THE FRIES REACTION

A. H. BLATT

Department of Chemistry, Queens College, Flushing, New York

Received February 27, 1940

The Fries reaction is the conversion of a phenol ester, on treatment with aluminum chloride, to an *o*- or a *p*-hydroxy ketone or to a mixture of *o*- and *p*-hydroxy ketones. The position, relative to the hydroxyl group, taken by the acyl group depends upon the temperature at which the reaction is run, upon the nature of the acyl group, and upon the structure of the phenol. Low reaction temperatures lead to *p*-hydroxy ketones, while high reaction temperatures lead to *o*-hydroxy ketones. As the size of the acyl group increases,—for aliphatic acyl groups,—the amount of *o*-hydroxy ketone formed increases. Para-substituted phenol esters furnish only *o*-hydroxy ketones. A methyl group in the ortho position in the phenol ester favors the formation of *p*-hydroxy ketones, while the same group in the meta-position favors the formation of *o*-hydroxy ketones. Nitro, acyl, or carboxyl groups in the phenol ester slow up or stop completely the Fries reaction. With certain di- and tri-alkylphenol esters the shift or elimination of alkyl groups has been observed in the Fries reaction. It is suggested that these abnormal reactions are due to the action of aluminum chloride on the normal Fries reaction products. Three mechanisms have been advanced for the Fries reaction: cleavage of the ester by aluminum chloride to form a phenolate and an acid chloride and acylation of the phenolate by the acid chloride; acylation of one molecule of a phenol ester by a second molecule; and a true intramolecular rearrangement without the intervention of normal valence compounds as intermediates. Evidence has been advanced to show that the reaction can proceed by any of these paths, but there is as yet no evidence which establishes any one or ones as the actual path. With those *p*-hydroxy ketones having a substituent ortho to the acyl group, a reversed Fries reaction, leading to the formation of a phenol ester, has been observed.

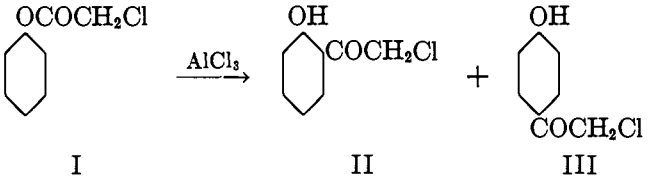
I. INTRODUCTION

The Fries reaction is an exceedingly convenient and general method for preparing phenol ketones from phenol esters. There is available in the chemical journals a large amount of information on the techniques for effecting the Fries reaction, on the generality and limitations of the reaction, and on the mechanism of the reaction. This information has never been made available in one place and it is necessary, in order to use the Fries reaction to full advantage in preparative work, to make a fairly complete survey of the original articles,—a survey which is time-consum-

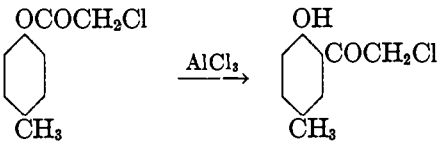
ing because of the number of articles, the mass of facts which they contain, and the contradictions with which they abound. The writer had occasion to make such a survey for his own use; it is presented here for others who may find it useful.

Before discussing the Fries reaction proper it is desirable to distinguish between it and the Friedel–Crafts reaction, of which it is essentially a minor variant. The basis for the distinction is that in the Friedel–Crafts reaction for the preparation of phenol ketones a phenol is treated with an acid chloride and aluminum chloride, while in the Fries reaction a phenol ester is treated with aluminum chloride. This may appear at first glance a perfect example of the academic distinction without a difference for, almost without exception, the same product can be prepared using either the Friedel–Crafts or the Fries reaction and it is, of course, true that phenols and acid chlorides react to form phenol esters. However, the distinction between the two reactions has a valid practical basis, for the Fries reaction usually gives much better results (18, 53, 60).

The Fries reaction was discovered in a successful attempt to avoid the difficulties encountered in preparing certain phenol ketones by the Friedel–Crafts reaction. Fries was seeking a method of preparing *o*-chloroacetyl phenols for use in synthesizing coumaranones. The reaction between phenols, chloroacetyl chloride, and aluminum chloride was not satisfactory since, often, two chloroacetyl groups were introduced into the phenols. Fries, therefore, heated phenyl chloroacetate (I) with aluminum chloride and obtained a mixture of *o*-(chloroacetyl)phenol (II) and *p*-(chloroacetyl)-phenol (III). From *p*-cresyl chloroacetate (IV) on similar treatment the sole product was the *o*-hydroxy ketone (V) (27, 28).



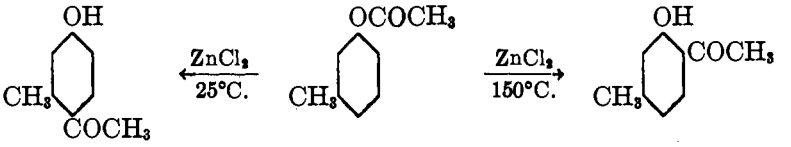
I II III



IV V

Four years prior to Fries' first publication, Eykmann (23, 24) had shown that *m*-cresol and acetyl chloride when treated with zinc chloride furnished, at the ordinary temperature, 2-methyl-4-hydroxyacetophenone (VI) and,

at higher temperatures, 2-hydroxy-4-methylacetophenone (VII). This was the first indication of the extremely important influence of the reaction temperature on the position taken by the acyl group. Eykmann used the crude reaction product obtained from *m*-cresol and acetyl chloride without isolating *m*-cresyl acetate.



VI VII

Another important factor in the Fries reaction, the use of nitrobenzene as a solvent, was indicated even earlier by Behn (14), who patented in 1897 a procedure for preparing phenol ketones by treating phenols and acid chlorides in nitrobenzene solution with aluminum chloride. And finally, going still earlier, Döbner (22) in 1881 prepared phenyl benzoate and, without purifying the crude ester, heated it with benzoyl chloride and aluminum chloride to obtain the benzoate of *p*-hydroxybenzophenone.

II. TECHNIQUES

By far the most important single article on the technique of the Fries reaction is that by Rosenmund and Schnurr (52). These authors showed that earlier workers had used too drastic conditions for the reaction and had unnecessarily prolonged the time of reaction. They developed two general procedures, the first for preparing *p*-hydroxy ketones and the second for preparing *o*-hydroxy ketones. In both procedures 1 mole of aluminum chloride is required to convert 1 mole of a phenol ester to a hydroxy ketone (compare, however, the guaiacol esters on page 426). Using technical aluminum chloride it is advisable to employ up to a 25 per cent excess in order to allow for inert ingredients.

The preparation of *p*-hydroxy ketones is based on Behn's patent (14): a solution of a phenol ester and aluminum chloride in nitrobenzene is kept for 24 hr. at room temperature or for 1 hr. at 60°C. The use of nitrobenzene reduces by 80° to 100°C. the temperature necessary for the reaction to proceed at a useful rate (compare reference 13). The importance of this will be seen when the effect of temperature on the course of the reaction is considered (page 417). The preparation of *o*-hydroxy ketones requires higher temperatures, and the preferred procedure consists in heating an intimate mixture of a phenol ester and aluminum chloride without a solvent for from 20 to 40 min. at about 140°C.

These generalized procedures work well and give excellent yields of

phenol ketones with a variety of phenol esters. It is, of course, advisable with some compounds to modify slightly the reaction times and temperatures just described in order to secure maximum yields, but such modifications are seldom essential. Other techniques have been recommended from time to time, but only a few require mention. Zinc chloride has been used in numerous Fries reactions, but it offers no advantages over aluminum chloride in either convenience or economy. Boron fluoride has been successfully used for the low-temperature reaction leading to *p*-hydroxy ketones (10, 46). Chlorobenzene (60) and tetrachloroethane (15) have been used as solvents in Fries reactions run at high temperatures, instead of heating an ester with aluminum chloride without a solvent. Carbon disulfide has been used to ensure complete mixing of the aluminum chloride and ester in reactions where high-temperature heating is to be employed. The reactants are dissolved in carbon disulfide, which is then removed by distillation and the residue is heated to the desired temperature (19, 25, 26).

The claim that phenol esters will undergo a Fries reaction on heating alone (56) has not been confirmed (5).

III. APPLICABILITY

The Fries reaction is of wide applicability, since both the acids and the phenols from which the phenol esters are derived can be varied within extensive limits and since, in many cases, it is possible to prepare at will either an *o*- or a *p*-hydroxy ketone from the same ester. The precise position, relative to the hydroxyl group, which will be taken by the acyl group depends upon the temperature at which the reaction is run, upon the nature of the acyl group, and upon the structure of the phenol. These three factors will be considered in the order in which they have been listed, but a brief summary, first, of the variety of esters which has been used in the Fries reaction will give an idea of the material to be covered.

The acids from which the phenol esters are derived may be aliphatic, aromatic, or mixed aliphatic-aromatic. They may be of low or high molecular weight and saturated or unsaturated. The phenols may be derived from benzene, naphthalene, phenanthrene, biphenyl, or coumarin. Hydroxy derivatives of benzene have been most extensively used, and they have been mono-, di-, or tri-hydroxy compounds. Using monohydroxybenzenes, as long as there is an ortho- or para-position available the presence of a single alkyl group or halogen atom in the nucleus introduces no complications (see, however, pages 417 to 425 for the polyalkylphenols). A nitro or a benzoyl group in either the ortho- or the para-position to the hydroxyl group stops the reaction (52). A carboxyl group or an acetyl group in the ortho-position does not interfere, but either group in the

para-position does stop the reaction (19). Attempts to run Fries reactions with acyl derivatives of 3,5-dihydroxybenzoic acid (44) and 1,3,5-triaminobenzene (34) were unsuccessful.

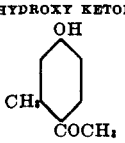
The effect of temperature on the course of the Fries reaction, first observed by Eykmann (23, 24), has been remarked by numerous workers and was examined in detail by Rosenmund and Schnurr (52). Their results with *m*-cresyl acetate are reproduced in table 1.

The obvious conclusion is that low temperatures favor the formation of *p*-hydroxy ketones, while high temperatures favor the formation of *o*-hydroxy ketones, and this conclusion is confirmed by the results with *m*-cresyl benzoate. At 100°C. this ester furnishes exclusively a *p*-hydroxy ketone, while at 165°C. the sole product is an *o*-hydroxy ketone. The temperature effect does not, however, permit the preparation in every

TABLE 1

Effect of temperature on the Fries reaction

(In each experiment 10 g. of *m*-cresyl acetate was used)

TEMPERATURE	*p*-HYDROXY KETONE 	*o*-HYDROXY KETONE 
°C.	*grams*	*grams*
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

case of either an *o*- or a *p*-hydroxy ketone, for the nature of the acyl group and the structure of the phenol also play important rôles in determining the course of the Fries reaction. Rosenmund and Schnurr (52) and later Stoughton (58) showed that *p*-hydroxy ketones on heating with aluminum chloride furnish *o*-hydroxy ketones, and this may be the explanation of the temperature effect. With para-substituted phenols, such as *p*-cresol, the formation of an *o*-hydroxy ketone obviously does not involve a *p*-hydroxy ketone as an intermediate.

The influence of the acyl group in the phenol ester on the course of the Fries reaction must now be considered. First, there are striking differences

in the rates with which different acyl groups shift from oxygen to the nucleus. For example, in nitrobenzene solution at 20°C., thymyl acetate undergoes 60 per cent conversion to thymyl methyl ketone in 5 hr. Under the same conditions thymyl benzoate undergoes only 4 per cent conversion to the corresponding phenyl ketone. From observations of this sort the various acyl groups have been arranged in the following order of decreasing rates of shift (52):

$$C_nH_{2n+1}CO \text{ (where } n = 1 \ldots 5) > C_6H_5CH_2CO > C_6H_5CH_2CH_2CO > C_6H_5CH{=}CHCO > C_6H_5CO$$

No differences were observed between benzoyl and substituted benzoyl groups. The same comparative order holds whether the groups shift to the para- or the ortho-position relative to the hydroxyl group. The importance of this series in setting limits to the usefulness of the Fries re-

TABLE 2

Effect of the size of the acyl group on the product formed

ESTER	REACTION TEMPERATURE	YIELD OF o-HYDROXY KETONE
	°C.	*per cent*
m-Cresyl propionate	25	67
	2	65
m-Cresyl butyrate	25	66
	2	72
m-Cresyl valerate	25	67
m-Cresyl caproate	25	62

action is twofold. With certain acyl groups the rate of shift to the para-position is so slow that the preparation of *p*-hydroxy ketones is impracticable; attempts to increase the rate of para conversion by increasing the temperature are futile, for they result instead in the formation of *o*-hydroxy ketones. Examples are furnished by the esters of α-naphthol, which are considered later (page 427). With other acyl groups the conversion to *p*-hydroxy ketones is practicable, but the temperatures required for the formation of *o*-hydroxy ketones are so high that the material is destroyed in the process. *p*-Cresyl cinnamate, which cannot be converted to 2-hydroxy-5-methylbenzalacetophenone, offers an illustration.

The size of the acyl group is also of importance in determining whether an *o*- or a *p*-hydroxy ketone will be formed in a Fries reaction. This factor was discovered by Coulthard, Marshall, and Pyman (17), and studied in detail by Baltzly and Bass (12; compare also 31). The latter workers examined a series of esters of *m*-cresol and aliphatic acids. Only the

acetate furnished a *p*-hydroxy ketone as the principal product. With all the other esters the principal product was an *o*-hydroxy ketone, even when the reaction was run at low temperatures. A selection from the data of Baltzly and Bass, given in table 2, is illustrative.

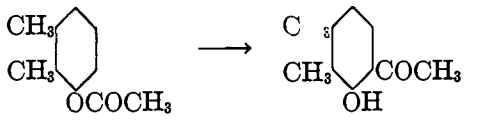
These results do not contradict those of Rosenmund and Schnurr with *m*-cresyl acetate given in table 1, but they do make questionable any generalization from that data as to the decisiveness of the temperature effect in the Fries reaction. Baltzly and Bass concluded that the temperature at which the reaction is run and the structure of the phenol are the primary factors determining the course of a Fries reaction but that, when these factors counterbalance, the size of the acyl group will control the course of the reaction. Additional information on this question, using esters of other phenols than *m*-cresol, would be desirable. At present we are in the rather awkward situation of having two generalizations, each of which limits the other and neither of which is of sufficient generality to inspire confidence.

The third factor in determining the course of the Fries reaction, the structure of the phenol from which the phenol ester is derived, remains now to be considered. When esters of phenol and the three cresols are employed the reaction takes place without complications. *p*-Cresyl esters and esters of other para-substituted phenols furnish only *o*-hydroxy ketones. This fact and the relatively high temperature required for the ortho shift account for certain apparently anomalous statements in the original literature. For example, it is reported (36) that *p*-cresol, benzoyl chloride, and aluminum chloride furnish *p*-cresyl benzoate and not 2-hydroxy-5-methylbenzophenone. The reaction reported was not run at a sufficiently high temperature to bring about formation of the *o*-hydroxy ketone. Esters of *o*-cresol furnish only *p*-hydroxy ketones, while aliphatic esters of *m*-cresol, with the exception of the acetate, furnish only *o*-hydroxy ketones. The effect of a methyl group ortho or meta to the phenolic hydroxyl, leading in the former case to the formation of *p*-hydroxy ketones and in the latter case to the formation of *o*-hydroxy ketones, is probably general for other alkyl groups.

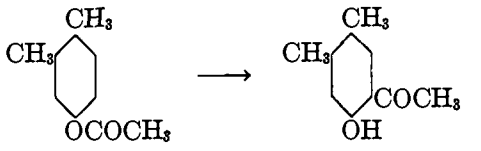
A considerable number of esters of di- and tri-alkylphenols have been examined, principally by Auwers and his associates. Certain of these were esters of 2,4,6-trialkylphenols, so that the migration or elimination of an alkyl group was necessary in order for the Fries reaction to take place. Other trialkylphenol esters and all the dialkylphenol esters contained at least one unsubstituted ortho- or para-position, yet in certain of these compounds an alkyl group was either eliminated or changed its position during the reaction. This shift or elimination of an alkyl group

is of importance, for it makes uncertain the structures of the phenol ketones formed in the Fries reaction and thereby seriously decreases the usefulness of the reaction. Consequently it is necessary to examine these abnormal Fries reactions in detail. The most satisfactory procedure is to divide the material into three parts and to consider in order the dialkylphenol esters, the trialkylphenol esters having at least one unsubstituted ortho- or para-position, and the 2,4,6-trialkylphenol esters.

A representative picture of the behavior of the dialkylphenol esters is given by the six xylenyl acetates which were examined by Auwers and his associates.



VIII (6)



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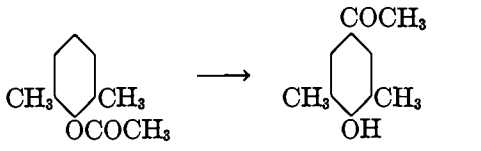

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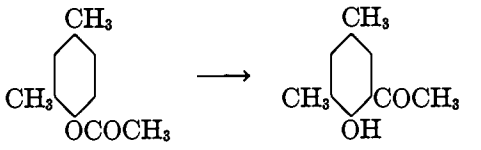

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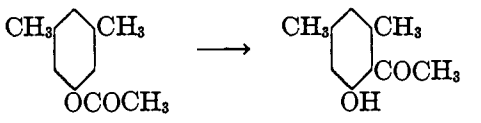
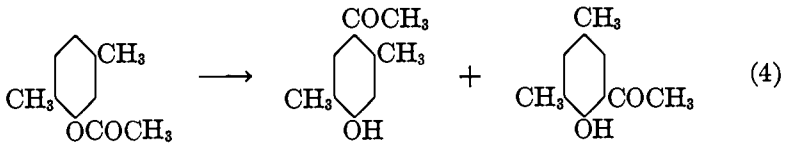


XII (1, 2)



XIII XIV XV (4)

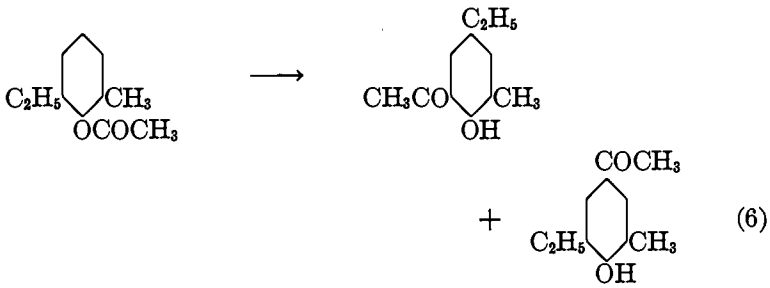
The most striking feature about these results is that with only a single ester (XIII) does an alkyl shift occur. Even with this ester—although in the descriptive portion of the original article only the abnormal product (XV) is mentioned—rearrangement is a distinctly subordinate process. For, in the experimental portion of the article referred to, it is found that *p*-xylenyl acetate (XIII) furnishes the normal product (XIV) in a 70 per cent yield, while the yield of the rearranged product (XV) is only 17 per cent. It is unfortunate that, unless the experimental details in the original article are consulted, the impression given is that the abnormal product is the only product. In the opinion of the present writer the alkyl shift observed with *p*-xylenyl acetate has no direct connection with the Fries reaction. It is, instead, a secondary reaction between the normal product (XIV) and aluminum chloride, a reaction which was encountered as a result of the use of too drastic experimental conditions.

There is considerable evidence in support of the explanation just suggested for the formation of the abnormal product from *p*-xylenyl acetate. The experiments with this ester were reported before Rosenmund and Schnurr's paper (52) on techniques appeared and, after the appearance of that paper, Auwers remarked (8) that the Rosenmund technique was not sufficiently drastic to cause alkyl wandering. The question raidse by the alkyl shift with *p*-xylenyl acetate is subject to an experimental clarification, and it is desirable that this clarification be attempted.

A second striking feature of the experiments with the xylenyl acetates is the large number of *o*-hydroxy ketones obtained. Of course, the acetates (IX and XI) in which the para-position is occupied would be expected to furnish *o*-hydroxy ketones, and the acetate (X) in which both ortho-positions are occupied would be expected to furnish a *p*-hydroxy ketone. Of the three remaining acetates, however, only XIII does yield a *p*-hydroxy ketone. This result may be due to the presence in each of the three acetates (VIII, XII, and XIII) of at least one methyl group meta to the ester group, for such a substituent is known to favor the formation of *o*-hydroxy ketones (compare page 419). It may, however, be due to the high temperature used in the experiments. The behavior of the xylenyl acetates (VIII, XII, and XIII) under mild experimental

conditions which should lead to the formation of *p*-hydroxy ketones has apparently never been studied.

The remaining information about the behavior of esters of dialkylphenols in the Fries reaction is summarized in the following equations:



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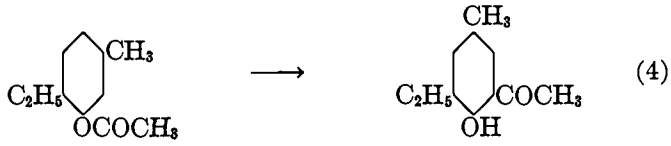

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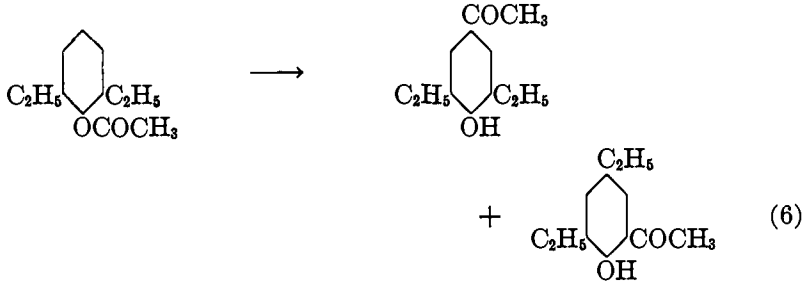

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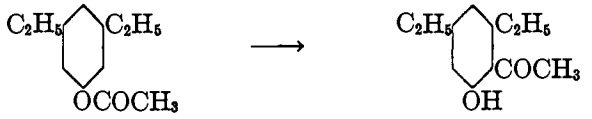

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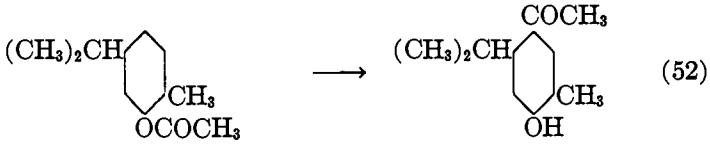

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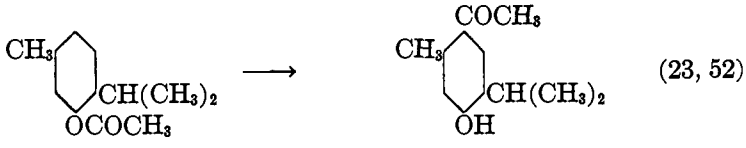
XVI

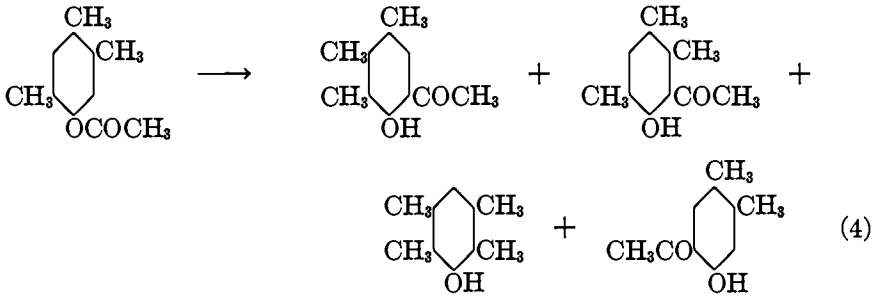


(23, 52)

XVII

Precisely the same comment made about the alkyl shift with *p*-xylenyl acetate applies to these reactions, and that comment receives confirmation from the fact that the two esters, carvacryl acetate (XVI) and thymyl acetate (XVII), which were rearranged using mild experimental conditions behaved normally.

Seven trialkylphenol esters having at least one free ortho- or para-position have been examined by Auwers. The results are shown in the following equations. When more than one product is formed, the principal product is the one immediately following the arrow.



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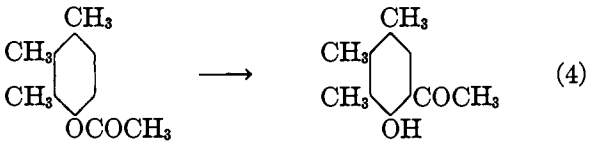

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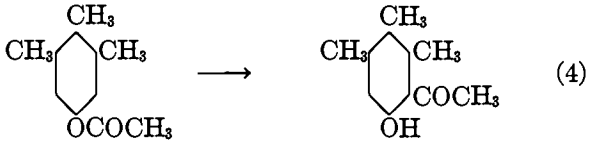

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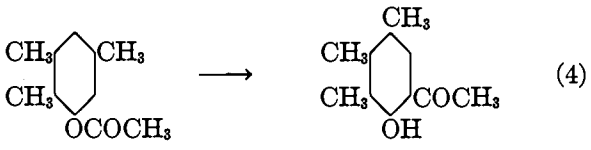

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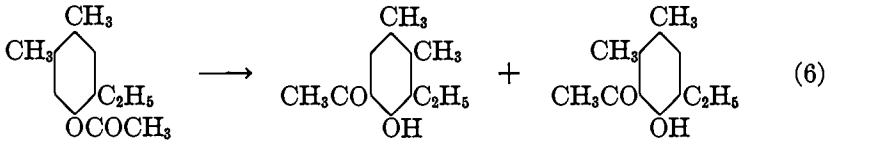

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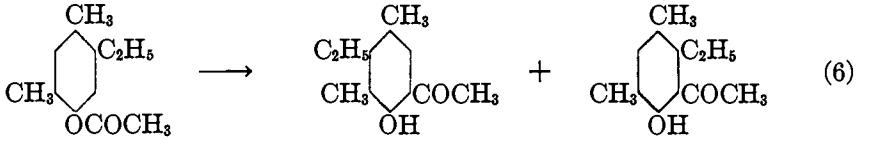

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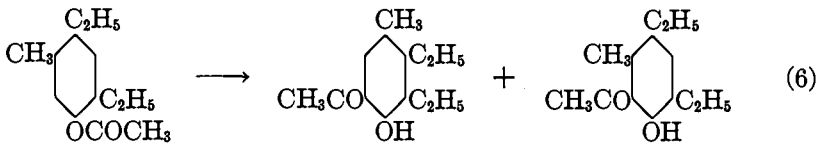


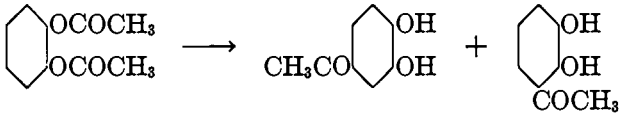
(6)

Here alkyl shifts are more common than with the dialkylphenol esters. However, the same question that was raised in connection with the dialkylphenol esters can and should be raised: Are these alkyl shifts an integral part of the Fries reaction, or do they represent a secondary reaction which has taken place between the normal product and aluminum chloride because of the high temperatures used? Again the present writer's opinion is that the second alternative is correct, and there is support for this opinion in the experimental data. Thus, whenever an alkyl shift has occurred, some of the normal product was obtained, indicating that less drastic experimental conditions would furnish more of the normal product. Further, the experimental conditions used were in one instance at least,—that of 2,4,5-trimethylphenyl acetate,—sufficiently severe to bring about alkylation and dealkylation of the type that is known to occur on treating alkylbenzenes with aluminum chloride. It is not our intention to say that every alkylphenol ester with at least one unsubstituted ortho- or para-position will undergo a normal Fries reaction. All the facts are consistent, however, with the view that *p*-hydroxy ketones can and will be formed without alkyl shifts if a suitable experimental technique is used. Whether these *p*-hydroxy ketones can be converted to *o*-hydroxy ketones or whether the direct conversion of esters to *o*-hydroxy ketones can generally be effected without the occurrence of alkyl shifts is much less certain. There is no experimental evidence so far to show that alkyl shifts are an integral part of the Fries reaction.

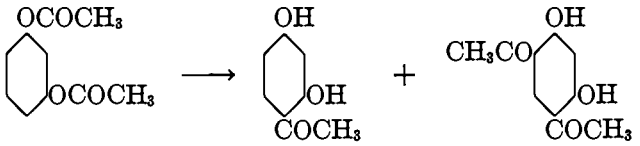
Auwers and his collaborators (4, 6, 9) have examined the behavior of twenty-two trialkylphenol esters in which the alkyl groups occupy the 2-, 4-, and 6-positions. With these esters the shift or elimination of an alkyl group must occur if a Fries reaction is to take place. The experiments serve to show, therefore, which alkyl groups are most readily displaced and should be discussed with other data on the firmness of attachment of alkyl groups rather than in relation to the Fries reaction. The reader is accordingly referred to the original articles for details.

Our discussion of the Fries reaction with esters of hydroxy derivatives of benzene other than phenol and the alkylphenols will be brief. Esters of the three dihydroxybenzenes have been examined. Hydroquinone diacetate is reported not to undergo a Fries reaction (35). Catechol and resorcinol esters may be converted to the corresponding dihydroxy ketones by the usual technique (38, 50), but a better procedure is to treat an

equimolar mixture of the diester and the free phenol with aluminum chloride (51, 53). Improved procedures for preparing acylcatechols have recently appeared (47). Acylresorcinols can so readily be prepared from resorcinol and acid chlorides in a single step that the use of the Fries reaction is superfluous (20). Catechol esters furnish predominantly the 4-acyl derivatives and only secondarily the 3-acyl isomers.

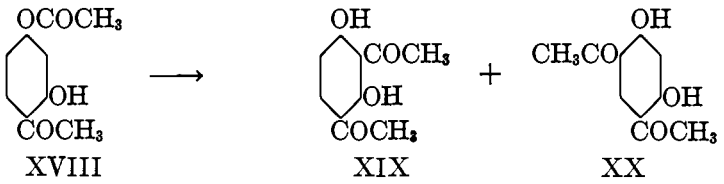


From resorcinol both mono- and di-acyl derivatives may be obtained.

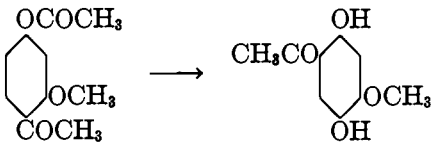


For the preparation of 2-acylresorcinols see page 428.

Orientation effects worthy of mention have been observed in Fries reactions with the acetates of 4-acetylresorcinol (XVIII) and its methyl ether (XXI). These substances would be expected to form symmetrical 1,3,4,6-tetrasubstituted products, and the ether (XXI) does furnish such a product (XXII). The hydroxy compound (XVIII), however, furnishes a mixture of 58 per cent of the unsymmetrical (XIX) and 42 per cent of the symmetrical (XX) products. These results have been explained as due to hydrogen bonding in the hydroxy compound (XVIII),—the bonding stabilizing that Kekulé form which leads to the unsymmetrical product (11).

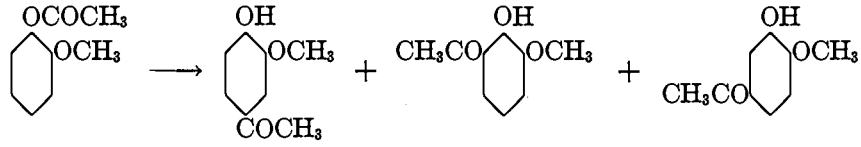


XVIII XIX XX



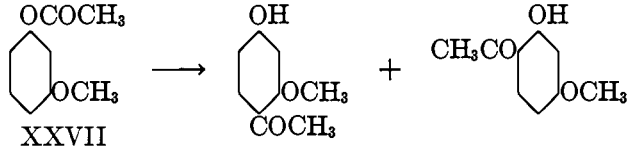
XXI XXII

The acetate of guaiacol (XXIII) has received considerable attention. It illustrates the effectiveness of nitrobenzene in facilitating the Fries reaction. Without a solvent this acetate and aluminum chloride do not react at the ordinary temperature but they do in nitrobenzene solution to furnish apocynin (XXIV) (13). The acetate (XXIII) also requires 2 moles rather than 1 mole of aluminum chloride to bring about reaction (17). One mole of the halide is apparently utilized in complex formation with the methoxyl group.



XXIII XXIV XXV XXVI

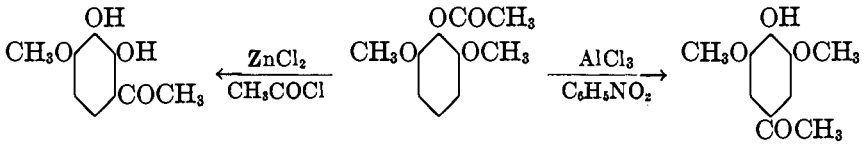
Reichstein (49) obtained from guaiacol acetate (XXIII) the three products XXIV, XXV, and XXVI. The first two of these are to be expected, but the formation of the third (XXVI) is most unusual, for the shift of an acyl group in a Fries reaction to a position meta to the hydroxyl group is rare. (The diacetate of catechol (see page 425) furnishes some 3-acetylcatechol, but this may be the result of an ortho shift from the 2-position rather than a meta shift from the 1-position.) The Friedel–Crafts reaction with guaiacol and acetyl chloride furnishes the same three products as does the Fries reaction with guaiacol acetate, so the formation of the *m*-hydroxy ketone (XXVI) is not a peculiarity of the Fries reaction. The resorcinol derivative (XXVII), which corresponds to the acetate of guaiacol, yields both an *o*-hydroxy and a *p*-hydroxy ketone but does not yield a *m*-hydroxy ketone (44).



XXVII

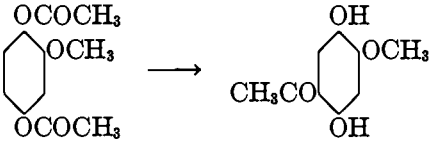
Esters of pyrogallol (35), phloroglucinol (33, 35, 45) and 1,2,4-trihydroxybenzene (45) undergo the Fries reaction, and the products are those to be expected. Similarly, esters of various hydroxydimethoxybenzenes and dihydroxymethoxybenzenes have been examined. Generally these esters yield the expected products but one or two unusual results are to be noted, together with the general comment that it would be desirable if the work on this group of compounds were confirmed and amplified. 2,6-Dimethoxyphenyl acetate (XXVIII) with zinc chloride at room

temperature in acetyl chloride as a solvent furnishes compound XXIX, the acetyl group taking a meta-position (42). With the same ester and aluminum chloride the acetyl group takes the para-position to yield compound XXX (43).



XXIX XXVIII XXX

And, although hydroquinone diacetate does not undergo a Fries reaction, the diacetate of 2-methoxy-1,4-dihydroxybenzene (XXXI) does to furnish compound XXXII (44).

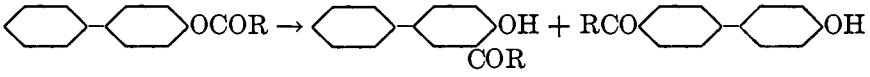


XXXI XXXII

Esters of α- and β-naphthol, of the three hydroxybiphenyls, and of the 2-, 3-, and 9-hydroxyphenanthrenes have been used in the Fries reaction. Esters of α-naphthol furnish 4-acyl-1-naphthols at low temperatures (59, 39, 58). As the size of the acyl group increases, the yields of the 4-acylnaphthols decrease and with certain acyl groups, such as phenylacetyl and benzoyl, the rate of formation of the 4-acyl derivatives is so small that their preparation is impracticable. If the temperature at which the reaction is run is increased, the result is an increase in the amounts of 2-acylnaphthols and 2,4-diacylnaphthols formed. Separate experiments with the 4-acyl-1-naphthols showed that, on heating with aluminum chloride, they were converted to 2-acyl-1-naphthols and 2,4-diacyl-1-naphthols. The failure to recognize the effect of temperature on the course of the reaction and/or the shift of the acyl group from the 4-position in the 4-acyl-1-naphthols led to much confusion in the early literature on the acyl-1-naphthols. β-Naphthyl acetate in the Fries reaction furnishes 1-acetyl-2-naphthol together with 6-acetyl-2-naphthol, the acetyl group entering a different nucleus from that containing the hydroxyl group (59, 29, 30).

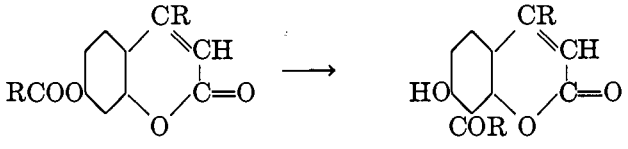
The shift of an acyl group to a hydroxyl-free ring, the formation of heteronuclear hydroxy ketones, has also been encountered in the biphenyl series. Aliphatic esters of 2-hydroxybiphenyl are reported to furnish

mixtures of 3- and 5-acyl-2-hydroxybiphenyls (3), the yield of the 3-acyl derivatives increasing with the size of the acyl group (31). The structures assigned the hydroxy ketones are reasonable but have never been proved. Esters of 3-hydroxybiphenyl are reported to furnish 4-acyl-3-hydroxybiphenyls (31). Esters of 4-hydroxybiphenyl furnish both the 3-acyl and the 4′-acyl derivatives (15, 32, 25, 26, 16).

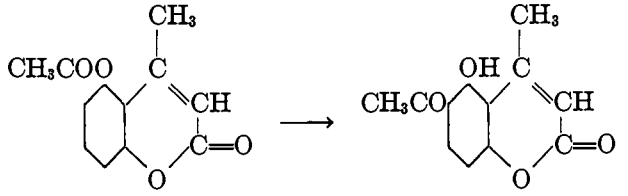


Esters of the 3,4- and 2,5-dihydroxybiphenyls yield tars only (31). In the phenanthrene series, the Fries reaction leads to hydroxy ketones whose structures in certain cases have not been unequivocally established and the reaction offers no advantages over the Friedel–Crafts reaction (48).

Considerable attention has been given the hydroxycoumarin esters and it has been shown that the reaction proceeds normally in this series, leading to the formation of *o*-hydroxy ketones.

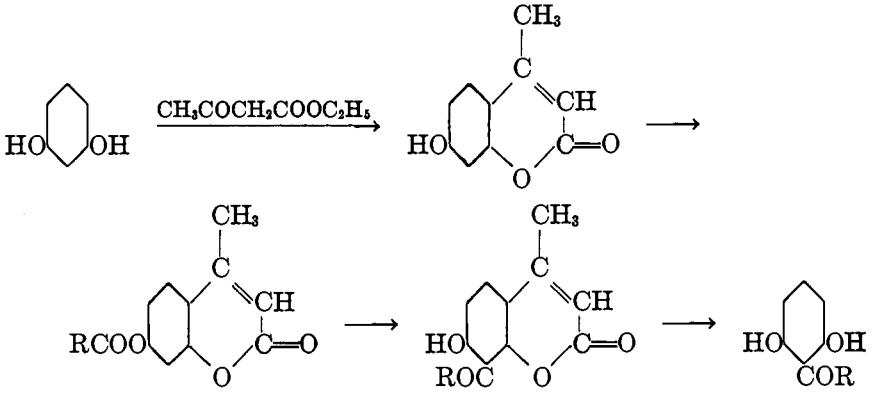


(21, 40, 41)

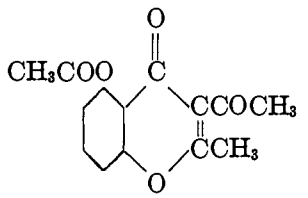


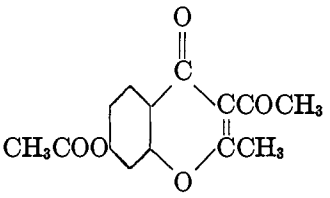
(54)

The importance of the Fries reaction with these materials is that it permits the synthesis of 2-acylresorcinols.



Unsuccessful attempts to carry out Fries reactions have been reported with the following esters (37):

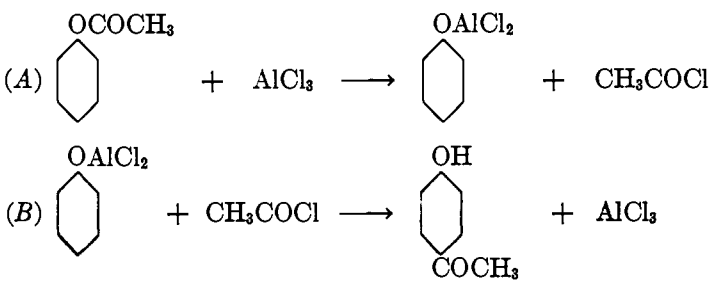




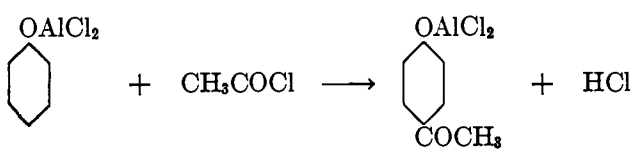
IV. MECHANISM

Three mechanisms for the Fries reaction have received serious consideration and, interestingly enough, while evidence has been presented to show that the reaction can proceed by each of the three proposed mechanisms, there is as yet no decisive evidence in favor of or against any one of the three. This situation, although somewhat unusual, is not too surprising, for when a reagent as powerful as aluminum chloride is used under the conditions of the Fries reaction, many different reactions may and probably do take place, so that the task of proving which one or ones of these alternatives is the reaction path is not easy.

The first mechanism to be considered involves two successive steps: the decomposition of a phenol ester by aluminum chloride to furnish a phenolate and an acid chloride, followed by the nuclear acylation of the phenolate by means of the acid chloride. It is usually represented as follows:

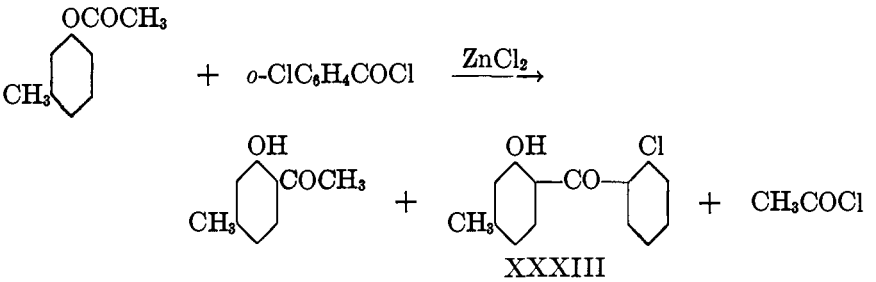


The second step should probably be written



for hydrogen chloride is evolved during the reaction (52).

Skraup and later Cox favored this mechanism and advanced evidence for it. Skraup and Poller (55) heated *m*-cresyl acetate and zinc chloride at 140°C. in a current of hydrogen but failed to isolate the acetyl chloride which they expected according to step *A* above. This failure they explained by the assumption that the acetyl chloride formed was utilized too rapidly in step *B* to permit its isolation. When they heated *m*-cresyl acetate, zinc chloride, and *o*-chlorobenzoyl chloride under the same conditions they were able to isolate small amounts of acetyl chloride and of the benzophenone derivative (XXXIII).



XXXIII

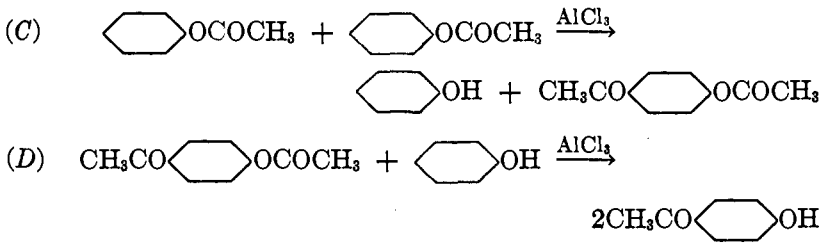
Skraup and Poller felt that this experiment established the mechanism of the Fries reaction. Actually, while the results of the experiment are consistent with the mechanism under discussion, they do not establish that mechanism. Skraup's experiment shows that the Fries reaction can proceed in the way proposed, but it does not show that the reaction does proceed in that way nor does it eliminate alternative reaction paths.

The evidence presented by Cox (19) is from three sources. When Fries reactions are run in diphenyl ether as a solvent, *p*-acyl diphenyl ethers are formed. When the cresyl acetates are rearranged in the presence of absolute alcohol, ethyl acetate is formed. When 2,4,6-trichlorophenyl acetate is heated with aluminum chloride, acetyl chloride is obtained. The same comment made about Skraup's work applies here. This evidence, it seems to the writer, shows that reaction *A*, above, can take place and it shows that the Fries reaction can take place according to the mechanism favored by Skraup and by Cox. It does not, however, show that reaction *A* is a necessary step in the process.

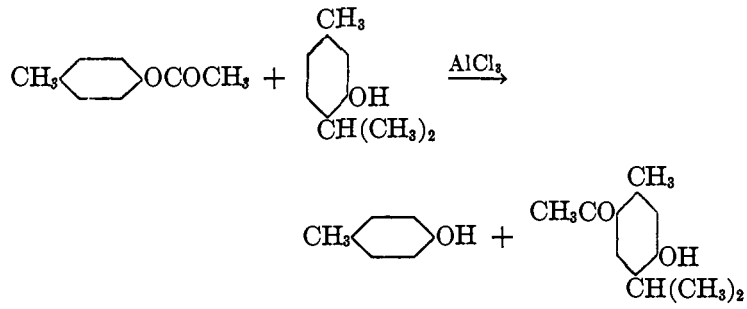
Skraup and Poller (55) also performed some experiments to determine the source of the *o*- and *p*-hydroxy ketones obtained from *m*-cresyl acetate. They found that this ester with zinc chloride at 140°C. gave the *o*-hydroxy ketone, a result consistent with the findings of other workers. They also found that *m*-cresyl acetate did not undergo any reaction when treated

with aluminum chloride at room temperature but that if hydrogen chloride was present a Fries reaction took place and both the *o*-and *p*-hydroxy ketones were formed. From the yields of *o*- and *p*-hydroxy ketones in several experiments they concluded that the *o*-hydroxy ketone was the first product and that the *p*-hydroxy ketone was formed from the *o*-hydroxy ketone when hydrogen chloride was present (compare 57). These results should be confirmed, for they contradict completely all the other evidence on this point. There is no other recorded example of the conversion of an *o*- to a *p*-hydroxy ketone, and Skraup and Poller never carried out a direct conversion of this type. An explanation of their results would be possible if one assumed that zinc chloride and aluminum chloride act differently in the Fries reaction (compare the data on the acetate (XXVIII) on page 426), but these results are so strikingly out of line with those of other workers that an attempt to account for them is idle until they have been verified.

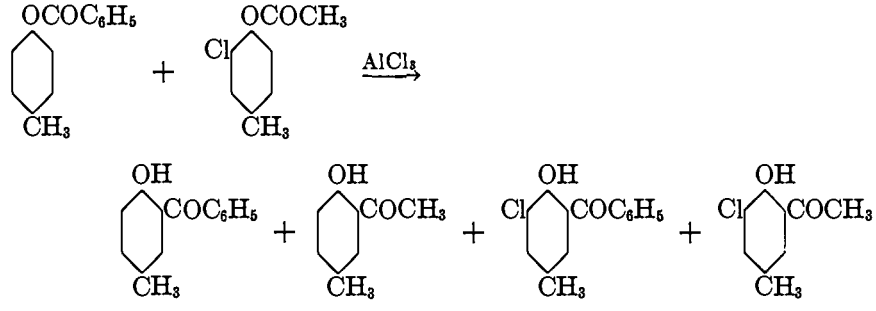
The second mechanism for the Fries reaction is that proposed by Rosenmund and Schnurr (52), who suggested that the reaction was bimolecular with one molecule of ester serving to acylate a second molecule.



In support of this suggestion Rosenmund and Schnurr showed that when *p*-cresyl acetate in nitrobenzene was treated with aluminum chloride no appreciable reaction took place in 24 hr. at room temperature. If, however, to the reaction mixture just described one equivalent of thymol was added, a 60 per cent yield of thymyl methyl ketone, together with *p*-cresol, was obtained in 8 hr. The explanation given for these results was the following: *p*-Cresyl acetate did not react at room temperature, for the only reaction possible is that leading to an *o*-hydroxy ketone, and the rate of this reaction is negligible under these conditions. Thymol, however, can yield a *p*-hydroxy ketone, and *p*-hydroxy ketones are formed at room temperature. The *p*-cresyl acetate served as the acetylating agent; that is, reaction *C* above took place between two different substances instead of between two molecules of the same substance.

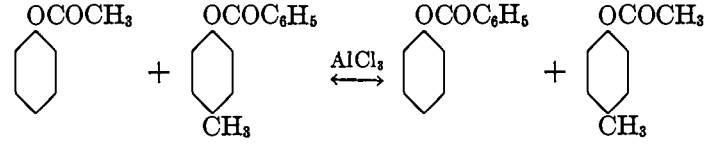


Rosenmund and Schnurr also showed that when a mixture of *p*-cresyl benzoate and 2-chloro-4-methylphenyl acetate was heated with aluminum chloride, all four possible products were formed.

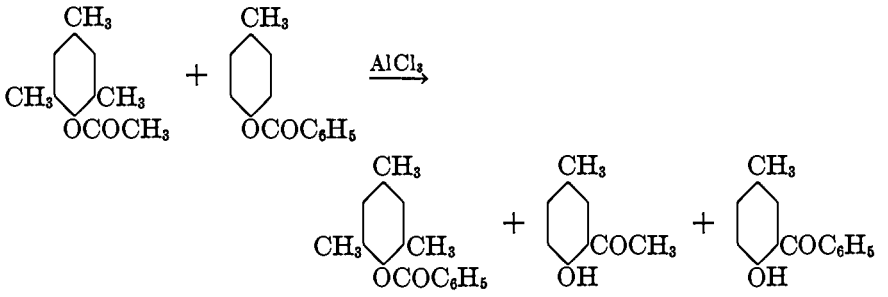


This experiment was interpreted as an example of reaction *C* above. Each ester served to acylate another molecule of the same ester and also to acylate a molecule of the other ester.

It is clear that Rosenmund and Schnurr's results follow very neatly from their mechanism. It must be pointed out that they are explicable equally well on the basis of the first mechanism considered and also as a result of an acyl interchange. Thus if a reaction of the following sort takes place, Rosenmund and Schnurr's experiments lose their significance.

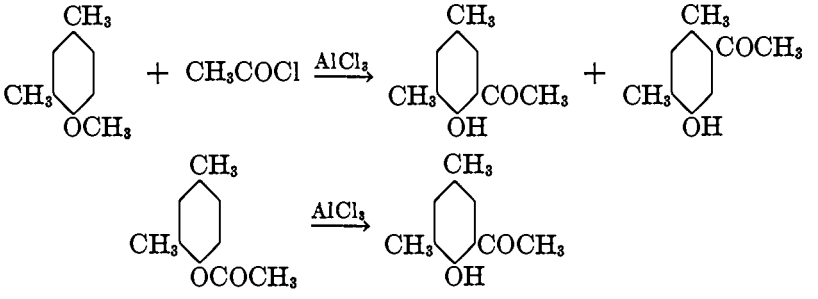


Auwers and Mauss (8) established the occurrence of an acyl interchange when they heated 2,4,6-trimethylphenyl acetate and *p*-cresyl benzoate with aluminum chloride and obtained the three products shown in the equation below.



The situation with respect to Rosenmund and Schnurr's mechanism is then precisely the same as the situation with respect to the first mechanism considered. The Rosenmund and Schnurr mechanism is a perfectly possible one, but there is no evidence which establishes its correctness and eliminates the other alternatives.

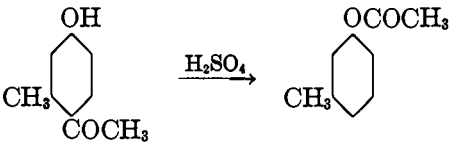
The third mechanism, which considers the Fries reaction to be a true intramolecular rearrangement without the intervention of normal valence compounds as intermediates, has been championed principally by Auwers. His argument is that there is a difference in the course of the reaction leading to a hydroxy ketone depending upon whether the acyl group comes from within the reacting molecule (Fries reaction) or from another molecule (Friedel–Crafts reaction). Auwers and Mauss (7, 8) illustrate this with the following typical experiments:



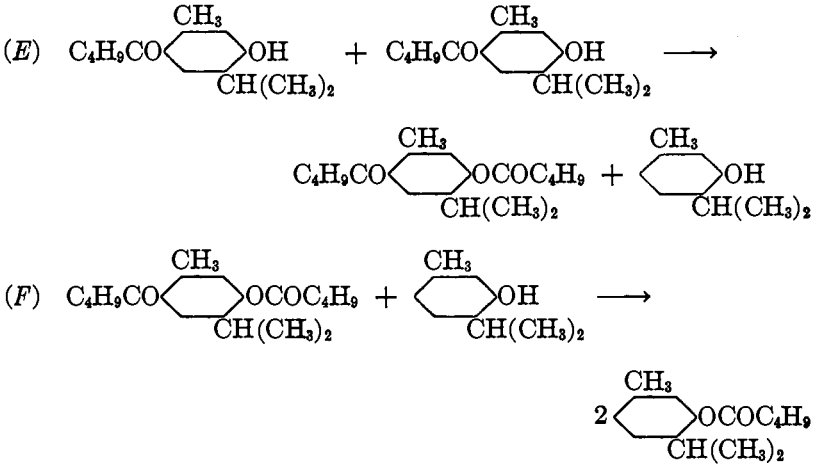
The value of this comparison between two different reactions using different starting materials is difficult to assess. Auwers stresses the statement that, while the Friedel–Crafts reaction with a phenol ether may lead to a *m*-hydroxy ketone, the Fries reaction with a phenol ester always leads to *o*- or *p*-hydroxy ketones. However, the formation of *m*-hydroxy ketones, though rare, is not unknown in the Fries reaction, for guaiacol acetate gives just such a product (49) (compare page 426). The best one can say about the view that the Fries reaction is a true intramolecular rearrangement is the same statement that was made about the other mechanisms,—it has been neither proved nor disproved.

V. REVERSAL OF THE FRIES REACTION

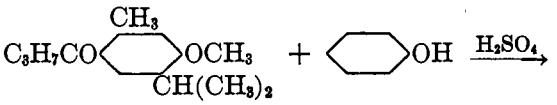
Rosenmund and Schnurr (52) found that with certain *p*-hydroxy ketones the Fries reaction could be reversed, that is, the hydroxy ketones could be converted to phenol esters. The requisites, structural and experimental, for the reverse reaction have been carefully determined. The *p*-hydroxy ketone must contain a substituent ortho to the acyl group and the reversal is effected by heating with sulfuric, camphorsulfonic, or phosphoric acid.



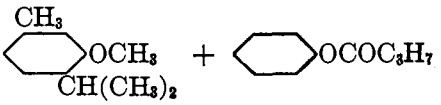
Rosenmund and Schnurr believe that this reverse Fries reaction, like the Fries reaction itself, involves two molecules of the reactants and takes place in two steps. These two steps are the reversal of the two steps (reactions *C* and *D* above) which were suggested for the mechanism of the Fries reaction.



Using the phenol ketone shown in equation *E* it was possible to stop the process at the stage represented by this equation. For when this phenol ketone was heated in high vacuum with the catalyst, thymol was removed as fast as it was formed. Reaction *E* could also be effected between two unlike molecules, for the ketone (XXXIV), which on heating with acid alone is unchanged, reacts as follows when heated with acid and phenol:



XXXIV



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