressed. We know that unsaturation in the alkyl radicle results in a comparatively loosely held halogen. The kind of halogen also has a bearing on the strength of such bonds. Points four and five hardly need comment, but not so with point six. Claisen found that the influence of the medium was unexpectedly great, especially upon the proportions of the ether and the mono- alkyl or benzyl compound in the reaction mixture. The use of a dissociable medium gave over 90% of the ether, while a non-dissociable medium, such as toluene, resulted in a yield of 60-70% of the "anomalous" alkyl or benzyl phenol. While it is not easy to explain how it is so, it is probably true that such media as toluene cause a loosening of the valence bonds between the alkyl or benzyl radicle and the halogen, thus facilitating the "anomalous" substitution.

Before making a definite statement of our problem, it is necessary to call attention to a reaction carried out according to Claisen's method by Schorigin in 1925. (Ber. 58B, 2033) He prepared sodium o- cresolate, suspended in toluene as a medium, and treated it with benzyl chloride. He named the crystalline product which he obtained 2-methyl 6-benzyl phenol, and stated that it melted at 51-52° and boiled at 187-188° (15 mm.) It will appear later that his benzyl phenol is identical with that which we prepared for the purpose of comparison with the condensation product of benzyl alcohol and o- cresol with AlCl_3 . Our work was

begun before Schorigin's report came to our attention, however; and we record some additional data regarding the compound, which he evidently did not study extensively.

The Problem Stated

There are, then, two general methods by which o- cresol can be benzylated. Claisen's method should give an o- product, which might properly bear the name which Schorigin gave it. The product of the AlCl_3 condensation of benzyl alcohol and o- cresol should, according to Gattermann and others, be a p- product, which might be named 2-methyl 4-benzyl phenol; but if Claisen and Holleman are right, it should be a mixture of the p- and o- compounds, the p- predominating.

Our problem, therefore, has been to benzylate o- cresol by the two methods; to purify the products; to look for any evidence that either of them is a mixture; to determine whether or not they are identical, and, if not, to distinguish them from each other by appropriate means, such as melting points, boiling points, solubilities, crystal forms, and the character and behaviour of some of their simple derivatives; and to note the bearing of previous work and our own findings on the configuration of the molecules of the two compounds. All these details, together with a discussion of certain by-products, are given in the following sections.

EXPERIMENTAL WORK

Benzylation of O- Cresol by Claisen's Method

$\frac{1}{2}$ mol of freshly chipped sodium was suspended in 130 g. of toluene in a 1-liter Florence flask and treated in the cold with $\frac{1}{2}$ mol of o- cresol. The reaction began at once. Heat was evolved and hydrogen given off. The reaction seemed to be complete in two hours, but the flask was fitted with a reflux condenser and gently heated for an hour longer. When the contents of the flask had cooled to room temperature, $\frac{1}{2}$ mol of benzyl chloride was added through the condenser. A gentle reaction began, the light gray, pasty mass of sodium cresolate dissolving smoothly to a reddish-brown liquid with a precipitate of NaCl. The mixture was let stand over night and then heated on an oil bath for 5 hours at 150-160°. After cooling, the NaCl precipitate was dissolved out by washing twice with water in a separatory funnel, and the trace of water and the toluene removed by distilling the mixture, stopping the distillation at 125°.

The residue, consisting of a mixture of the reaction products, was dissolved in 250 cc. of Claisen's methyl alcoholic potash, (Ann. 442, 224) and shaken out with 200 cc. of ligroin in 50 cc. portions. The ligroin used here and throughout the experimental work was Central Scientific Company's 40-60° petrolic ether. The purpose of this treatment was to form the ligroin-insoluble potassium salt of the substituted phenol, so that the ether fraction and

other substances in the mixture could be separated from it by extraction. After the removal of the ligroin extract by means of a separatory funnel, the residual brown solution was made distinctly acid with 1:1 HCl, thus precipitating KCl and re-forming the free substituted phenol. This phenol was extracted three times with ether and the ether was removed by heating on a water bath, the residue being a reddish-brown oil.

A further quantity of both the ligroin and the ether extracts was prepared by repeating the procedure described above, the corresponding extracts being united and fractionally distilled, with the following results:

Ligroin Extract

250-280° (Atmospheric pressure) 16.0 g.

No further study of this product, a yellow oil, was made, as it was probably 2-methyl phenyl benzyl ether, a compound in which we were not directly interested, except to get some idea of the proportion of it formed during the reaction. 16.0 g. is 8.1% of the theoretical yield.

(Practically all came over at 285°-290° - Stadel, Ann 217, 45 (1883))

Ether Extract

Third fractionation, - 5 mm.

90- 140°	15.0 g.
140-155° (Mostly 150-152°)	62.0 g.
155-250°	25.0 g.
Residue (Black tar)	29.0 g.

Fraction 140-155° solidified in the receiver and was

recrystallized from ligroin to constant melting point. No change occurred after the fourth crystallization. Ten trials of the melting point were made. It was found to be 49.5-50.5°, which differs from that reported by Schorigin by 1.5°. A test made with the purified crystals gave the boiling point of the compound as 150-152° (5 mm.), as compared with Schorigin's reported 187-188° (15 mm.); but the differences are not great enough to raise any doubt as to the identity of the compounds, for the reacting substances were the same and the procedures much alike. The yield, 62.0 g., is 31.3% of theory.

As a means of shortening the time needed to secure purified crystals the following plan was pursued: At each step in the recrystallizing process the mass of crystals was dissolved in the minimum possible quantity of boiling ligroin, the solution was set in the coldest possible available place, and the mother liquor was pressed out of the thick felted mass of crystals which soon formed under such conditions. This mother liquor was allowed to evaporate, yielding comparatively impure crystals, while the felted crystal mass was dissolved in fresh ligroin and the solution evaporated, yielding much purer crystals. Before evaporation had proceeded to dryness, in all cases the last few cubic centimeters of mother liquor were poured off into a beaker containing a less pure product. In this way a few

days' time was sufficient for the production of crystals of constant melting point.

Benylation of O- Cresol by AlCl_3 Condensation

A mixture of 100 g. of redistilled o- cresol and 100 g. of pure benzyl alcohol was suspended in 200 g. of ligroin in a tall 1-liter condensation jar, which was set in a water bath as a means of controlling the temperature. While constantly agitating the mixture by means of a motor stirrer, its temperature was gradually raised to 35° and maintained as nearly as possible at that level while 65 g. of anhydrous AlCl_3 was slowly added in small portions over a period of about an hour. The whole operation was carried out in the hood on account of the copious evolution of HCl gas which accompanied the reaction; and at times troublesome frothing occurred, which could be controlled only by the addition of further portions of cold ligroin. When the evolution of gas had nearly ceased, the mixture was let stand over night in the hood.

The crude condensation product was a light grayish-brown, semi-gummy, semi-granular precipitate. It was decomposed by mixing it with shaved ice in a large beaker, adding a little 1:1 HCl toward the end to aid in the separation. The mixture was extracted three times with ether, the combined ether extracts let stand several days over anhydrous K_2CO_3 , and the dried solution freed from ether

on the water bath. Two more lots were made up in the same way, and the ether-free residues were combined and fractionally distilled.

Fifth fractionation, - 5 mm.

90 -150°	36.7 g.
150-160°	118.3 g.
160-180° (Mostly below 170°)	33.6 g.
180-215°	9.8 g.
215-235° (Mostly at 225-230°)	77.2 g.
235-280°	29.2 g.
Residue (Brown tar)	11.2 g.

Fraction 150-160° crystallized in 30 minutes, and fraction 160-180° in four hours, in the ice-box. The crystals were pressed between filter papers and repeatedly recrystallized from ligroin, using the method that has been described in connection with the discussion of the Claisen's method product. Six recrystallizations were necessary before a substance of constant melting point was obtained. The melting point was found to be the same as that of the other compound, - 49.5-50.5°.- but when the purified crystals were tested for boiling point, this turned out to be 167-169° (5 mm.). This was somewhat of a surprise, since the greater portion of the crude product had come over below 160°. The yield of the two fractions, 150-160° and 160-180°, a total of 151.9 g., is 27.6% of theory, though one is not justified in classing all of

this total as the yield of the pure p- compound.

The first direct evidence, aside from the question of boiling point, that the two products were not identical was an unmistakable difference in solubility and in crystal form,- points which will be more fully treated in a later section. Then it was discovered that the mother liquor, or washings, obtained at the beginning of the second crystallization of the AlCl_3 condensation product produced crystals very similar in form to those of the Claisen product; and a test of these crystals showed that they consisted chiefly of a substance whose boiling point was 150-152° under 5 mm. pressure, thus affording further evidence of the identity suggested by the crystal form.

These facts, together with the additional fact that the entire fraction of the AlCl_3 product from 150-180° formed crystals which were comparatively difficult to purify to constant melting point, are evidence that this product was a mixture; and, while more proof will be given later, we may say at this juncture that the mixture consisted of a large proportion of the p- product and a small proportion of the o- product. Not having foreseen this outcome sufficiently early, it was too late to determine definitely the proportions of the two products by means of fractional distillation, so that a clearer idea of this point must come from a repetition of the experiment.

Comparative Tests and Further Data

Reference has already been made to some evidence that the two compounds which were the chief subject of our investigation are not identical. For the sake of brevity the AlCl_3 condensation product will hereafter be designated by A and the Claisen's method product by B. We have seen that A and B have the same melting point, but that their boiling points differ by 17° , and that there is an apparent difference of crystal form.

Tests of solubility in ligroin were made. 50 cc. of solutions of each compound, saturated at 20° , were pipetted into tared beakers, evaporated to dryness, and the weight of the residues ascertained. These are the results:

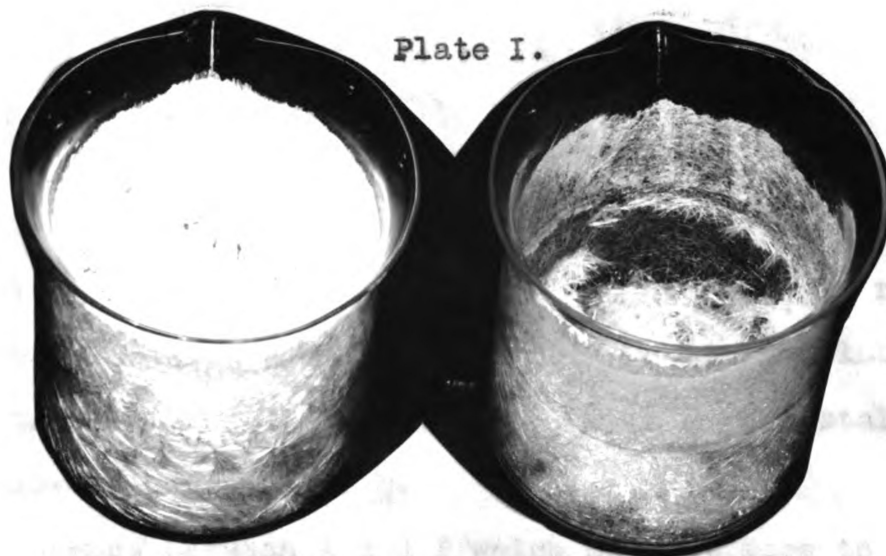
<u>A</u>	Trial I.	.5715 g.	Trial II.	.5743 g.
<u>B</u>	Trial I.	2.7210 g.	Trial II.	2.7392 g.

Thus we see that B is approximately five times as soluble in ligroin as A. A more concrete idea of comparative solubility may be obtained by looking at Plate I., page 20, which is a photograph of the two beakers containing the residues of Trial II.

This solubility test was also applied to the small quantity of impure crystals which came from the first washings of A, which had the same boiling point and crystal form as B. The available quantity was not sufficient to provide 50 cc. of solution, so 25 cc. was used. The residue weighed 1.3796 g. on first trial and 1.3889 g. on

Plate I.

B



A

Views of beakers containing the dried residues from ligroin solubility tests.

Plate II.



B

Above and to the right are shown natural size views of the crystal forms as they collect on the sides of the beakers during crystallization. The photographs were taken with the camera lens pointing obliquely downward toward the bottom of the beakers, and the tangled masses of A and the bundles and parallel arrangement of B are both clearly seen.

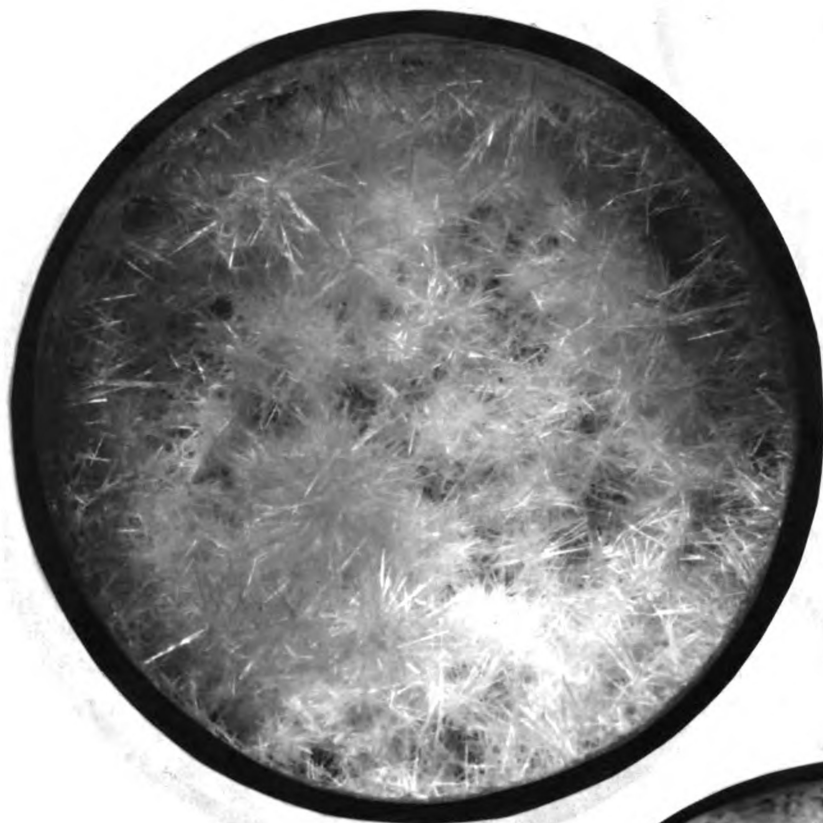
A



second trial. Since these crystals still contained some oily impurity, which was quite soluble in ligroin, the results check closely enough with those of the other solubility tests to amount to further evidence that the crystals were identical with those of B.

A difference between A and B which may not seem to be of much significance at present, but which may at some time prove to have a bearing on the relation of color to Chemical constitution, was also noted. While both compounds were colorless when freshly prepared, upon standing for some time, especially if exposed to the light, A began to develop a trace of pink color, and B of yellow. The presence of the oily impurity normally found in the crude products greatly hastened the appearance of these colors.

The crystal forms characteristic of A and B are hard to describe adequately. A gives white, flattened needles, or elongated platelets, with a hard, glassy glitter and a tendency to form in much-tangled masses. B gives long creamy-white needles, or fibers, with a soft, silky sheen and a tendency to lie parallel or form in bundles. This parallel arrangement can best be seen on the side of the beaker where the fibers cling during the process of crystallization. Plates II., III., IV., and V., found on pages 20, 22, 23, and 24, are natural size photographs of crystal masses formed under comparable conditions, and they help to give a clearer idea of comparative crystal forms.



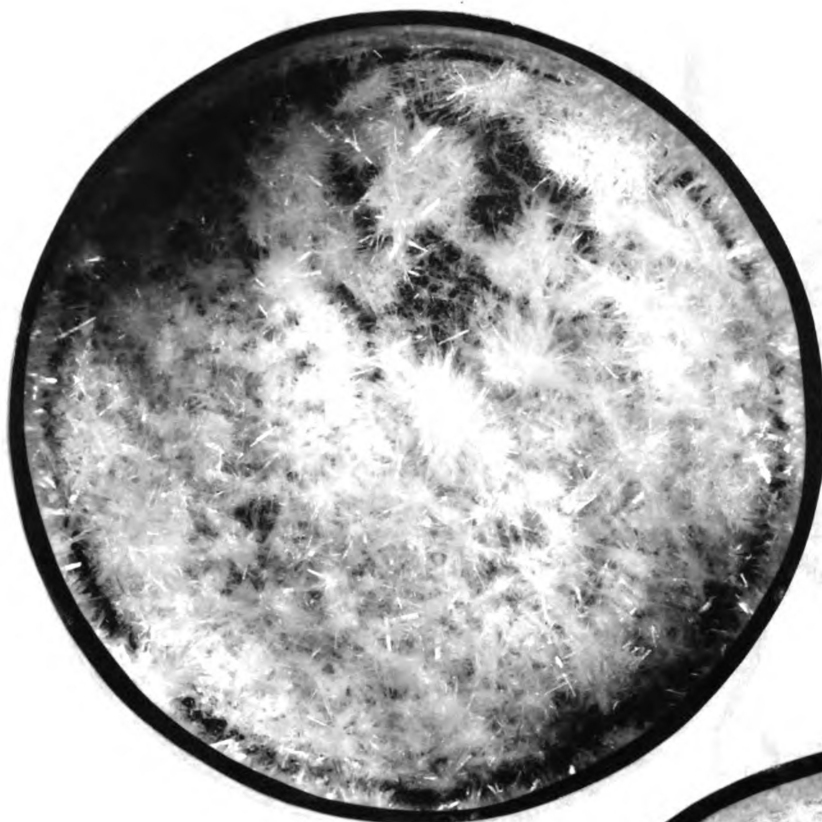
A

Plate III.

Natural size views of the crystal forms of A and B as they appear when looking down into a large beaker. The crystals shown in this plate were formed from saturated ligroin solutions in a room where the temperature was about 25°, and the air circulation good. Being formed rapidly, they are comparatively small and fine, those of B felting together somewhat.



B



A

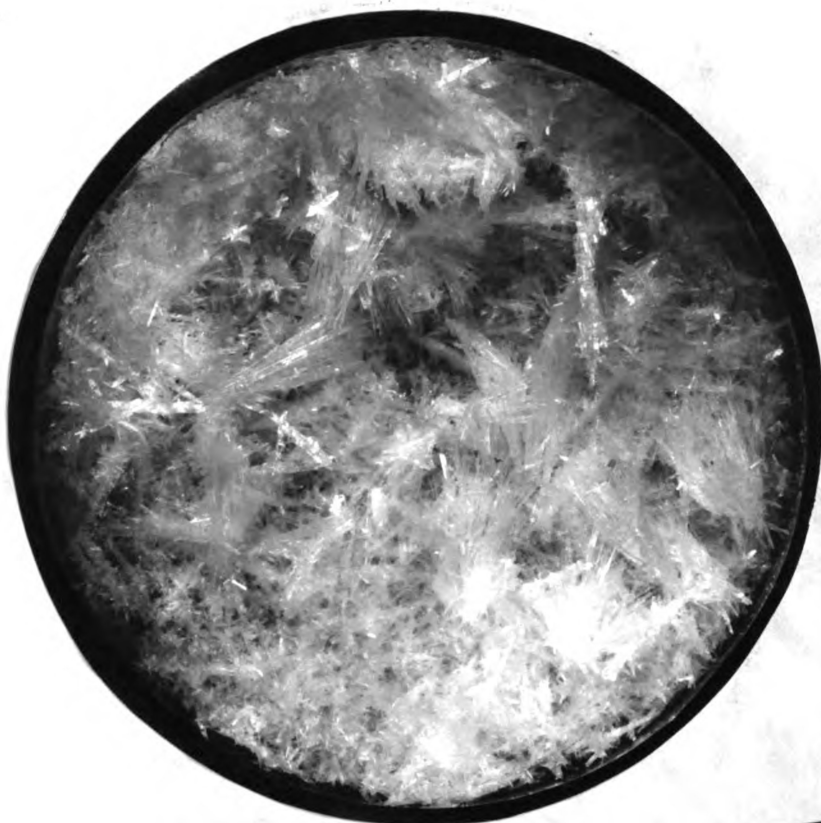
Plate IV.

These views were taken in the same way as those of Plate III, but the crystals were formed at a temperature of about 200° instead of 250° . Since evaporation was slower, there was more time for the crystals to build up into larger forms. In B there is no further sign of felting, but the crystal bundles begin to appear.

crystals in a few places, - 150° or 200° , - and adding a little more material. and from time to time after the crystals began to grow.



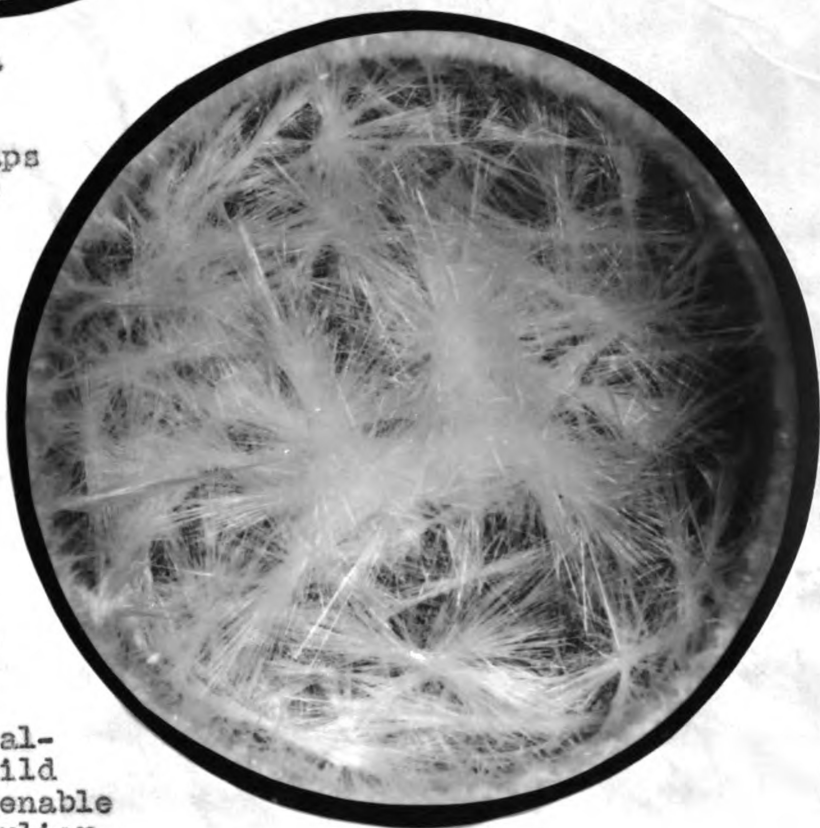
B



A

Plate V.

This plate gives perhaps the clearest idea of the difference between the crystal forms of A and B. The photographs were taken in the same way as those of the two previous plates. The crystals were formed slowly. Starting with solutions hardly saturated at 10° , placing the beakers in a cool place, - 15° or under, - and adding a little more saturated solution from time to time after the crystals began to form, allowed the crystals to build up to such a size as to enable one to discern their peculiar characteristics very plainly.



B

Further attempts were made to distinguish A from B by means of bromine and benzoyl derivatives. Here considerable difficulty was encountered. The bromine derivative of B was readily formed by treating it in CHCl_3 solution with an equivalent quantity of bromine. When recrystallized from ligroin it formed characteristic rosette-shaped crystals with a melting point of $63-64^\circ$. The reaction in CHCl_3 solution seemed to take place with A as readily as with B, but no crystals would form. Finally, in order to get some comparative data, larger quantities of the bromine derivatives were made and tested for boiling points. That of A boiled at $180-182^\circ$, (5 mm.), but that of B proved to have the unexpectedly high boiling point of $241-244^\circ$ under the same pressure. This great difference in boiling points led to a question as to whether the two compounds were really analogous bromine derivatives; and to settle this question a Parr bomb bromine determination was made, following the general method suggested by Lemp and Broderson. (J. Am. Ch. Soc. 39, 2069) The following are the results:

	Sample	AgBr	% Br_2
<u>A</u>	I. .2582 g.	.1763 g.	28.68
	II. .2071 g.	.1426 g.	28.87
<u>B</u>	I. .2259 g.	.1550 g.	28.82
	II. .2867 g.	.1961 g.	28.65

Theory, - for mono- brom derivatives, - is 28.48% of Br_2 .
This determination, therefore settled the question as to

the relation between the two compounds, indicating clearly that they were of the same empirical composition, and, taken in connection with their greatly differing boiling points, affording more evidence that the phenols from which they were derived, while doubtless isomeric, were surely not identical.

The benzoyl derivative of A was prepared without any difficulty. The phenol dissolved readily in an equivalent amount of 5% KOH. When this solution was treated with the calculated quantity of benzoyl chloride, a sticky mass of pale pink oil was formed. This gradually hardened when put in the ice-box. When washed with water till free from KCl, dissolved in ligroin, and purified by recrystallization from the same solvent, it formed small, colorless, transparent, rhombic crystals, with a melting point of 54-55°. The quantity available was too small to permit of making a boiling point test.

On the other hand, all attempts to prepare a crystalline benzoyl derivative of B resulted only in the formation of benzoic acid crystals and a small quantity of a nearly colorless oil. B would not dissolve in 5% KOH, even when five times the calculated quantity was used. It would dissolve in an equivalent amount of 50% KOH with a little warming, but separated again when the solution was diluted to 25% or less. The solution in 50% solidified on cooling, but appeared to react readily with benzoyl chloride if warmed again.

While the attempt to form a crystalline benzoyl derivative of B failed, yet the visible evidence that a reaction always occurred, and the presence of the oil along with the benzoic acid crystals, led to the idea that fractional distillation of this oil might yield a definite compound whose boiling point would distinguish it from other possible substances in the mixture, and thus establish it as the sought-for benzoyl derivative. Consequently a new and larger lot of the derivative was carefully prepared and fractionated. It yielded about 3 g. of a very viscous, light yellow oil, boiling sharply at 216-218° (5 mm.). This did not correspond with the boiling point of the original phenol, or of benzoic acid, or of any other known substance which could be present in the reaction mixture, hence there was no hesitation in pronouncing the oil the benzoyl derivative of B.

A study of the reactions which resulted in the formation of A and B led to the conclusion that they were isomeric, if not identical. More evidence of their isomerism has been found, notably the bromine content of their brom derivatives. Still further proof was afforded by combustion tests made on the two compounds:

Theory:	$C_{14}H_{14}O$:	C, 84.8%	H, 7.12%		
Found:	Subst.	CO ₂	H ₂ O	%C	%H
<u>A</u> (Huston)	.1523 g.	.4746 g.	.0971 g.	84.99	7.19
<u>B</u> (Swartout)	.1443 g.	.4473 g.	.0915 g.	84.50	7.07

A further word should be said about by-products. The ether which was formed along with B has already been mentioned. But during the distillation of the mixture which contained B, no evidence of the presence of any considerable quantity of any substance with a definite boiling point above 155° was seen. This was not true with the AlCl_3 condensation product. The large fraction boiling between 215° and 235° was significant, so this fraction was made the basis of further fractional distillation, nearly the whole of it finally coming over at $225\text{--}227^{\circ}$ (5 mm.). It was a thick yellow oil, which slowly darkened to an orange color. The yield, 77.2 g., was 19.0% of theory. This oil could not be made to produce crystals. An account of its behaviour toward alkali and benzyl chloride will be found in the conclusion, because of its bearing on the question of molecular configuration, which is discussed there; but it may be said here that we were led to believe the oil to be 2-methyl 4-6-dibenzyl phenol. A combustion made to test this idea gave the following results:

Theory: $\text{C}_{21}\text{H}_{20}\text{O}$: C, 87.45% H, 7.00%					
Found:	Subst.	CO_2	H_2O	%C	%H
	.4294 g.	1.3723 g.	.2686 g.	87.62	7.01

These results amount to a confirmation of our opinion.

CONCLUSION

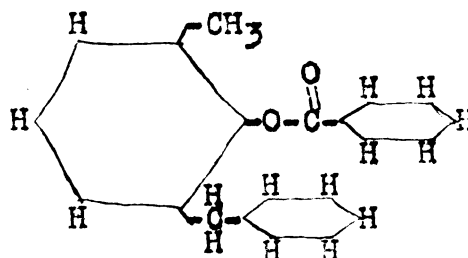
O- cresol has been benzylated by two different methods, yielding products which have been designated by A and B. That A and B were isomeric is not only theoretically

probable, but it has been proved true by analysis of bromine derivatives and by combustion tests. That they were not identical was proved by different boiling points, different solubilities in ligroin, different crystal forms, and differences as to the formation and character of their bromine and benzoyl derivatives. But it was also proved that the AlCl_3 condensation process resulted in the formation of a small proportion of a compound identical with B and a larger proportion of a high-boiling substance, along with the main product, which was designated by A.

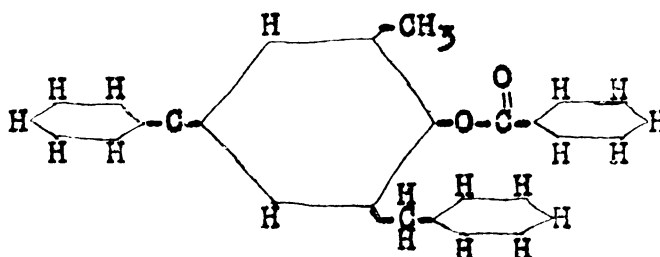
That this high-boiling compound was a phenol, and not an ether, was proved by its forming a solution in Claisen's methyl alcoholic potash, from which solution ligroin would extract nothing. We were unable, however, to prepare its benzoyl derivative, for though it slightly dissolved and turned blue and gummy in hot 50% KOH, benzoyl chloride did not react with it. It was upon these grounds, in addition to the combustion test, that this compound was named 2-methyl 4- 6-dibenzyl phenol.

According to the views of Claisen and other investigators, A was a p- and B an o- product, and we now have added evidence that these views are correct. The two substances were not identical, and one of them must have been the o- compound. The comparative difficulty of preparing the benzoyl derivative of B was strong evidence that this

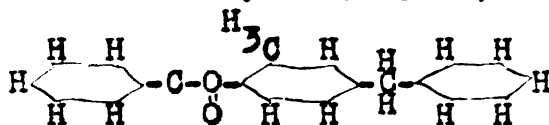
was the one, for such a derivative must have the following configuration:



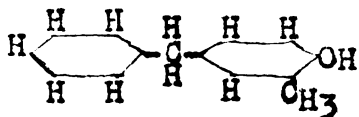
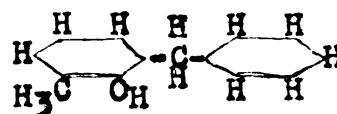
The difficulty of overcoming steric hindrance and heaping the methyl, the benzoyl, and the benzyl groups on adjacent carbon atoms must be considerable. And we should expect the same difficulty with the dibenzyl derivative, whose benzoyl derivative must be constituted thus:



On the other hand, the benzoyl derivative of the p- compound should be easy to prepare, for its configuration must be:



Since these conclusions accord so well with the observed behaviour of A and B, we not only conclude that they were different, but that A was 2-methyl 4-benzyl phenol, and B was 2-methyl 6-benzyl phenol.

AB

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