A SYNTHESIS OF 3-ACETYL-6-METHOXYBENZALDEHYDE UTILIZING THE FRIES REACTION

by

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INTRODUCTION

In the years since World War II there has been an increasing number of attempts to produce various types of effective herbicides, and as a result of the extensive time and labor required for random testing of synthetic compounds, the search for selective plant-killers has turned toward naturally occurring substances.

A notable example of this latter method has been provided by Gray and Bonner who observed that a species of desert shrub, *Encelia farinosa*, was always found growing in an area forsaken by virtually all other plant species. Accordingly, these men assumed that *Encelia farinosa* must contain a compound with strong herbicidal properties. Operating on this assumption, extracts of the leaves of this shrub were obtained and exhaustive studies were made on them. Among the compounds isolated from these extracts, Gray and Bonner identified one as 3-acetyl-6-methoxybenzaldehyde. Dilute solutions of this compound were found capable of killing a large number of tomato plant seedlings in a matter of hours.

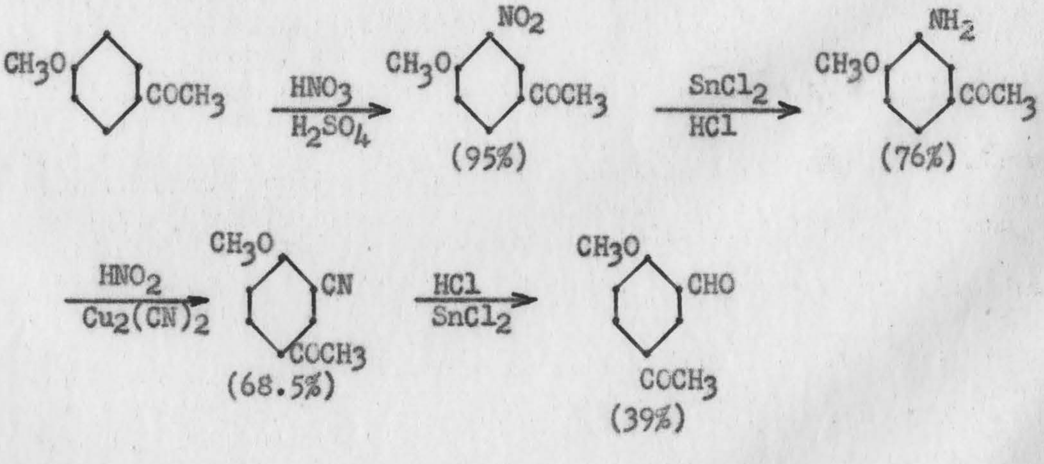
The comparative rarity of *Encelia farinosa* and the small quantities of 3-acetyl-6-methoxybenzaldehyde obtainable from each plant, however, prevented the performance of more extensive tests. Consequently, in order to determine the true value of the compound as a herbicide it became necessary to devise a synthetic method of preparation. Gray and Bonner, after some study, were able to synthesize the compound in small amounts. Their method, however, was so involved and the overall yield so low that it has been deemed impractical. Since this original synthesis several further attempts have been made to develop a more usable procedure, but thus far these methods have been unsuccessful. Therefore, it is again the purpose of this thesis to devise an efficient and more direct method for synthesizing 3-acetyl-6-methoxybenzaldehyde.

As a secondary objective of this thesis, an attempt has been made to evaluate the Fries reaction as a tool in organic syntheses. This task was undertaken primarily because most of the previous attempts to synthesize 3-acetyl-6-methoxybenzaldehyde have unsuccessfully employed several types of Fries reactions. To be sure, the chemical literature is not wanting in information on the Fries reaction, but the available information is at best poorly correlated and frequently contradictory. It is hoped, therefore, that the brief review presented in this thesis will serve in some measure to clarify the merits and limitations of the ubiquitous but elusive Fries reaction.

Part I: A Synthesis of 3-Acetyl-6-methoxybenzaldehyde

LITERATURE REVIEW

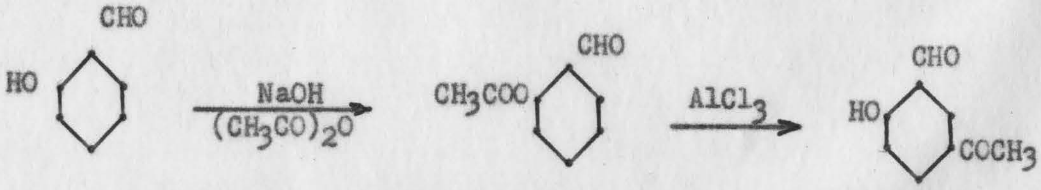
The original synthesis of 3-acetyl-6-methoxybenzaldehyde as made by Gray and Bonner[7] involves the introduction of the carbonyl group into the ring of p-methoxyacetophenone. The reactions for this procedure are shown below with the percentage yield for each step shown in parentheses.



From the above reactions it is readily seen that this method is rather involved and the total conversion is low. In addition, this series of reactions requires a considerable length of time to perform[6].

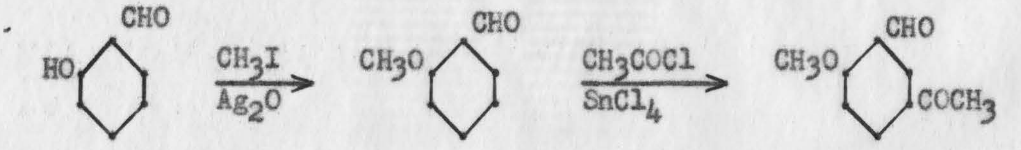
A number of attempts have since been made in order to improve the overall yield and to reduce the amount of time required.

Grymes[16] devised a method using salicylaldehyde as a starting material. In this method the salicylaldehyde was converted to the acetate which was to be rearranged to 3-acetyl-6-hydroxybenzaldehyde by means of a Fries reaction as is shown in the following series:



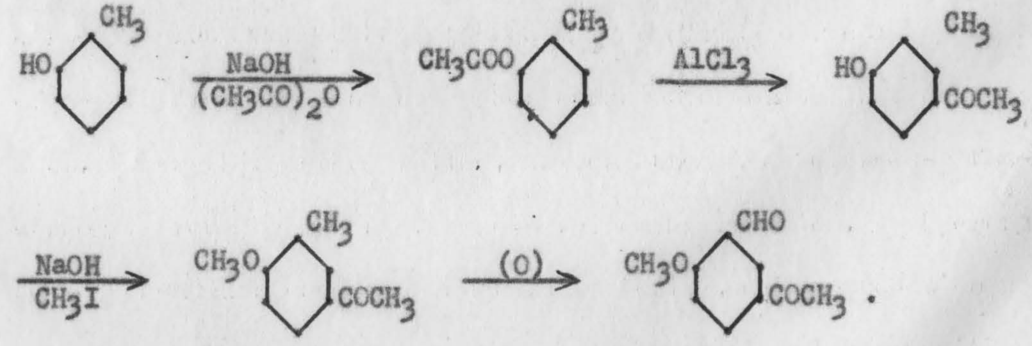
The Fries reaction, however, produced a resinous material from which no product was isolated. If this reaction had succeeded the hydroxyl group was to be methylated with methyl iodide in an alkaline solution. In another method attempted by Grymes the carbonyl group was to be introduced in the ring directly by means of N-methylformanilide using phosphorus oxychloride as a catalyst. When this method failed, Grymes attempted to produce the carbonyl group by means of a Reimer-Tiemann reaction. p-Hydroxyacetophenone was used as a starting material, but no reaction was observed to take place presumably because of the electron withdrawing effect of the acetyl group.

Several series of reactions were devised by Jackson[17] who investigated two lines of approaching the synthesis of 3-acetyl-6-methoxybenzaldehyde. In his first method Jackson used salicylaldehyde as a starting material. The reactions can be shown as follows:

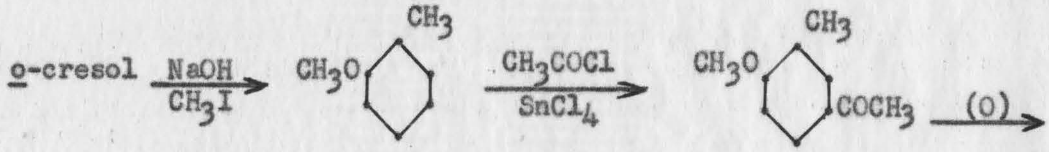


The methylation was carried out in good yields (76%), but the Friedel-Crafts reaction produced a solid material from which the catalyst could not be separated. This latter reaction was modified by using acetic anhydride with a $ZnCl_2$ catalyst, but the results were again disappointing and no product was obtained.

In a second method Jackson[17] used o-cresol as a starting material where the synthesis was to take place as shown below:



The rearrangement of o-cresyl acetate produced such low yields, however, that the above method was discarded in favor of a modified version:



Jackson reports the synthesis of 3-acetyl-6-methoxytoluene as successful though the yields are not given. Two types of oxidations were attempted in this method, one using acetic anhydride with chromic oxide, and another using manganese dioxide with sulfuric acid, but neither set of conditions seems to have met with any success.

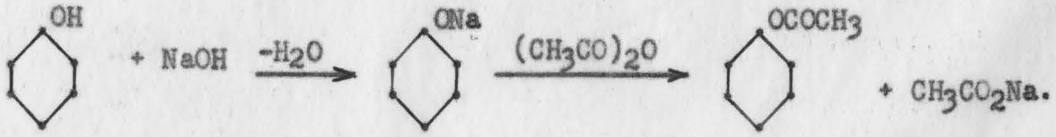
In a more recent investigation by Potter[28] the Fries reaction on o-cresyl acetate was again attempted, but the yields were very low (20-25%). Consequently, Potter attempted the synthesis of 3-acetyl-6-methoxytoluene by a series of reactions similar to that used by Jackson except that the acetylation of o-methoxytoluene was to be accomplished by acetic anhydride in the presence of $AlCl_3$ rather than the acetyl chloride-stannic chloride method employed by Jackson. This acetylation proved totally unsuccessful, and the synthesis was abandoned at this point.

EXPERIMENTAL

In deciding on the most satisfactory approach to the synthesis of 3-acetyl-6-methoxybenzaldehyde, it was considered advisable to ascertain the true value of various Fries reactions which had hitherto been suggested or attempted by other workers as first steps in the synthesis. Grymes[16] reported a successful yield of p-hydroxyacetophenone by the Fries rearrangement of phenyl acetate. This acetate was prepared in a yield of 57%, but the yield of the ketone was not reported. A Fries reaction was also attempted unsuccessfully by Grymes on the acetate of salicylaldehyde. This reaction was not repeated in this work, however, because of the recognized inhibiting effect of the carbonyl group. The third Fries reaction which might serve as the first step in the synthesis of 3-acetyl-6-methoxygenzaldehyde employs o-cresol acetate as the starting materia. This reaction has been investigated recently by Jackson[17] and Potter[28] who have reported yields of 20-25% of the theoretical quantity of 3-acetyl-6-hydroxytoluene. The findings of these men are supported by Thomas[37], but Blatt[1] has listed a yield of 80-85%. Thus, it has been one of the objects of this work to ascertain the yields which may be expected from the reaction.

Preparation of the Acetates of Phenol and the Three Cresols

In a number of preparations using different concentration ratios of reactants the yields of the esters were found to vary from 59% to 89%. The reactions for the esterification may be illustrated as shown below:



In the preparations carried out the most efficient procedure was found to be as follows:

1. One hundred eight grams (1.0 mole) of practical grade o-cresol is added to a solution of 40g (1.0 mole) sodium hydroxide in 300ml of water.
2. The solution is cooled in an ice bath, and 100g of ice are added to it to reduce the temperature to 5°C or less.
3. To the cold solution 102g (1.0 mole) of chilled acetic anhydride are added over a period of 15 minutes taking care that the temperature does not rise above 10°C. More ice may be added for this purpose if necessary.
4. The resulting mixture is allowed to stand 1/2 hour permitting the ester layer to separate. The density of ester layer, however, is so close to that of the water that the

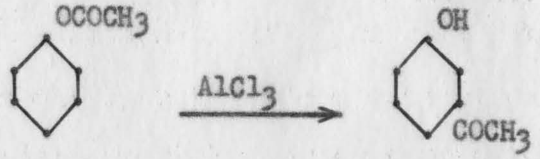
ester may either settle to the bottom or rise to the top depending on the concentration of dissolved salts. In either case an appreciable quantity of ester remains suspended in the water layer.

5. The organic layer, which is usually orange in color, is drawn off, dried with 5g of anhydrous magnesium sulfate, and distilled.
6. An additional 8-10g of the ester may be obtained from the water layer if desired by fractional distillation.

Using this procedure a yield of 135g (89%) of o-cresol acetate was obtained by simple distillation of the organic layer, and the ester so obtained boiled at 206°-208°C. This distillate had a specific gravity of 1.0963_{4}^{28} and a refractive index (n_D^{21}) of 1.5060. The amounts of the reactants in this procedure are rather critical for the yields were found to decrease when either acetic anhydride or o-cresol was used in excess. When sodium hydroxide was used in excess of the amount equivalent to the amount of o-cresol the yield of ester was again found to decrease. Slightly less than equivalent amounts of sodium hydroxide, however, tended to slightly favor the yield of ester. The yield from this method seems to be essentially independent of the volume of the solution.

This procedure is not restricted to the formation of o-cresyl acetate alone since approximately the same percentage yield of the desired ester was obtained when phenol, m-cresol, and p-cresol were substituted for the o-cresol.

Preparation of p-Hydroxyacetophenone



Five attempts were made to prepare p-hydroxyacetophenone by the above reaction, but of these attempts two were unsuccessful. In the first attempt 0.1 mole of phenyl acetate was dissolved in 30ml of nitrobenzene, and the solution was heated to 80°C. To the hot solution 0.15 mole of anhydrous aluminum chloride was added. After an hour the reaction mixture was poured into 200ml of ice and dilute HCl, and the nitrobenzene was removed by steam distillation. Since no crystals were observed in the residue from the distillation the mixture was discarded[16].

In a second unsuccessful attempt a mixture of 8g of aluminum chloride and 10g of phenyl acetate was heated at 140°C for 15 minutes, but on treating the reaction mixture with 1:1 HCl in ice no crystals were observed in the solution so the mixture was again discarded[1,31]. In both of these instances the yields would probably have been very low, and the fact that no product was observed may be attributed to an insufficient length of time for crystallization.

In the third attempt 0.075 mole of aluminum chloride was added portionwise to a solution of 0.05 mole of phenyl acetate in 50ml of nitrobenzene. This mixture was heated at 50°C for three hours and then 40ml of chilled 1:1 HCl was added. The nitrobenzene was removed by steam distillation. The residue from the distillation was evaporated to 50ml and cooled in an ice bath. After standing for a brief period this residue was filtered, and the crystals were collected and washed with 15ml of 1:1 HCl. These crystals were pink in color indicating an appreciable amount of impurities. Consequently, they were recrystallized from boiling water, but the discoloration persisted and even seemed to increase on heating indicating that the impurities consisted primarily of o-hydroxyacetophenone and complex aluminum salts. The weight of these crystals was 2.3g (33.8%) and they melted at 107°-108.5°C, or slightly below the reference melting point of 109°C.

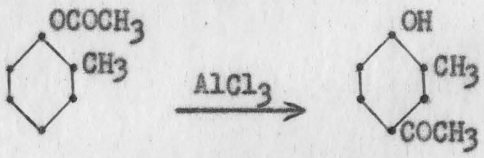
In the fourth attempt to prepare p-hydroxyacetophenone 0.15 mole of anhydrous aluminum chloride was added to a solution of 0.10 mole of phenyl acetate in 75ml of nitrobenzene. The mixture was allowed to stand overnight at room temperature[39] after which it was poured into 100ml of 25% HCl and steam-distilled. The residue was allowed to stand for two days. At the end of this time 1.3g (10%) of colorless crystals were collected which melted at 108.3°-109°C.

In the final preparation of p-hydroxyacetophenone 0.225 mole of anhydrous aluminum chloride was slowly added to a solution of 0.15 mole of phenyl acetate in 100ml of nitrobenzene. The mixture was heated at 60°-70°C for 3 hours with thorough stirring. During this reaction time a large amount of HCl was evolved. Next, the reaction mixture was poured into 100ml of 1:1 HCl and steam distilled. The residue was filtered after standing two days to give 4.3g of pale orange crystals. The filtrate was evaporated to about one-third of its volume to give on standing an additional 1.4g of light orange needles. The total yield from this preparation was then 5.7g (27%) of p-hydroxyacetophenone melting at about 108°-109°C.

The low yields in these preparations may be attributed to a number of factors, the most important being a slow reaction rate at low temperatures. Other factors include incomplete decomposition of the intermediate complex as shown by the persistent red color, reversal of the reaction during the steam distillation, and incomplete crystallization.

It is interesting to note that a conflict exists in the previously reported yields of p-hydroxyacetophenone from the Fries reaction. Several investigators[1] have reported yields of 75%, but Thomas[37] lists a probable yield of 30% for the o-hydroxyacetophenone implying that p-hydroxyacetophenone is formed in a yield of 30% or less since phenyl acetate apparently possesses no structural or electronic effects that should tend to favor the yield of the *para* derivative. This lower value is supported by the present work.

Preparation of 3-Acetyl-6-hydroxytoluene



A total of twelve attempts were made to prepare 3-acetyl-6-hydroxytoluene by the Fries rearrangement of o-cresyl acetate. This study was made using a variety of reaction conditions and concentration ratios in order to resolve the confusion existing between the reported yields of Blatt (80-85%)[1] and Thomas[37], Potter[28], and Jackson[17] (20-25%).

In the first three attempts 0.05 mole of o-cresyl acetate was heated with 0.075 mole of anhydrous aluminum chloride in 50ml of nitrobenzene[39] at temperatures of about 50°, 70°, and

80°C for three hours. No product was isolated from these preparations because of insufficient crystallization time. It was observed, however, that only very small amounts of HCl were evolved at temperatures below 70°C. Upon addition of cold dilute HCl to the reaction mixture a very heavy gelatinous precipitate, consisting mostly of aluminum oxides, was obtained. This precipitate proved very troublesome in view of the fact that it was readily precipitated or dissolved in the same aqueous media as the desired product.

* * * * *

Preparation 4: In this attempt 0.075 mole of aluminum chloride was again added to a solution of 0.05 mole of o-cresyl acetate in 50ml of nitrobenzene, and the resulting mixture was heated to 60°C for two hours. The mixture from the reaction was poured into 100ml of cold water to which 100ml of 25% HCl was added. This mixture was heated on a water bath until nearly colorless and was then extracted with 100ml of ether. The ether extract was in turn extracted with 30ml of 25% KOH. The alkaline extract was acidified with 1:1 HCl and allowed to stand until crystals had formed. A yield of 1.7g (23%) of near-white crystals was obtained.

Preparation 5: Using the quantities of ester and catalyst mentioned before in 35ml of nitrobenzene, the mixture was allowed to stand overnight at room temperature. The reaction mixture was then poured into 100ml of cold water to which 100ml of 25% HCl was added. This mixture was heated on a water bath, but it was observed that in this case the heating seemed to darken the mixture. Nevertheless, the mixture was extracted with 100ml of ether, and the ether was extracted with 15% aqueous KOH. No crystals were obtained by acidifying the KOH extract with 1:1 HCl.

Preparation 6: Using the same ratio of reactants as in the preceding preparations and 40ml of nitrobenzene as solvent, the mixture was heated at 60°C for two hours. The reaction mixture was poured slowly into 100ml of 10% NaOH solution and mixed thoroughly. The nitrobenzene was then removed by steam distillation. The residue was acidified with 1:1 HCl and extracted with 75ml of chloroform. After removing the chloroform by vacuum evaporation, approximately 0.5g of a dark red resin was obtained. The formation of this resinous material was attributed at the time to the use of an exceedingly active sample of anhydrous aluminum chloride which may have caused a more rapid reaction than desired.

Preparation 7: Using the same amounts of materials as in Preparation 6, the mixture was heated at 50°C for 2 hours, poured slowly into 100ml of 10% NaOH solution, and steam-distilled to remove the nitrobenzene. The residue from the distillation was acidified with concentrated HCl and extracted with 75ml of ether. The ether was then extracted with 15% NaOH. The entire extraction process was repeated using the same ether but fresh sodium hydroxide solution. The alkaline extracts were then acidified with concentrate HCl.

The various solutions obtained during this preparation were allowed to stand for about 24 hours with the following results:

(A) A portion of the acidified solution remaining from the steam distillation was filtered to remove the inorganic precipitate and allowed to stand. After about four hours the appearance of a few coarse needle-like crystals was noted. These crystals were straw-colored and melted sharply at 109°C. The molten substance was dark red, but on solidification the original color reappeared.

(B) The remainder of the aqueous solution after being extracted twice with ether was evaporated to a volume of 60ml. On standing, two distinct types of crystals were formed. One type consisted of coarse white granules which dissolved completely on the addition of a small amount of water. The second type was in the form of fine, light yellow needles which seemed to be unaffected by the addition of water. These needles were transformed to coarse, dark red granules by brief heating over a water bath. Prolonged heating changed the color to a light brown. The melting point of these crystals was 107-109°C.

(C) The ether solution after being extracted twice with NaOH was of an orange color. It was evaporated nearly to dryness, but only a very small amount of a viscous, dark red liquid was obtained.

(D) The first sodium hydroxide extract was acidified and allowed to stand overnight after which a thin layer of crystals appeared. The pattern of these crystals resembled that of an osazone. The crystals were predominantly white with some dark red discoloration, but on drying they became dark red and melted at about 105°C.

(E) The second sodium hydroxide extract was acidified and on standing produced the same type crystals described in (D). When these crystals were pulverized they became light gray, though on melting a dark red liquid was formed. The observed melting point was 107°C.

(F) The solid products of (B), (D), and (E) were assumed to be of approximately the same composition in view of the similarities of appearance and melting points. The combined weight of the mixed crystals was 2.3g. A portion (0.7g) of the combined solids was recrystallized from 27ml of boiling water and decolorized with charcoal. The purified crystals were white, flocculent needles weighing 0.37g, and melting at 109°C. It may be assumed, therefore, that the minimum yield from this particular preparation was 16%.

Preparation 8: In this attempt to prepare 3-acetyl-6-hydroxytoluene 20g (0.15 mole) of anhydrous aluminum chloride was added portionwise to a solution of 15g (0.10 mole) of o-cresyl acetate in 65ml of nitrobenzene. The mixture was heated at 40°C for 2.5 hours and then poured into 100ml of 15% KOH solution. The resulting mixture was steam-distilled to remove the nitrobenzene. The residue was made slightly acidic with concentrated HCl and filtered immediately to remove the inorganic sediment. The filtrate was then allowed to stand overnight. The crystals formed during this period were collected and recrystallized from 100ml of boiling water containing about 3g of charcoal.

The purified product weighed 2.4g (16%) and appeared as small white needles melting sharply at 109°C.

Preparation 9: Using the same quantities of material as in Preparation 8, the mixture was heated at 65-75°C for 30 minutes with thorough stirring to facilitate the evolution of HCl. During the heating the reaction mixture turned nearly black. The mixture was then poured into 100ml of 20% KOH which failed to completely neutralize the mixture. The acidic mixture was steam-distilled, and the residue from the distillation was poured into 100ml of 1:1 HCl. After standing overnight, the crystals formed were separated and recrystallized from boiling water containing 3g of charcoal. The weight of 3-acetyl-6-hydroxytoluene thus obtained was 2.7g (18%). The melting point of the product was 108-109°C.

Preparation 10: A solution of 75g (0.5 mole) o-cresyl acetate in 200ml of nitrobenzene was treated with 100g (0.75 mole) of anhydrous aluminum chloride and the mixture was heated at 60-70°C with stirring for 1.5 hours. At the end of this time it was poured into 100ml of 1:1 HCl and steam-distilled. The residue was allowed to stand for 48 hours and was then extracted with ether. The ether was extracted with NaOH solution which was then acidified. After standing, about 7.5g of impure 3-acetyl-6-hydroxytoluene was collected and recrystallized from boiling water to give a yield of 6.3g (8%) of crystals melting at 107-109°C.

In this preparation as in all previous instances in this work where a Fries reaction has been involved, a reddish black substance appears during the initial stages of the reaction. This substance appears first as an oil, but it quickly solidifies at room temperature. The solid presents the appearance of a heterogeneous resin so familiar in the very rapid Fries reactions, but in every case it was easily dissolved in NaOH solution and reprecipitated without change by neutralizing with HCl. Furthermore, a relatively pure sample of 3-acetyl-6-hydroxytoluene in the form of white crystals will yield a significant amount of the dark oil when the crystals are dissolved in boiling water. The dark colored solid was at first thought to be a mixture of aluminum oxides and aluminum salts of the ortho and para-hydroxy ketones, but this conjecture is open to serious question. Apparently, however, heating seems to greatly favor its formation up to a point.

Approximately 30g of the solid material was obtained in this preparation. When this dark red substance was dissolved in aqueous NaOH, the solution possessed a reddish brown color. Several samples of this solution were heated to boiling with a little charcoal and acidified with HCl. The mixture was then filtered while hot. The filtrate upon cooling produced a surprisingly large amount of yellow, needle-shaped crystals which melted at 107-108.5°C. Subsequent investigations have shown that by the application of heat, neutralization, and decolorization a large portion of the resin-like substance can be transformed into pale yellow to colorless crystals. That is, at least 50% of the dark colored material is, or is converted to 3-acetyl-6-hydroxytoluene. The time required to obtain the product in the form of clear crystals, however, is so great that this method is hardly practical on more than a very small scale.

Preparation 11: In this preparation 62.5g (0.50 mole) of anhydrous aluminum chloride was added over a period of 15 minutes to a solution of 45g (0.30 mole) of o-cresyl acetate in 100ml of nitrobenzene. The mixture was allowed to stand overnight with thorough stirring, and was then poured very slowly into 100ml of 25% NaOH. This mixture was steam-distilled and poured slowly into 200ml of chilled 20% HCl. The resulting mixture was allowed to stand about two days after which it was filtered, and the impure solid was recrystallized from boiling water. The purified product weighed 16.4g (36.5%).

Preparation 12: Seventy-five grams (0.5 mole) of o-cresyl acetate was dissolved in 300ml of nitrobenzene. To this solution 100g (0.75 mole) of anhydrous aluminum chloride was added in portions, and the resulting solution was allowed to stand with stirring for 48 hours. After this time had elapsed the reaction mixture was poured into one liter of 1M NaOH. The mixture was then steam-distilled until nitrobenzene ceased to be carried over. The residue was acidified with 1:1 HCl and the steam distillation repeated. Only about a gram of impure 5-acetyl-6-hydroxytoluene was obtained[3]. The residue from the second distillation was evaporated to one-third of its original volume and allowed to stand. The yield of 3-acetyl-6-hydroxytoluene was estimated as somewhat less than 20%, but the crystals were not purified. The organic layer of the first steam-distillate, which turned dark orange on standing, was washed first with 5% NaOH and then with water, dried with magnesium sulfate, and distilled. The distillate boiling at 205-212°C was collected. This distillate weighed 207g and was assumed to consist solely of nitrobenzene and o-cresyl acetate. A sample of the distillate weighing 26.62g was saponified by refluxing for one hour with 75ml of 0.873M alcoholic KOH. By titrating the saponified solution with 0.10N HCl using a methyl orange indicator the content of o-cresyl acetate was found to be 29.8g for the total distillate. A second sample of the distillate weighing 26.85g was saponified using 75ml of 0.873M KOH and refluxing for 1.5 hours. The total content of o-cresyl acetate in the distillate on the basis of the second sample was 33.9g. In other words, these saponification values indicate respectively that only 39.8% and 45.3% of the original amount of o-cresyl acetate was not used up in the Fries reaction. These values are obviously far below the true value since a portion of the steam distillate was discarded and the possibility of saponification during the steam-distillation of the alkaline mixture is ignored. An investigation of the ester content was also made by a comparison of refractive indices. This investigation showed that the distillate contained 8 mole per cent of o-cresyl acetate. If it is assumed that the entire amount of solvent is steam-distilled along with a consistent amount of o-cresyl acetate, the amount of unreacted ester is 78.9% of the original amount. This value compares favorably with that of 65% obtained by similar methods in another preparation where the yield of 3-acetyl-6-hydroxytoluene was somewhat higher.

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In the preceding preparations the detailed procedures have been given for the preparation of 3-acetyl-6-hydroxytoluene, and from these preparations it is possible to draw several conclusions.

First, the yield of 3-acetyl-6-hydroxytoluene obtainable by the Fries rearrangement of o-cresyl acetate is unlimited from the theoretical viewpoint, but there seems to be at present a practical limit which depends upon the procedure employed. Apparently an equilibrium exists between o-cresyl acetate, o-aceto-o-cresol, and p-aceto-o-cresol. This equilibrium is shifted away from the p-aceto-o-cresol by heat, but the reaction rate is too slow at room temperature to give a high yield of the p-hydroxy ketone. The optimum temperature seems to be 40-70°C. The ratio of solvent to ester has little effect on the reaction, but the most satisfactory ratio of catalyst to ester seems to be the accepted value of 3:2[39].

Second, the dark red resin described earlier evidently consists primarily of varying amounts of 3-acetyl-6-hydroxytoluene and an aluminum complex of the ketone with lesser amounts of solvent-catalyst complex, o-cresyl acetate, and various inorganic compounds.

Third, the doubt as to the true nature of the tetragonal clear crystals obtained from the rearrangement of o-cresyl acetate has been resolved. This doubt was occasioned by the discrepancy between the observed melting point of the crystals and the value of 104°C reported by Nencki and Stoeber[21] and by the similarities between the observed value and the melting point of p-hydroxyacetophenone. These facts led to the idea that an intermolecular migration of a methyl group, a phenomenon not unknown in Fries reactions, may have occurred. A considerable depression in a mixed melting point indicated that the compounds were not identical, but more positive confirmation seemed desirable. X-ray diffraction patterns of both 3-acetyl-6-hydroxytoluene, and p-hydroxyacetophenone were therefore made to determine if the two products were identical. A comparison of the two patterns showed that the two compounds were indeed similar, but the differences were sufficient to confirm the fact that the two compounds were not identical. Further proof was provided by the fact that an ether solution of p-hydroxyacetophenone showed total light absorption in the region 2200-3500Å whereas an ether solution of approximately the same concentration of 3-acetyl-6-hydroxytoluene showed total absorption in the region 2200-3600Å. A satisfactory identification of the crystals in question was obtained by a comparison of the molar refractivities. The refractive index of the crystals in doubt was found to be 1.62 (n_D). Using this value and 1.24g/ml as the density at the same temperature, the experimentally determined molar refractivity was 42.7 which is in very good agreement with the calculated value of 43.457. Using the same quantities the experimentally determined molar refractivity of p-hydroxyacetophenone was 29.4 which is in very poor agreement with the calculated value of 37.739. Both of the preceding

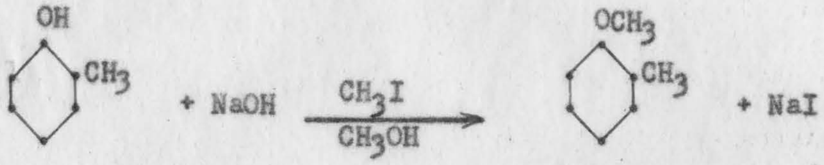
Table I. Effect of Conditions on Yields of 3-Acetyl-6-hydroxytoluene from o-Cresyl Acetate

Prep. No.	Volume of Solvent / Unit Vol. Ester	Time (hr.)	Temp. (°C)	Method of Decomposition	Method of Separation	Yield
4	7.4	2.0	60	10% HCl	ether extraction	23%
5	5.2	24	(25)	10% HCl	ether extraction	--
6	5.9	2.0	60	10% NaOH	steam dist. plus $CHCl_3$ extraction	--
7	5.9	2.0	50	10% NaOH	steam dist. plus Et_2O extr.	16%
8	4.8	2.5	40	15% KOH	steam dist.	16%
9	4.8	0.5	65-75	20% KOH	steam dist.	18%
10	3.0	1.5	60-70	1:1 HCl	steam dist.	8%
11	2.5	24	(25)	25% NaOH	steam dist.	36.5%
12	4.4	48	(25)	1M NaOH	steam dist.	20%

Note: In all preparations the catalyst-ester ratio was essentially constant at 1.5 moles of catalyst per mole of ester.

calculated molar refractivities include an exaltation factor of 1.76 as a result of the extranuclear conjugated double bond. It is therefore concluded that the product obtained in this work by the rearrangement of o-cresyl acetate is 3-acetyl-6-hydroxytoluene which has a melting point within the range 107.9-109.8°C.

Preparation of 3-Acetyl-6-methoxytoluene



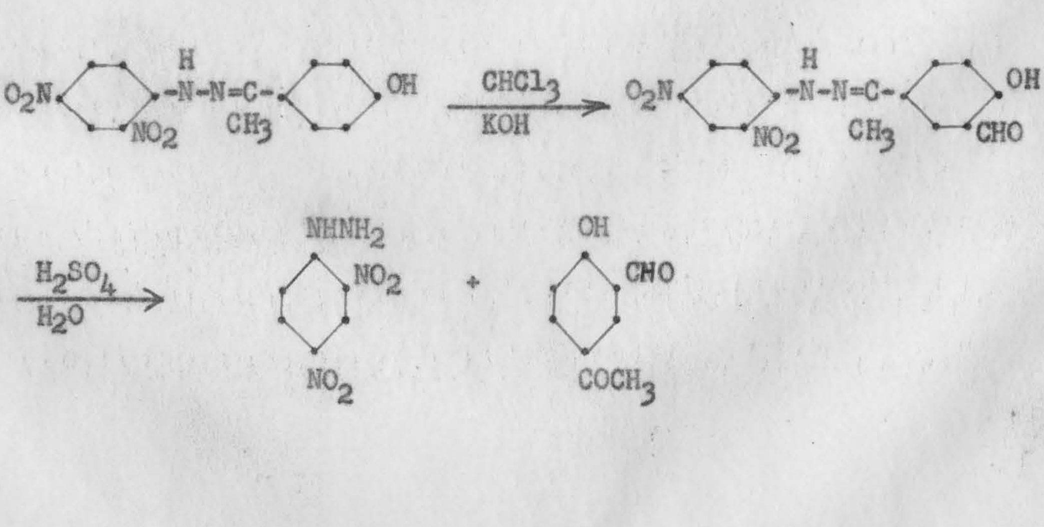
Several attempts were made to prepare 3-acetyl-6-methoxytoluene utilizing the information obtained by Jackson[17], Grymes[16], and Potter[28]. In the first attempt 3g (0.02 mole) of 3-acetyl-6-hydroxytoluene was dissolved in a solution of 2g (0.05 mole) NaOH in 20ml of methanol. To this solution 7.1g (0.05 mole) of methyl iodide was added, and the resulting solution was refluxed for one hour over a water bath. The reaction mixture was then poured into 100ml of 5% HCl and the mixture was evaporated to 1/3 of its original volume. After standing for two days at about 0°C, the crystals were collected and found to weigh 1.17g.

In a second preparation 1.4g (0.0093 mole) of 3-acetyl-6-hydroxytoluene was dissolved in a solution of 1g (0.025 mole) of NaOH in 20ml of methanol. Again 7.1g (0.05 mole) of methyl iodide was added, and the mixture was refluxed for 1.5 hours over a water bath. The reaction mixture was poured into 100ml of 10% HCl and evaporated to 1/2 volume. The mixture was then chilled in an ice-salt mixture for 15 hours. At the end of this time 0.883g of long, straw-colored needles were collected which melted considerably below 60°C.

In the final attempt to prepare 3-acetyl-6-methoxytoluene 4g (0.1 mole) of NaOH was added to a solution of 15g (0.1 mole) of 3-acetyl-6-hydroxytoluene in 300ml of methanol. To the resulting solution 21.3g (0.15 mole) of methyl iodide was added, and the mixture was refluxed for 1 hour and 15 minutes over a water bath. The reaction mixture was then distilled at atmospheric pressure. After collecting 250ml of distillate boiling at 64-65°C, the distillation was continued at a pressure of 30-40mm. The vacuum distillation failed to produce any appreciable distillate and the contents of the distilling flask charred very readily. This preparation resembles those of Potter[28] who obtained similar results. A paper by Noller and Adams[23] in which 3-acetyl-6-methoxytoluene was prepared in a 73% yield by the acylation of <u>o</u>-methoxytoluene, and a similar preparation by Jackson[17], however, indicate that the vacuum distillation should proceed without difficulty. The melting point of the compound given by Noller and Adams is 26-26.5°C and the boiling point is 116°C at 3mm or 273.5°C at 744 mm.

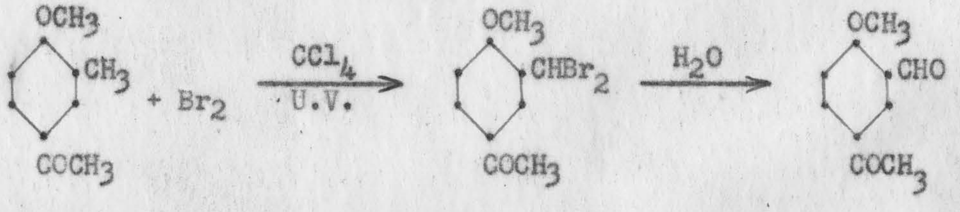
Preparation of 3-Acetyl-6-hydroxybenzaldehyde

In this preparation p-hydroxyacetophenone-2,4-dinitrophenylhydrazine (mp 68°C) was prepared in a nearly quantitative yield, and 3.2g (0.015 mole) of the addition product was dissolved in a solution of 5.6g (0.1 mole) KOH in 20ml of water. The resulting solution immediately turned nearly black. To this solution 12g (0.1 mole) of chloroform was added and the resulting mixture was refluxed for one hour. It was then steam-distilled to remove the excess chloroform and acidified with dilute sulfuric acid. On standing a dark brown solid was precipitated which formed in small clumps of reddish-brown, wool-like fibers on drying. This substance was found to give a positive Fehling's test, but it was not purified or examined further. The reaction presumably took place as shown below:



From a consideration of the preceding reactions it is probable that the positive Fehling's test was produced by the regenerated dinitrophenylhydrazine rather than by 3-acetyl-6-hydroxybenzaldehyde. Thus, the feasibility of a Reimer-Tieman reaction is very much open to question in this case[16] in spite of the analogous case where a 14.7% yield of the 2-aldehyde was obtained from p-hydroxybenzoic acid[2].

Preparation of 3-Acetyl-6-methoxybenzaldehyde

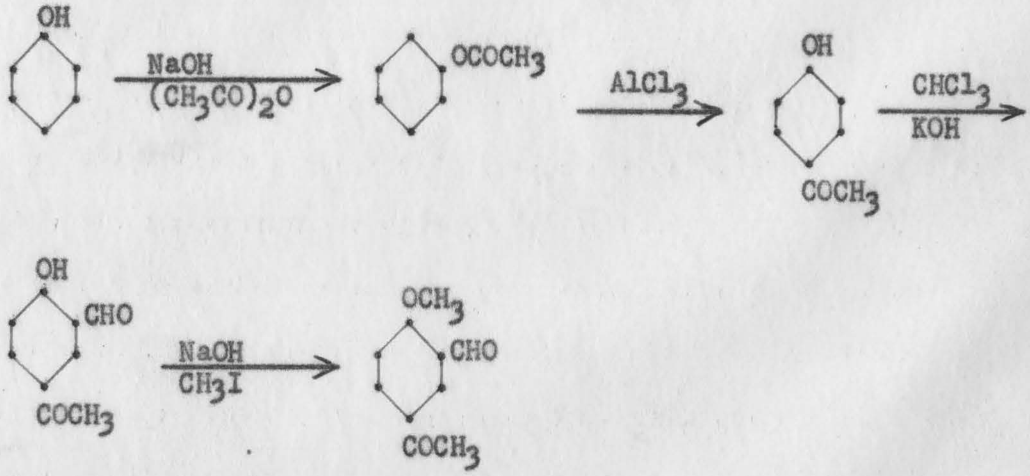


In order to decide the value of the above reactions an investigation of the facility of the addition or substitution of bromine was made on several compounds containing similar groups. It was known that bromine would displace two of the hydrogens on the methyl group of toluene and would not easily replace the third since a procedure had been developed for the formation of p-bromobenzal bromide from p-bromotoluene in a 60-69% yield[24]. Since the literature was apparently devoid of information on the side-chain bromination of sensitive polyfunctional aromatic molecules, however, several qualitative trials were made on the rate at which certain compounds would decolorize solutions of bromine in carbon tetrachloride. Accordingly, it was found that while toluene, anisole, and acetophenone decolorized the solution very rapidly, p-methoxyacetophenone was very much less active. It was concluded, therefore, that the bromination of 3-acetyl-6-methoxytoluene should occur to the greatest extent at the methyl group directly attached to the ring.

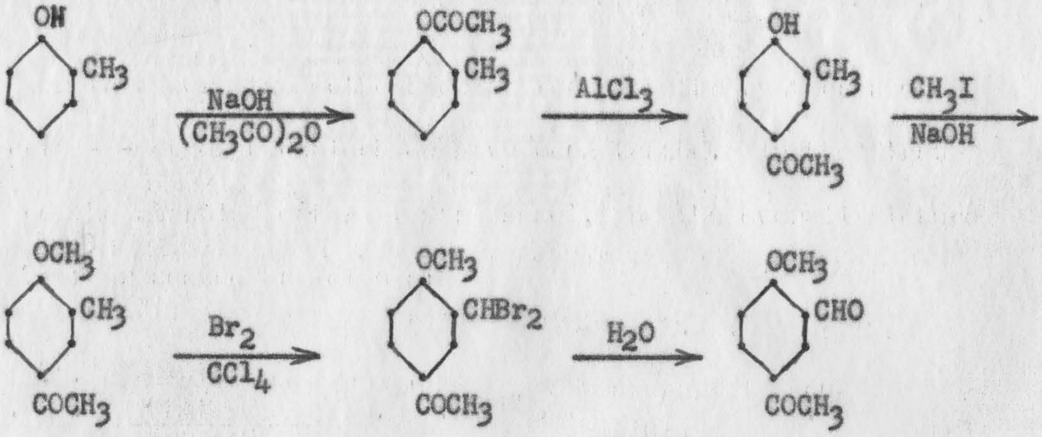
In this final stage of the synthesis of 3-acetyl-6-methoxybenzaldehyde approximately 0.6g of impure 3-acetyl-6-methoxytoluene was dissolved in 10ml of CCl_4 and 15ml of ethanol since it is rather insoluble in CCl_4 alone. This solution in a test tube was placed under a 150 watt, unfrosted tungsten filament lamp[24] at a temperature of 40-50°C. To this solution approximately one gram of bromine in 5ml of CCl_4 was added and the reaction was allowed to continue for 7 minutes. At this time, the solution was a pale yellow. Steam was then bubbled through the solution to hydrolyze the 3-acetyl-6-methoxybenzal bromide and simultaneously remove the CCl_4. During the hydrolysis the appearance of a flocculent precipitate was noticed in the test tube. This precipitate after drying appeared as reddish-orange grains. These grains were recrystallized once from boiling water to give approximately 0.2g of a white powder which melted at 142.3-143.5°C. This powder was soluble in hot water or ethanol and gave a pale yellow solution in both cases. It was insoluble, however, in cold water, cold ethanol, ether, and carbon tetrachloride. This powder was found to leave no residue on ignition. In all of these qualities this compound resembles the compound identified by Gray and Bonner[7] as 3-acetyl-6-methoxybenzaldehyde which melted at 144°C. In addition, this compound readily gave a positive Fehling's test, but it gave no color with alcoholic ferric chloride solution. The compound also formed a bright red solid with 2,4-dinitrophenylhydrazine which showed signs of decomposition at 121°C but was still in the solid state at 200°C.

SUMMARY

In this work two methods of approach to the synthesis of 3-acetyl-6-methoxybenzaldehyde have been tested. In the first method the starting material was phenol, and the overall picture may be represented as follows:



This method proved unsatisfactory as a result of the failure of the Reimer-Tieman reaction. In the second line of approach the starting material was <u>o</u>-cresol. The overall synthesis may be represented by the reactions shown below.



The above series of reactions proved successful and therefore represents a total synthesis of 3-acetyl-6-methoxybenzaldehyde. This synthesis has the advantage over that developed by Gray and Bonner (cf. page 1) in that the carbonyl carbon is originally present in the molecule. A further advantage of this synthesis is a relatively high yield for each step with the exception of the Fries reaction. Even in this step the unreacted ester is easily recovered and can be re-used. Finally, by considering 3-acetyl-6-methoxytoluene as a starting material comparable to the *p*-methoxyacetophenone used by Gray and Bonner it is seen that the number of reactions involved has been reduced from four to two which can be carried out *in situ* without isolating the intermediate.

In conclusion, it must be recalled that neither of the lines of approach utilized in this work are original, but only represent a continuation and enlargement of the work of Jackson[17], Potter[28], and Grymes[16]. This work has confimed, however, the expectations of Grymes in that a method of directly introducing the carbonyl group into a ring containing an acetyl group is most unlikely. This work has also shows that a Fries rearrangement of _o_-cresyl acetate may be employed with a high over-all yield in the synthesis of 3-acetyl-6-methoxybenzaldehyde.

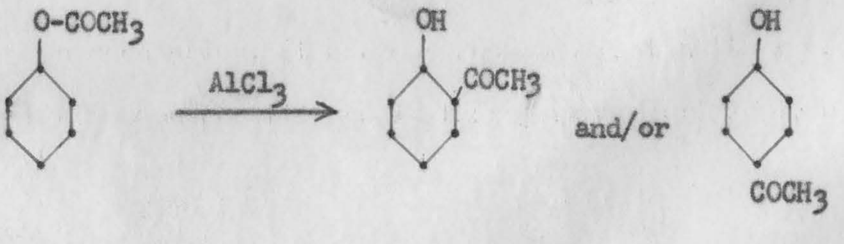
SUGGESTIONS FOR FUTURE RESEARCH

During the course of this work several features have come to light which obviously have an important bearing on the synthesis presented, but which have not been investigated. The most important of these is a study of the effect of various conditions on the efficiency of the bromination of 3-acetyl-6-methoxytoluene. Another phase of interest is a search for satisfactory methods of preparing 3-acetyl-6-methoxytoluene only three of which have apparently been found[17,23]. A third feature of great interest and importance in this work is an investigation of the kinetics of the Fries rearrangement of o-cresyl acetate. Such a study could not help having far-reaching effects in relating the many empirical observations governing this and other Fries reactions.

Part II: Review of the Fries Reaction

The Fries reaction was first recognized as a distinct type of reaction in about 1897 by the German chemist Karl Fries[10], but it was not until 1908 that information about this reaction appeared in the literature as abstracts from papers presented by Fries and G. Finck[11] at Marburg University. These papers dealt with a new method for producing hydroxy-acetophenones from the corresponding acetates, particularly 2-hydroxy-5-methyl- -chloroacetophenone, as intermediates in the preparation of various coumanones. In this work the *ortho* hydroxy-ketone derivatives of *m*- and *p*-tolyl acetates were obtained in yields of about 80%.

Since the discovery of the Fries reaction a great deal of information concerning various applications and mechanisms has been published with the net effect that the scope and value of the reaction in synthetic work is still a controversial matter. The general nature of the reaction may be shown, however, by the classical example of phenyl acetate which by varying the temperature can be made to undergo rearrangement to the *ortho* and *para* hydroxyacetophenones in the presence of anhydrous aluminum chloride.



(1)

The conditions affecting the Fries reaction are the nature of the ester, temperature, and solvent. The amount of reactants used does not seem to affect the product of the reaction, but it may show a pronounced effect on the yields obtained.

Nature of the Ester   A vast amount of study has been made on the scope of the Fries reaction with regard to the nature of esters which can be made to undergo rearrangement in appreciable amounts. In general, the reaction may be said to apply to any phenyl ester of a carboxylic acid, and Claisen (1912)[8] has shown that a similar reaction occurs with a number of phenyl-alkyl ethers. Unfortunately, very little work has been done in the way of an investigation of the Fries reaction in thio esters[36] and thio ethers, but it is quite reasonable to assume that the reaction will proceed in much the same manner with such compounds as it does with the corresponding oxygen-containing molecules.

The effect of substituents in the phenol has a pronounced effect on the course and extent of the Fries reaction. "The presence of a single alkyl group or halogen atom in the nucleus introduces no complications. A nitro or benzoyl group in either the ortho or para position to the hydroxy group stops the reaction"[5]. As a matter of fact, nearly all strongly meta-directing groups such as nitro, carboxylic, acyl, and carbonyl groups will show a marked inhibiting effect on the reaction if they are present in either an ortho or para position to the ester linkage; whereas electron-releasing groups such as alkyl, hydroxyl, alkoxy, amino, and imino groups will have very little effect on the reaction if they are present in either the ortho or para position. If, however, these electron-releasing groups are located in the meta position, they usually tend to facilitate the reaction. In some cases the presence of electron-releasing groups in the ortho position will have an inhibiting effect on the Fries reaction, but in such cases the effect is probably attributable to steric hindrance. These qualifications are rather well illustrated by the results obtained from experiments on the Fries reaction using acetates of the three cresols. m-Cresyl acetate gives a very high yield of both o- and p-hydroxyacetophenones, p- cresyl acetate gives fairly high yields of o-hydroxyacetophenone, but o-cresyl acetate gives low yields of both o- and p-hydroxyacetophenones. The methyl group, of course, remains unchanged by the reaction in every case. A rather thorough study and review of the effect of different alkyl substituents in a position meta to the hydroxy group[1,5,37] has shown that a methyl group has the most noticeable accelerating effect, and that the influence gradually with increases in chain length for chains of two to ten carbon atoms. Branched chain radicals in general exert a stronger influence on the reaction than the corresponding straight-chain groups.

The nature of the acid radical seems to exert only a slight influence on the ease with which a Fries reaction will take place. As examples, the phenyl esters of -chloro-[10,11], -hydroxy-, and -nitro-acetic acids will undergo rearrangement to the *p*-hydroxy ketones in yields of 75% or better[13]. "The length of the acyl chain does not appear to affect the relative yields of *p* and *o*-hydroxy ketones. Yields of *p* isomers as high as 74.2% were obtained with the C_{10} acyl chloride by heating 0.22 mole of $AlCl_3$, 0.11 mole of phenol, and 0.1 mole of RCOCl at 70°C for 3 hours"[29]. In addition, Sen and Parmar[32] have found that esters of crotonic acid can be rearranged in yields up to 96.8%. In a study of the effect of increasing acid chain length, Blatt found that for the *m*-cresyl esters of propionic, butyric, valeric, and caproic acids the yields of the *p*-hydroxy ketones ranged between 62% and 72% with no uniformity. In an investigation of phenyl-substituted acids a decrease in yields was observed with an increase in the length of the alkyl portion of the acid from a nearly quantitative yield of the *para* derivative for benzoic acid to about 70% for cinnamic acid using esters of unsubstituted phenols.

Polyalkylated phenols present a number of abnormal reactions when subjected to a Fries reaction. These abnormalities, however, may be classified in several groups. The first group is composed of those molecules which rearrange to give the normal derivative with respect to the acyl rearrangement, but one of the alkyl substituents is rearranged to another position on the ring. The second group contains for the most part those compounds in which an alkyl group is displaced by the acyl group, and the displaced group migrates to another position in the ring. The third group comprises those esters which in undergoing rearrangement suffer the complete loss of an alkyl group. This type of reaction is demonstrated by the use of such solvents as benzene which after the reaction is found to be partially converted to an alkylated benzene. It would seem that these abnormalities are the result of a reverse Friedel-Crafts reaction in which an alkyl radical is removed from the ring by the action of the catalyst, and then is resubstituted to another position. For this reason it is very difficult, nearly impossible, to predict with certainty the nature of the final products of a Fries reaction on a polyalkylated phenyl ester.

Nature of the Catalyst   The catalysts used in the Fries reaction are, for the most part, the same as those used in the Friedel-Crafts reaction. These catalysts are all strong acids, and as a result they react with the ester to form a complex salt as an intermediate. These intermediates usually impart a red or green color to the solution, and frequently they possess a high degree of stability. In some cases it is even necessary to reflux the complex in an acidic solution in order to decompose it. The catalyst by means of these intermediate products therefore serves to lower the energy requirements for rearrangement. This role of the catalyst is shown by the fact that some phenyl esters can be made to rearrange to the hydroxy ketones by the application of heat alone[39,40]. The most generally used Fries reaction catalysts in order of their decreasing reactivity are: $AlCl_3$, $FeCl_3$, $ZnCl_2$, H_3PO_4, BF_3. Boron trifluoride is seldom used because of its tendency to produce numerous undesirable side reactions. From the preceding list it should not be thought that because aluminum chloride is the most reactive catalyst that it is automatically the most efficient. The above list indicates only the relative facility with which a particular catalyst will cause a rearrangement. In reactive esters the higher members of the series will cause such a rapid reaction that the products are mostly tars. A very important feature of every Fries reaction catalyst is that its reactivity depends on being completely anhydrous. This requirement follows naturally from the effect of water in decreasing the acidic nature of the catalysts.

Effect of the Solvent   In the Fries reaction as in many other rearrangements the solvent plays an important role. A complete explanation of the solvent effect has not been found, but it can be said with certainty that the influence of the solvent is not limited solely to a reduction of the number of collisions between reacting particles, though this is undoubtedly a major feature. Another effect has been described as a catalyst sensitization where the catalyst forms a complex with the solvent[13]. A number of Fries reactions have been attempted without solvent other than the reactants themselves with noteworthy success, but in such instances the reaction must be run at relatively high temperatures where the yield of the para isomer is very low. Woodruff and Pierson[40], however, obtained total conversions of phenyl acetate approaching 80% of the theoretical by merely heating the ester to 160°-170°C without solvent. At this temperature the product consisted of a mixture of o- and p-hydroxyacetophenones.

The net purpose of a solvent in the Fries reaction is, therefore, to lower the minimum temperature at which the desired reaction will take place at a reasonable rate. With this conception in mind, Ralston, Ingle, and McCorkle[29] have made a thorough investigation of the most common solvents used in the Fries reaction recognizing, of course, that only those liquids which are virtually inert toward the Lewis acids can be used. The findings of these men may be summarized as follows:

1. The solvents studied included carbon disulfide, tetrachloroethane, nitrobenzene, and petroleum ether (61°-70°C).
2. Of the above liquids nitrobenzene was found to give the highest ratio of para to ortho derivatives.
3. Carbon disulfide gives the highest ration of ortho to para derivatives.

The most desirable amount of solvent to use in the Fries reaction is generally acknowledged to be approximately five times the weight of the ester[39].

Effect of Temperature   It has been mentioned previously that by varying the temperature at which a Fries reaction is run it is possible to vary the nature of the product. The effect of temperature upon the Fries reaction is one of its most distinguishing characteristics, and this effect can be predicted with certainty in every known case. The rule for anticipating which of the two normal products will be formed at a given temperature is that the number of acyl groups migrating to the *para* position begins to decrease rapidly above a certain low temperature, and the number of acyl groups migrating to the *ortho* position varies directly as the temperature. An excellent picture of the effect of increasing temperature on the Fries reaction is shown in Table II.

Table II. Effect of Temperature on Yields of *o*- and *p*- Hydroxy Ketones from 10g of *m*-Cresyl Acetate[5]

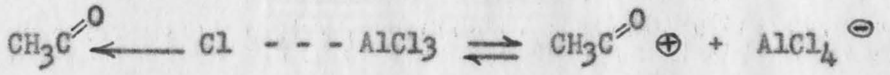
Temperature (°C)	2-Acetyl-5-hydroxytoluene, *p*-Hydroxy Ketone (g)	4-Acetyl-5-hydroxytoluene, *o*-Hydroxy Ketone (g)
25	8.0	0.0
50	8.4	0.1
75	8.8	0.2
100	3.7	6.0
120	2.7	7.0
150	1.0	8.0
165	0.0	9.5

Thus, it is found that the yields of para isomers are increased by brief heating at moderate temperatures. The maximum temperature favorable to the formation of the p-hydroxy ketone will of course vary with the choice of solvent, catalyst, and ester; but in no case has it been found to exceed 100°C. In fact, the highest yields from a number of esters have been obtained at temperatures of 50°-75°C. Mild heating reduces the optimum reaction time from 10-14 hours at room temperature to 1-2 hours at 70°C.

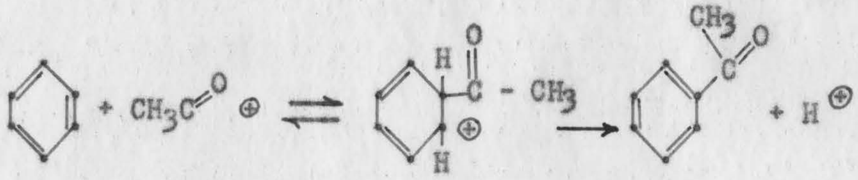
From Table II it is readily seen that more drastic conditions favor the yield of o-hydroxy ketones, and for this reason the reaction is carried out at temperatures above 120°C. At these high temperatures essentially all of the ester is converted either to the desired product or to resinous tars. Consequently, the ortho derivative in the form of a viscous oil may be removed in a high degree of purity by steam distillation[3,4], and the reaction does not require a solvent.

Mechanism of the Reaction At a first glance the Fries reaction would seem to closely resemble the Friedel-Crafts reaction, and interestingly enough there is abundant evidence that the resemblance is more than superficial. As a result, it seems fitting to first review an accepted mechanism of the

Friedel-Crafts reaction, taking the acetylation of benzene as an example[13,30]:



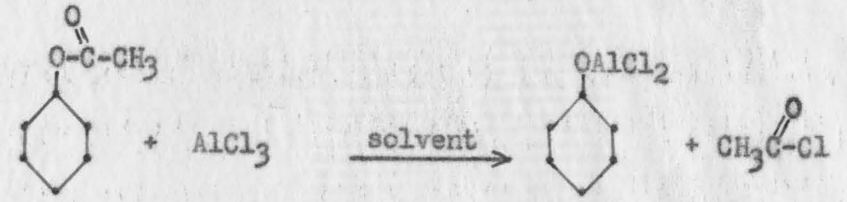
$$\mathrm{CH_3C^{\nearrow O}} \longleftarrow \mathrm{Cl} - - - \mathrm{AlCl_3} \rightleftharpoons \mathrm{CH_3C^{\nearrow O}} \oplus + \mathrm{AlCl_4}^{\ominus} \qquad (2)$$



(3)

Though the exact mechanism of the Fries reaction is still unknown, three different mechanisms have been proposed, all of which are supported by impressive experimental evidence. Accordingly, it seems somewhat dogmatic to expound the merits of one of the proposed mechanisms to the exclusion of the others. Instead, let it be assumed that the reaction may occur by one or more of the mechanisms simultaneously or that different mechanisms may operate in the cases of different esters.

The original mechanism suggested by Fries[10] and advocated by Auwers[4] and Witt[9] is a true intramolecular rearrangement represented by reaction (1). A second method recommended by Cox[9] and others is an auto-acylation reaction occurring as shown below: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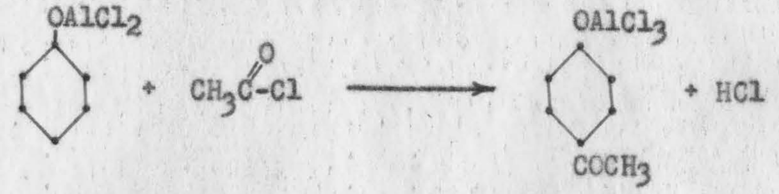
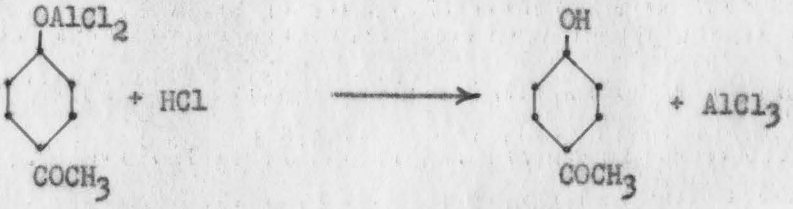
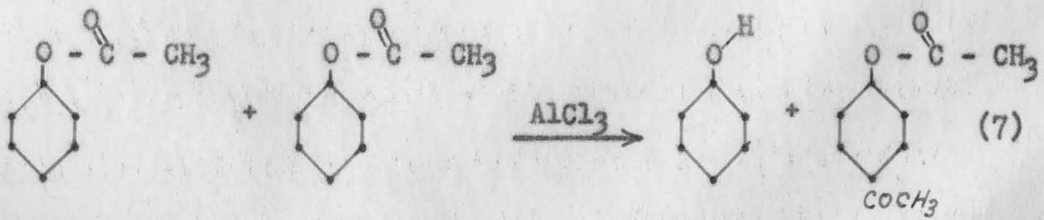

(5)


(6)

This mechanism has in its favor the formation of a colored complex, the evolution of hydrogen chloride, and the demonstrated existence of the acyl chloride as an intermediate. The third mechanism, proposed by Rosenmund and Schnurr and more recently supported by Thomas[37], is bimolecular where one molecule of the ester serves to acylate another as shown in the following reactions: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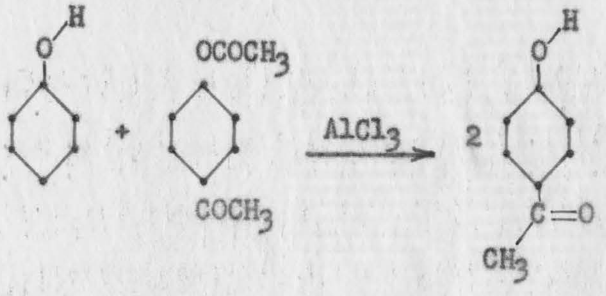


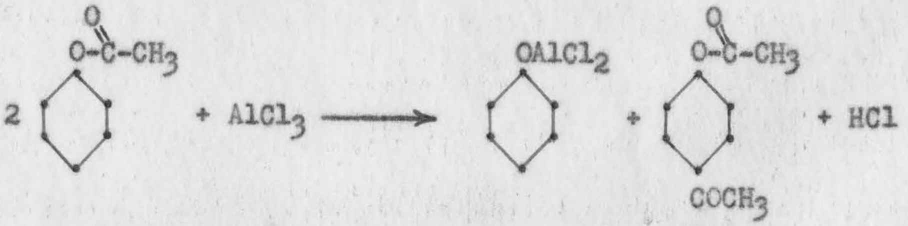
(8)

This last mechanism has the advantage of accounting for the so-called abnormal products obtained when mixtures of esters are subjected to the Fries reaction. Auwers and Mauss[4], however, have also accounted for the abnormal products by demonstrating an acyl interchange between different esters.

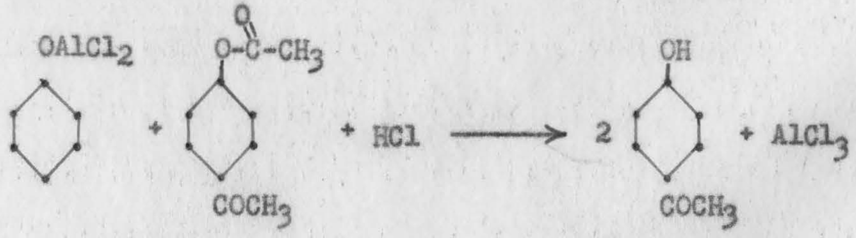
An interesting phenomenon which tends to support the intramolecular rearrangement mechanism is the occurrence of a reverse Fries reaction where p-hydroxy ketones having a substituent ortho to the acyl group undergo rearrangement to the ester on heating with sulfuric or phosphoric acids. Rosenmund and Schnurr[31], however, have again interpreted this phenomenon in the light of an intermolecular reaction.

New importance has recently been attached to this reverse Fries reaction[14,39] by considering the reversal to the ester as a necessary step preceding the formation of an o-hydroxy ketone. There is very little doubt as to the merit of this conjecture, and assuming it to be true makes the formation of the ortho derivative a three step process: (1) rearrangement of the ester to a *p*-hydroxy ketone; (2) reverse rearrangement of the *p*-hydroxy ketone to the ester; (3) rearrangement of the ester to the *o*-hydroxy ketone.

The intermediate existence of normal valence compounds is denied or ignored by the proponents of the intramolecular rearrangement and the bimolecular mechanisms, though such intermediates are acknowledged in the auto-acylation mechanism, and the possibility of similar compounds has also been pointed out recently in the bimolecular mechanism[35].

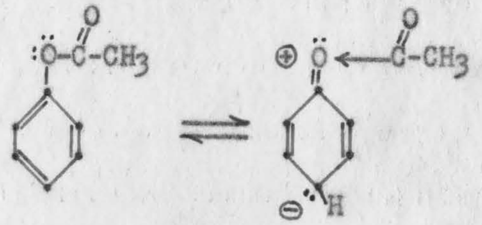


(9)

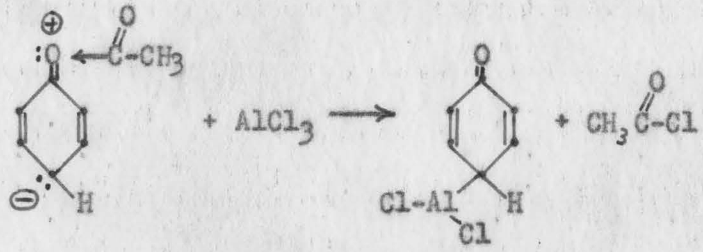


(10)

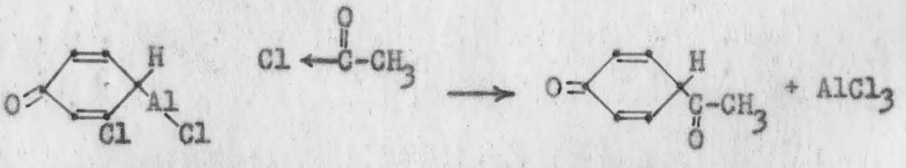
The extremely electrophilic nature of the Fries reaction as shown by the inhibiting effect of electrophilic substituents in the *meta* position with respect to the ester linkage indicates that the reaction must proceed by an ionic mechanism bearing a close resemblance to the Friedel-Crafts reaction. In such a case the ionic mechanism does not detract from the merits of the previously discussed mechanisms because the exact role of the catalyst is not fully understood. Some of the plausible electronic interpretations are shown below:


(A) (B)

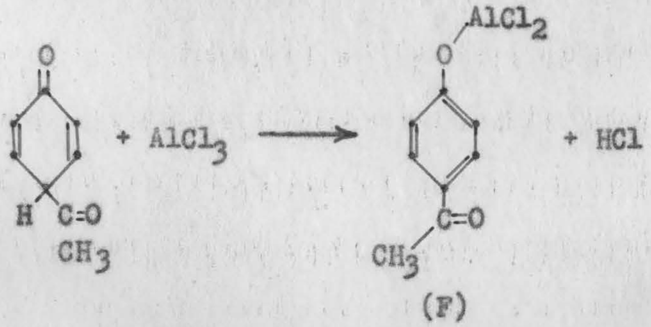
(11)


(C)

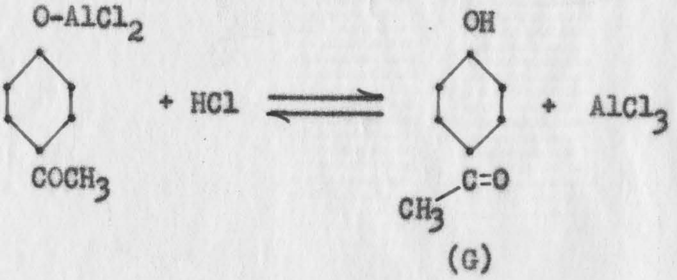
(12)


(D) (E)

(13)


(F)

(14)



(15)

Obviously, the above series of reactions does not show a complete picture of the Fries reaction, but if the bimolecular mechanism is disregarded on the basis of acyl exchange[4] then the preceding reactions take into account virtually all of the available information. In view of the accepted existence of the resonance structures (A) and (B) and the occurrence of ester cleavage at high temperatures in the absence of any catalyst, there are no grounds for postulating an initial catalyst attack on the phenolic oxygen. Therefore, a second guess would suggest an attack by the catalyst at the point of highest electron density with the subsequent release of a chloride ion to give a very short-lived complex (C)[19,34]. This chloride ion then could conceivably accelerate the cleavage of the ester to give the carbonium ion with which it immediately combines to give the acyl chloride. The remaining steps would then follow with subsequent regeneration of the carbonium ion as outlined in reactions (13), (14), and (15).

Summary The Fries reaction is a rearrangement reaction by which a number of phenyl esters can be made to undergo conversion at low temperatures to the corresponding p-hydroxy ketones and at relatively high temperatures to the o-hydroxy ketones. The acid radical may be either aliphatic or aromatic and of any size, but the phenol portion of the ester is strongly affected by substituents in the meta position to the hydroxyl group. The presence of meta-directing groups in this ring position strongly inhibits the reaction, or may even stop it entirely. Electron-releasing substituents in the meta position, however, generally enhance the yields of the reaction. The catalysts which have proved most satisfactory are those used in Friedel-Crafts acylations. Inert solvents may be used to lower the required temperature and also to increase yields of either of the normal products. Of the most common Fries reaction solvents nitrobenzene is the most desirable for obtaining the p-hydroxy ketones while carbon disulfide favors the highest yields of o-hydroxy ketones.

In the course of investigations on a large number of esters, a variety of abnormal products have been observed which may be accounted for by side reactions because though the mechanism of the Fries reaction is not fully understood at present its limitations are fairly well defined. Three principal mechanisms have been proposed which include true intramolecular rearrangement, auto-acylation, and bimolecular acylation. Each of these mechanisms is supported by experimental evidence, but they represent such different methods of approach that the exact process has not been chosen.

For additional information regarding the Fries reaction the reader is referred to the generalized experimental procedure by Weygand[39], and for theoretical considerations with tables of percentage yields for a large number of esters the publications of Cox[9], Thomas[37], Fuson[13], Gilman[15], and the excellent review by Blatt[1,5] should be consulted.

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