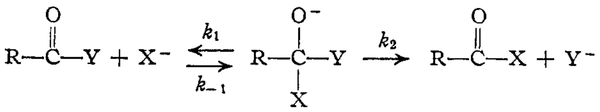
TABLE IV

THE REACTION OF SOME ANIONS WITH ACID DERIVATIVES

Compound	HO^-	HO_2^{-a}	$C_3H_7CO_2^{-b}$	I^{-c}
Ethyl acetate	+	−	−	−
Phenyl benzoate	+	+	−	−
Acetic anhydride	+	+	+	−
Benzoyl chloride	+	+	+	+

[a] Ethyl acetate is known not to react with hydroperoxide ion (ref. 4). Phenyl benzoate has been found to react rapidly (unpublished results), and both acetic anhydride and benzoyl chloride react with hydroperoxide ion to give acetyl and benzoyl peroxides, presumably through the peracid (A. M. Clover and G. F. Richmond, *Am. Chem. J.*, **29**, 182 (1903); H. v. Pechmann and L. Vanino, *Ber.*, **27**, 1511 (1894)). [b] The reaction of ethyl acetate and phenyl benzoate with butyrate ion would give an anhydride and ethoxide or phenoxide ion. Thus, the reaction goes in the reverse rather than forward direction. Acetic anhydride reacts with butyrate ion to give butyric anhydride (A. Michael and R. Hartman, *Ber.*, **34**, 918 (1901)) and mixed anhydrides are commonly prepared by the reaction of carboxylic acid salts with benzoyl chloride (L. Chiozza, *Ann.*, **84**, 108 (1852)). [c] The reaction of esters or anhydrides with iodide ion would give an acyl iodide and an alkoxide or carboxylic acid salt. Thus, the reaction goes in the reverse rather than forward direction. Benzoyl iodide has been prepared by the reaction of iodide ion with benzoyl chloride (H. Staudinger and E. Anthes, *Ber.*, **46**, 1423 (1913)).



$$R{-}\overset{\overset{O}{\|}}{C}{-}Y + X^- \overset{k_1}{\underset{k_{-1}}{\leftrightarrows}} R{-}\underset{\underset{X}{|}}{\overset{\overset{O^-}{|}}{C}}{-}Y \xrightarrow{k_2} R{-}\overset{\overset{O}{\|}}{C}{-}X + Y^-$$

philicity of the attacking ion, whereas the latter should be in some measure a function of the relative basicity of X^- and Y^-. Thus, if X^- is a weaker base than Y^-, the reaction should not proceed. But, if X^- is a stronger base than Y^-, the reaction should proceed and the rate of reaction should be largely a function of the nucleophilicity of X^-.

This hypothesis is borne out in the case of phenyl benzoate. Here, phenol is a stronger acid than hydrogen peroxide, and therefore this ester should react with both hydroxyl ion and hydroperoxide ion, and the rate of reaction should be larger for the latter ion. This has been found to be the case.[12] Another test may be found in the reaction of benzoyl chloride with various ions because of the wider range of useful groups. A study of this type is now planned.

[12] The details of this investigation will be published in a later communication.

SEATTLE, WASHINGTON

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Mechanisms of the Fries Reaction[1]

BY RICHARD BALTZLY, WALTER S. IDE AND ARTHUR P. PHILLIPS

RECEIVED NOVEMBER 10, 1954

The Fries reaction is interpreted as proceeding through a complex of phenol ester and aluminum chloride which, when sufficiently polarized, becomes capable of acylating a different molecule or of rearranging. The former process follows the usual rules of orientation while the latter affords only *o*-hydroxy ketone. As a rule the rearrangement is favored only at high temperatures, but it is facilitated by electron-repelling groups in the phenolic portion and can predominate even at low temperatures if those groups activate an *ortho* position. It has been found that conditions favoring formation of *p*-hydroxy ketone also favor reaction with a competitor substance, in this case diphenyl ether. Under other conditions both of these processes can be minimized or suppressed.

The present communication describes work carried out over a period of several years and intended to decide whether or not the *ortho* shift of the Fries reaction is in substantial degree the result of an intramolecular rearrangement. During the investigation our view-point has been altered materially and it appears most expeditious to state at the beginning the conclusions we have reached, thereafter relating the experimental findings to these conclusions.

It is perhaps well to state at this point that, although it was our constant desire to devise and perform a critical experiment settling this question no single experiment devised to that end has given a decisive result. The failure of these efforts is itself a datum and it is therefore an important characteristic of the mechanism to be presented that no critical experiment should in fact be possible. Despite this disadvantage, we believe the cumulative effect of the evidence to be presented is sufficient to establish a general picture of the Fries reaction.[2]

In the presence of a sufficient excess of aluminum chloride, phenol esters may be considered to be completely coördinated and there is reason to believe that the reaction rate is of first order with respect to this conjugate acid.[3] This coördination complex may be represented by the scheme shown wherein the covalent complex Ia and the ion-pair I∞ are obviously limiting states which may never be approximated and between which not one but many intermediate stages (symbolized by Ia) of increasing polarization may intervene.[4] The states of lower polarization may be presumed to

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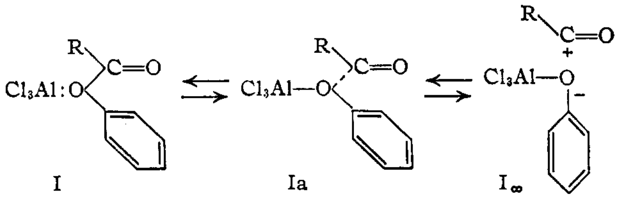
[1] Presented in part before the Organic Division of the American Chemical Society, Chicago, Ill., Sept., 1953.

[2] General reviews of the literature up to 1943 have been published by A. H. Blatt, *Chem. Revs.*, **27**, 429 (1940); "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 342.

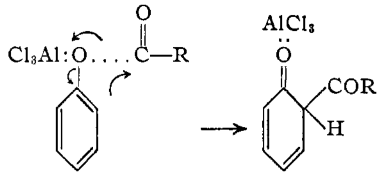
[3] R. Baltzly and A. P. Phillips, THIS JOURNAL, **70**, 4191 (1948). Parallel experiments to the same effect have been reported in some detail with boron fluoride catalyst (Kästner, Thesis, Marburg, 1937, in "Newer Methods of Preparative Organic Chemistry," First American Edition, Interscience Publishers, Inc., New York, N. Y., 1948, pp. 284–291).

[4] It is obvious that similar polarized but not ionized complexes may be the reagents in the Friedel–Crafts reaction itself. The Friedel–Crafts reaction proceeds more rapidly than the Fries reaction, so one may expect that polarization is more facile with $Cl_3Al{\cdot\cdot}ClCOR$ than with $Cl_3Al{\cdot}O(Ph){\cdot}COR$. It is arguable also that discrete oxo-carbonium ions ought to attack compounds such as nitrobenzene and *o*-dichlorobenzene that are notoriously not affected by Friedel–Crafts reagents. Unfortunately only relatively stable oxo-carbonium ions have been demonstrated unambiguously as having discrete existence (*cf.* H. P. Treffers and L. P. Hammett, THIS JOURNAL, **59**, 1708 (1937)). Nitrobenzene does not appear to be attacked appreciably by mesitylenecarboxylic acid dissolved in 100% sulfuric acid.


I Ia I$_\infty$

be normal while those of higher polarization with I$_\infty$ as the limiting condition would be activated states. Depending on the susceptibility of various aromatic species present to electrophilic attack, various degrees of polarization would suffice to produce rapid substitution. Thus, for any particular aromatic species the reaction rate could be of first order in respect to the conjugate acid, but this rate need not be the same with a different aromatic species for which a different level of polarization could operate. With certain species, second-order kinetics might be demonstrable, but no such instance has been reported to date.

It should be noted that as the polarization of the conjugate acid increases, not only does the acyl portion become more electrophilic, but also the phenolic portion acquires a higher electron density and is itself more subject to attack. By and large, it may be presumed that attack is readiest *para* to the oxygen and substitution by another molecule will take place there by preference. At the same time the *ortho* positions to the oxygen will become somewhat sensitive. The activation energy in the *ortho* positions will tend to be greater than in the *para*, and it is believed that little intermolecular *ortho* substitution occurs where the *para* position is available. Steric factors, however, do favor an *ortho* shift which can be regarded either as an intramolecular electrophilic substitution or, in reverse, as a nucleophilic rearrangement of the Whitmore type.


I II

The intermediate II will presumably lose a proton and simultaneously or subsequently a chloride ion restoring an aromatic system.[5] In general, this intramolecular rearrangement, requiring a higher state of activation, can predominate only at higher temperatures. When, however, independent electronic influences within the phenolic portion of the system activate an *ortho* position, the rearrangement may predominate even under mild conditions. Thus it has long been known[6,7] that aliphatic esters of *m*-cresol afford mainly *o*-hydroxy ketones at room temperature in nitrobenzene solution—under which conditions the formation of *p*-hydroxy ketones is usually favored.[8] Similarly, Kindler and Oelschläger[9] have reported recently that esters of 4-chloro-3-methylphenol undergo the Fries (with boron-trifluoride catalyst) much more readily than esters of 4-chlorophenol.

It is our view, accordingly, that the intermolecular process results in substitution in those positions normally expected in aromatic compounds. The rearrangement process affords only *o*-hydroxy ketone but may not predominate in cases—*e.g.*, with the esters of *p*-cresol—in which an intermolecular process would also give *ortho* substitution. In fact, we should expect that rearrangement would be more rapid in *m*-cresyl esters than in *p*-cresyl esters despite the fact that only an *ortho* shift can occur in the latter.[10]

General Considerations

In the controversy between v. Auwers and Rosenmund as to the mechanism of the Fries reaction, the major objections of the latter to an intermolecular mechanism were based on the feeling that the products of the Fries were not those to be expected of an ordinary aromatic substitution. While this argument has considerable force it is rather hard to evaluate since it is not known in any instance into what particular species substitution really occurs. All of the types: Cl_2AlOAr, Cl_3AlOAr^-, RCOOAr and $Cl_3AlO(COR)Ar$ probably occur to varying extents and it is most unlikely that their relative amounts are identical in different circumstances or that even under one set of conditions only one species is the sole source of the product. Further, only with the simple phenol esters have there been studies of orientation.

We have examined the products from the bromination of *m*-cresol and *m*-cresyl acetate in nitrobenzene solution in the presence and in the absence of excess aluminum chloride and in none of these experiments was evidence obtained for other than *para* monobromination. The solution containing *m*-cresol and aluminum chloride released a considerable amount of hydrogen chloride before the bromine was added. It therefore is reasonable to suppose that it contained the species $Cl_3AlO(H)Ar$ and Cl_2AlOAr which appear to approximate the first two species probable in the Fries.[11] The simple ester[12] and its conjugate with aluminum chloride also

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(5) Similar eliminations of hydrogen chloride are, of course, to be presumed in all other reactions of the Friedel-Crafts type.

(6) C. E. Coulthard, J. Marshall and F. L. Pyman, *J. Chem. Soc.*, 280 (1930).

(7) R. Baltzly and A. Bass, THIS JOURNAL, **55**, 4292 (1933).

(8) *Cf.* K. W. Rosenmund and W. Schnurr, *Ann.*, **460**, 56 (1927). These authors are responsible for the general rule that high temperatures favor the *ortho* shift and low (using nitrobenzene as a solvent) the *para*. General observation[2] has confirmed their thesis in its main practical aspects. In regard to detail they were frequently unreliable, stating, for example, that *m*-cresyl acetate yields no appreciable *o*-hydroxy ketone below 60° and that the higher *m*-cresyl esters behave in the same way. Coulthard, Marshall and Pyman (ref. 6) shortly demonstrated that the latter part of this statement was incorrect. From evidence to be presented later we can say that the first part is also wrong.

(9) K. Kindler and H. Oelschläger, *Ber.*, **87**, 194 (1954). This latter point is, of course, consistent with either mechanism.

(10) The preponderance of the *para* shift with *o*-cresyl esters (refs. 2, 3) may be attributed not only to the halving of the available *ortho* positions but to the *ortho* methyl group preventing the ester from assuming the spatial position needed for a rearrangement.

(11) It is not apparent to us how the species Cl_3AlOAr^- may be produced unambiguously for study. For the present argument, it seems clear that if a neutral particle Cl_2AlOAr, where Ar is *m*-tolyl, directs *para* to the oxygen, the anion corresponding must also be *para* directing.

(12) C. R. Hauser and E. H. Man (*J. Org. Chem.*, **17**, 390 (1952)) have produced evidence that under certain conditions the ester is a principal object of attack. Whether unconjugated ester is available must depend on the conditions of the reaction.

TABLE I

FRIES REACTIONS OF PHENYL ESTERS UNDER VARIOUS CONDITIONS

Expt.	Ester	Ester, mmoles	$AlCl_3$, mmoles	Solvent	Vol. of solvent, cc.	*T*, °C.	Time, hr.	Yields of ketones, %	
								o-Hydroxy	*p*-Hydroxy
I	Benzoate	200	220	$PhNO_2$	300	98	5	8.6	64
II	Benzoate	200	220	$PhNO_2$	300	120	2	15	54
III	Heptoate	200	400	$PhNO_2$	500	37.5	44.5	14	72
IV	Heptoate	200	400	$PhNO_2$	2000	37.5	44.5	18.5	50
V	Propionate	320	380	Heptane[a]	410	80–90	7	53	36
VI	Propionate	320	640	Heptane[a]	410	80–90	5	51	33
VII	Propionate	320	380	$C_2H_2Cl_4$	300	95	5	36.5	36.4
VIII	Propionate	320	380	$C_2H_2Cl_4$	1100	95	5	33	30
IX	Propionate	320	380	$C_2H_2Cl_4$	610	95	5	43	30
X	Butyrate	320	380	$C_2H_2Cl_4$	360	95	6	49.5	43
XI	Butyrate	330	400	Heptane[a]	400	80–90	6	40	50

[a] Skellysolve C distilled from sodium.

orient *para*. Thus the *m*-cresyl esters which give predominantly *o*-hydroxy ketones in the Fries should be expected to afford *para* substitution products from intermolecular electrophilic substitution.

A second major difficulty in interpreting the Fries exclusively on an intermolecular basis is the fact that as the temperature of the reaction rises, the *ortho* shift not only increases in relative importance—which would be expected as in nitration—but becomes heavily predominant. On the assumption that the activation energy for *para* substitution in this type of compound is less than for *ortho*, present theory cannot account for a heavy predominance of *ortho* substitution under any conditions except by postulating either heavy steric preference (as above) or instability of the *para* product relative to the *ortho*. Conversion of *para*-hydroxy ketone to the *ortho* isomer has been claimed[8] only under more drastic conditions than employed in the Fries and has not been duplicated by later investigators.[2] Explanation of the phenomena through a sterically favored process of somewhat higher activation energy leads readily to the rearrangement mechanism.

Preliminary Experiments Leading to a Choice of Conditions

If the *para* shift should require a complete ionization, the *ortho* proceeding through an intermediate polarization, the *para* shift would be favored by a more polar solvent. Some evidence is available to this effect,[13,14] but the case is inconclusive. The main difficulty in pursuing this line of argument is that while less-polar solvents may dissolve the phenol ester and aluminum chloride or bromide separately in satisfactory fashion, the intermediate complexes and final products are alike insoluble and form second phases of unknown polarity and composition.

A number of reactions, intended largely for preparative purposes, were carried out under various conditions of solvent and temperature. These experiments, whose results are shown in Table I, are roughly comparable to the series of Marey, Baddar and Awad.[14] While inconclusive, they do indicate (in particular, experiments III and IV) that the *para* shift is less predominant at lower temperatures than has been supposed.[2,8,15]

During this same period a mixed Fries was run by the "baking procedure" as a check to the similar experiment of Rosenmund and Schnurr.[8] The esters were *m*-cresyl caproate and 2,6-dimethylphenyl acetate. The *m*-cresyl component was accounted for in almost quantitative fashion as 6-caproyl-*m*-cresol and 6-acetyl-*m*-cresol in the proportion of 5-1. It was possible to isolate 4-acetyl-2,6-dimethylphenol and 4-caproyl-2,6-dimethylphenol in a ratio of 6-1 and in 82% yield (based on the 2,6-dimethylphenol residues available).[16] The proportion of cross-product was somewhat smaller than in Rosenmund and Schnurr's experiment (1–3) but the result is in the same direction and open to the same objections.[2] On the other hand, the proportion of cross-product was entirely comparable to the results obtained in later competitive experiments under different conditions.

Because of the demonstrated possibilities of ester exchange[2] it was decided that experiments of this type were incapable of giving a critical result and it seemed preferable to employ a competitive receptor for intermolecular acylation that was not itself an ester. Such a receptor ought to afford products that would be readily separable from the normal products of a Fries. Diphenyl ether, which is known to be an effective competitor,[17] was selected. It also seemed clear that operations should be in nitrobenzene solution since only that solvent could be expected to maintain a one-phase system through a number of variations. This in turn directed attention to *m*-cresyl esters as known to give large amounts of *o*-hydroxy ketones at acceptable temperatures and as especially likely to form these through a true rearrangement.

Experiments with Aliphatic Esters of *m*-Cresol

Previous work with higher esters of *m*-cresol has

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(13) L. Szekeres and B. Karsay, *Gazz. chim. ital.*, **77**, 471 (1947); *C. A.*, **42**, 3356^e (1948).

(14) A. F. Marey, F. G. Baddar and W. I. Awad, *Nature*, **172**, 1186 (1953).

(15) The results of these two experiments also suggest some deviation from first-order kinetics for the formation of the *p*-hydroxy ketone in this particular system. Experiments I and II were performed to explore the temperature limits of the nitrobenzene technique. At these higher temperatures, especially at 120°, the *p*-hydroxy ketone is rather heavily contaminated with red impurities perhaps of the nature of benzaurin.

(16) These figures involve the quantities of the substances isolated in pure form and also those reasonably deduced from the quantities and properties of small intermediate fractions.

(17) A. W. Ralston, M. R. McCorkle and S. T. Bauer, *J. Org. Chem.*, **5**, 645 (1940).

TABLE II

FRIES REACTIONS OF *m*-CRESYL ESTERS IN NITROBENZENE AT 25–30°

Expt.	Ester	Ester, mmoles	$AlCl_3$, mmoles	Solvent, cc.	Time, hr.	Yields of ketones, % *o*-Hydroxy	Yields of ketones, % *p*-Hydroxy
XII	Acetate	200	400	400	66	28	63.5[a]
XIII	Acetate	200	224	200	92	45	30
XIV	Propionate	200	400	400	66	79	15[b]
XV	Propionate	190	380	310[c]	66	67	9.5[b]
XVI	Butyrate	200	400	400	66	65	11[d]
XVII	Butyrate	200	220	250	66	70	4[d]
XVIII	Valerate	200	400	400	66	69	11[e]
XIX	Valerate	200	400	400	24	69	14[e]
XX	Valerate	250	280	300	24	70	4[e]
XXI	Caproate	280	500	600	48	64	4.3[f]
XXII	Heptoate	200	400	400	66	82	10[f]
XXIII	*p*-Cresyl caproate	100	200	300	72	60	. .

[a] Ref. 8. [b] Ref. 7. [c] Plus 830 cc. of tetrachloroethane. [d] Ref. 6. [e] Colorless needle-prisms from hexane or aqueous methanol, m.p. 88–89°. *Anal.* Calcd. for $C_{12}H_{16}O_2$: C, 75.0; H, 8.3. Found: C, 75.1; H, 8.7. [f] New compound: see Experimental.

been largely of a preparative nature and while good yields of *o*-hydroxy ketone had been obtained the presence or absence of *p*-hydroxy ketone had not been demonstrated. Accordingly the series of reactions whose results are presented in Table II were run and the amount of minor product as well as of major estimated as accurately as possible. Except with *m*-cresyl acetate which affords substantial amounts of *p*-hydroxy ketone the results were quite consistent throughout the series. It also was observed regularly that an increase in the quantity of catalyst beyond a 1:1 ratio favored the *para* shift (this also has been observed by Ralston and coworkers[17,18]). Examination of the data reveals that the time allowed was usually greater than necessary and that the effect of excess of aluminum chloride was principally on the yield of *p*-hydroxy ketone, the conversion to *o*-hydroxy ketone being remarkably constant (run XXI was a very early one and the isolation of products may have been less complete than in later operations). Run XXIII, with *p*-cresyl caproate was performed for purposes of comparison. Rosenmund and Schnurr have stated that *p*-cresyl acetate gave only a trace of ketone in 24 hours. This is not to be expected from the mechanism we propose and, for *p*-cresyl esters in general, clearly does not correspond to the facts.[19] It is, however, probable that the reaction is somewhat slower with *p*-cresyl esters—as would be expected.

The competitive Fries reactions whose results are shown in Table III are only roughly comparable to the runs without competitor. This arises from a difficulty which was encountered in the first of these reactions (Experiment XXVI): namely, that diphenyl ether itself coördinates aluminum chloride to some extent.[20] If one of the simple Fries reactions is altered merely by addition of competitor, the acidity is somewhat diminished. Thus we had expected to obtain a more complete conversion in XXVI than in the preceding run XXI by extending the time of reaction from 48 to 114 hours, but the actual conversion was no greater and perhaps somewhat less. It is, however, uncertain how much more catalyst should be added to restore the balance. It also did not seem desirable to attempt competitive runs through the whole series of esters. With the higher members, separation of the products was excellent but the boiling points of the mid-series hydroxy ketones were less removed from those of diphenyl ether than seemed desirable. The lower runs XXIV and XXV presented considerable difficulties and it was necessary to isolate the *o*-hydroxy ketone as its phenylhydrazone. It is furthermore to be observed that the volume was usually less when smaller excesses of aluminum chloride were present.[21] Thus the concentration effects, in so far as they operated, would have tended to increase the amount of bimolecular reaction in those cases in which the least of it was observed. That this consideration is of some consequence is shown by the result of experiment XXV in which a rather inconveniently large volume of solvent was em-

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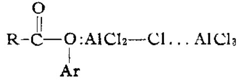
(18) Two explanations of this phenomenon occur to us. The excess of aluminum chloride could operate by increasing the polarity of the solution, thus favoring a higher degree of polarization. Alternatively, it is possible that complexes can be formed not only from $AlCl_3$ but from Al_2Cl_6. The latter type, presumably  $R\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}\underset{\underset{\displaystyle Ar}{|}}{O}\text{:}AlCl_2\text{—}Cl\ldots AlCl_3$ should be more highly polarized and more likely to attack another molecule. Ralston's group (*cf.* A. W. Ralston, M. R. McCorkle and E. W. Segebrecht, *J. Org. Chem.*, **6**, 750 (1941)) also found that *less* than equimolecular amounts of aluminum chloride again favored the *para* shift. They interpret this as due to the influence of such catalysts as Cl_2AlOPh, but their findings also are consistent with the fact that they would have had large amounts of uncoördinated ester which would be more susceptible to electrophilic attack than the coördinated. On the reasonable assumption that a *p*-hydroxy ketone would have some tendency to bind *two* molecules of catalyst, a Fries run with a bare equivalent or a slight excess of aluminum chloride would gradually result in the presence of uncoördinated ester. This would account for the second finding that the *ortho* shift predominated at the start (first 15–30 minutes) and the *para* shift later in their reactions. A detailed analysis is not possible since not all their systems were homogeneous.

(19) Rosenmund and Schnurr do not seem to have appreciated the value of the ferric chloride test in detecting the presence of chelate hydroxy ketones. Properly employed, it permits rapid decision as to which fractions or samples deserve serious examination for the presence of such compounds.

(20) That such coördination does take place is shown by the fact that addition of diphenyl ether to a solution of aluminum chloride in nitrobenzene immediately changes the olive-brown color to a more chocolate-brown hue.

(21) We generally employed slightly more nitrobenzene than was necessary to dissolve the aluminum chloride. This was partly for convenience in the working up and partly because it was felt that large amounts of nitrobenzene (which has feeble basic properties) might slow the reaction unduly.

TABLE III

FRIES REACTIONS OF *m*-CRESYL ESTERS IN THE PRESENCE OF DIPHENYL ETHER AT 25–30°

Expt.	Ester	Ester, mmoles	Ph_2O, mmoles	$AlCl_3$, mmoles	Vol. of $PhNO_2$, cc.	Time, hr.	Yields of ketones, %[a]		
							o-Hydroxy	*p*-Hydroxy	Acyldiphenyl ether
XXIV	Acetate	300	400	400	400	257	46[b]	27	20[c]
XXV	Acetate	300	400	400	2000	429	51[b]	6.5	2–5[c]
XXVI	Caproate	125	200	250	400	114	54	Total involatile, 6–15	
XXVII	Caproate	200	220	600	550	66	45	11	37.5[d]
XXVIII	Caproate	200	220	400	400	162	60.5	7.5	24.5[d]
XXIX	Caproate	230	310	300	300	330	75	3.3	16.5[d]
XXX	Heptoate	190	200	600	550	93	60	7.5	32[e]
XXXI	Heptoate	200	220	600	550	66	57.5	7	35.7[e]
XXXII	Heptoate	250	310	300	300	287	76	1.6	10[e]
XXXIII	*p*-Cresyl heptoate	200	310	700	900	113	31.5[f]	. .	50[e]

[a] Calculated on the amount of ester, as the source of acyl groups. [b] Isolated as the phenylhydrazone (R. Anschütz and M. E. Scholl, *Ann.*, **379**, 333 (1911)). [c] Ref. 39. [d] New compound; see Experimental. [e] M.p. 36°. *Anal.* Calcd. for $C_{19}H_{22}O_2$: C, 80.8; H, 7.9. Found: C, 80.8; H, 8.0. [f] B.p. 158° at 8 mm. The phenylhydrazone forms pale yellow needles from alcohol and melts at 107–108°. *Anal.* Calcd. for $C_{20}H_{26}N_2O$: C, 77.4; H, 8.5. Found: C, 77.4; H, 8.7.

ployed. The total conversion was rather poor but the yields of *p*-hydroxy ketone and acyldiphenyl ether were greatly diminished. This in itself suggests that these two products are the result of intermolecular reaction while the *o*-hydroxy ketone is not.

Despite these drawbacks the pattern is fairly clear: the conditions that favor formation of the *p*-hydroxy ketone also favor reaction with the competitor. It is difficult to avoid the conclusion that the bulk of the *o*-hydroxy ketone must be formed by a process distinct from that resulting in the other products. Again, the result of experiment XXXIII is consistent with our general hypothesis on the basis of which it was predicted that esters of *p*-cresol would tend to rearrange less than those of *m*-cresol and to react more predominantly in an *inter*-molecular fashion.

Consideration of these competitive reactions does lead, however, to the conclusion that formation of acyldiphenyl ether is at the expense of both the hydroxy ketones and not solely of the *para*. This is inconsistent with the supposition that intermolecular reaction requires separation of discrete oxocarbonium ions. It is not inconsistent with the mechanism here proposed if we suppose that diphenyl ether is somewhat too reactive a competitor. Should polarized ester conjugates, capable of rearranging *or* of reacting intermolecularly be offered the opportunity of attacking another species more sensitive than themselves, it seems logical to suppose that a greater proportion of intermolecular reaction would ensue.

An experiment was devised to test this supposition, acetyl chloride being allowed to react at room temperature with diphenyl ether and *m*-cresyl *m*-chlorobenzoate[22] in the presence of excess aluminum chloride. From the reaction mixture 4-phenoxyacetophenone was isolated in 71–82% yield, and 77% of the possible amount of *m*-chlorobenzoic acid was recovered. Small quantities of 4-hydroxy-2-methylacetophenone (1%), 4-hydroxy-2-methyl-3′-chlorobenzophenone (4.5%) and 4-phenoxy-3′-chlorobenzophenone (6–10%) also were isolated (*o*-hydroxy ketones were present in traces). It is evident that both acetyl and benzoyl moieties attacked diphenyl ether more readily than the *m*-cresyl ester.

Experiments with Aromatic Esters of Phenols

The work described in this and the following section was undertaken largely on the hypothesis that intermolecular reaction required a discrete cation. It is presented briefly as having only a subsidiary relation to our present thesis.

It was expected that the *para* shift could be encouraged by electron-repelling substitution in the acyl portion and discouraged by electron-attracting substitution. This line demanded, for practical purposes, the use of esters of benzoic acids. Consideration of the environment of the Fries suggested that a *p*-methyl *group* and *m*-chlorine would be acceptable and perhaps optimal examples of the two effects. Accordingly experiments XXXIV–XXXIX, whose results are shown in Table IV, were performed. Comparison of experiments XXXIV, XXXVI and XXXVII shows that the variations were in the expected direction, the *p*-toluate of *m*-cresol reacting somewhat faster than the benzoate

TABLE IV

RESULTS OF FRIES REACTIONS WITH AROMATIC ESTERS OF PHENOLS

In all cases, 0.1 mole of ester and 0.2 mole of aluminum chloride reacted in 300 cc. of nitrobenzene; experiment XXXV stood for 90 hours and XXXIX 66 hours at 25–30°; the other experiments ran 18 hours at 62–63° except XXXVII which was allowed 72 hours.

Expt.	Ester	*o*-Hydroxyketone, %	*p*-Hydroxyketone, %	Conversion, %
XXXIV	*m*-Cresyl benzoate	15	42	59
XXXV	*m*-Cresyl benzoate	4.5	45	49.5
XXXVI	*m*-Cresyl *p*-toluate[a]	16[b]	50[c]	66
XXXVII	*m*-Cresyl *m*-chlorobenzoate[d]	28[d]	40[d]	68
XXXVIII	3,5-Dimethylphenyl benzoate[d]	80[d]	0	80
XXXIX	3,5-Dimethylphenyl benzoate	55	0	55

[a] Crystallized from hexane, m.p. 66°. *Anal.* Calcd. for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2. Found: C, 79.8; H, 6.3. [b] L. Chardonnens and A. Würmli, *Helv. Chim. Acta*, 29, 922 (1946). [c] Colorless crystals from ether–hexane, m.p., 108–109°. *Anal.* Calcd. for $C_{15}H_{14}O_2$: C, 79.6; H. 6.2. Found: C, 79.6; H, 5.9. [d] See Experimental section.

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(22) This ester was chosen on the basis of the evidence (presented in the next section), that it underwent a rather slow Fries isomerization.

and affording more *p*-hydroxy ketone. The *m*-chlorobenzoate reacted less rapidly and gave more *o*-hydroxy ketone. However, while the variations observed were beyond experimental error, they were much less marked than had been anticipated. Experiments XXXVIII and XXXIX with 3,5-dimethylphenyl benzoate accorded with predictions that a rearrangement should be further facilitated by a second methyl group in a suitable position. In this instance it is clear that the *ortho* shift is going faster than the combined isomerizations in the other compounds of this series. A competitive run in the presence of diphenyl ether resulted, however, in 40% of the benzoyl moieties being attached to diphenyl ether. It would appear that rearrangement is rapid at a degree of polarization permitting the attack on diphenyl ether but substantially excluding that on another ester molecule.

Experiments with Pivalic Esters

It has long been known[23] that pivaloyl chloride is decomposed by aluminum chloride with liberation of carbon monoxide. This cleavage may be rationalized as a breakdown of the oxo-carbonium ion $\mathrm{Me_3C{-}\overset{+}{C}{=}O}$ or a polarized precursor to form $\mathrm{Me_3C^+}$. As a result, pivaloyl chloride is of rather irregular utility in Friedel–Crafts reactions.[24] It would be expected therefore that a process dependent on formation of a carbonium ion would fail with esters of pivalic acid while a rearrangement process might succeed. In agreement with this supposition, Tarbell and Fanta[25] report that 2,6-dichlorophenyl pivalate gave no rearrangement product after 24 hours in nitrobenzene at room temperature. Thirty per cent. of the ester was recovered unchanged and a 40% yield of the phenol was isolated. This presumably resulted from cleavage as suggested above. In carbon bisulfide as solvent and with diphenyl ether present about a 10% yield of pivaloyl diphenyl ether was isolated.

Pivalic esters were prepared from *m*-cresol and *p*-cresol. In the baking procedure (110–140°) *m*-cresyl pivalate gave off copious amounts of carbon monoxide and only traces of ketonic material could be demonstrated. In nitrobenzene at room temperature evolution of carbon monoxide was not grossly observable and 2-hydroxy-4-methylpivalophenone was isolated in 22% yield (as the phenylhydrazone). Under identical conditions 2-hydroxy-5-methylpivalophenone was obtained from *p*-cresyl pivalate in not over 3% yield.

In a Friedel–Crafts reaction of pivaloyl chloride and diphenyl ether in nitrobenzene at room temperature much carbon monoxide was evolved and a maximum of 5–6% of ketonic material could be demonstrated. This was not homogeneous and the only crystalline semicarbazone that could be isolated had the composition of a *t*-butylphenoxypivalophenone semicarbazone.

Absorption Spectra

The rearrangement product of 3,5-dimethylphenyl benzoate is of rather especial interest. Its melting point, appearance and solubilities are unusual for an *o*-hydroxy ketone and it does not give a positive ferric chloride test. Despite these facts it is undoubtedly 2-hydroxy-4,6-dimethylbenzophenone since it is identical with the compound prepared in a high-temperature Fries[26,27] and converted to a coumarin.[26]

Such behavior can be accounted for by steric interference and should correspond to marked peculiarities in the absorption spectrum.[28] Accordingly the absorption spectra of the 2-hydroxy-4,6-di-

TABLE V

ABSORPTION SPECTRA OF SOME HYDROXY- AND METHOXY-BENZOPHENONES

*p*H[a]	λ_{max}, mμ	E_{max}, $\times 10^{-3}$	λ_{min}, mμ	E_{min}, $\times 10^{-3}$
		2-OH-4-Me		
1	276	13.4	237	6.6
	330	4.5	307	3.4
11	240	16.6	315	1.42
	(275) infl.	(9.3)		
	375	3.3		
13	240	18.5		
	(275) infl.	8.0	310	0.7
	380	4.0		
		2-OMe-4-Me[b]		
	250	15.5		
	(300–310) plateau	3.1		
		4-OH-2-Me		
1	252	12.3	225	7.6
	290	9.0	273	7.6
11	250	14.5	282	3.1
	340	14.1		
		4-OMe-2-Me[c]		
	248	11.4	268	6.4
	285	8.6		
		2-OH-4,6-$\mathrm{Me_2}$		
1	253–255	14.8	232	5.9
	(280–290) infl.	4.0–3.5		
11	245	17.4		
	(280) shoulder	6.0	330–335	0.7
	370–380	1.0		
		2-OMe-4,6-$\mathrm{Me_2}$[d]		
	253–255	14.6	233	7.0
	(290) faint shoulder	(3.3)		

[a] The values at *p*H 1 were determined in methanol, those at *p*H 11 in 90% methanol and the figure for *p*H 13 in approximately 10% methanol. The ethers gave identical curves in acid and alkaline solution. [b] By methylation of the hydroxy ketone with methyl sulfate and alcoholic alkali; colorless solid from aqueous alcohol; m.p. 78°. *Anal.* Calcd. for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2. Found: C, 79.4; H, 6.2. [c] N. P. Buu-Hoi, R. Boyer and B. Eckert, *J. Org. Chem.*, **17**, 1463 (1952). [d] By action of diazomethane on corresponding phenol; colorless solid from hexane; m.p. 78–79°. *Anal.* Calcd. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 79.9; H, 6.8.

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[23] J. Böeseken, *Rec. trav. chim.*, **29**, 100 (1910).

[24] Very few examples of use of this acid chloride appear in the literature. Tarbell and Fanta[25] report a 70% yield in an acylation of diphenyl ether "by the usual procedure," presumably in carbon bisulfide. An early attempt in this Laboratory to prepare pivalophenone using excess benzene as solvent gave no isolable product. It seems likely that successful use of the acid chloride is dependent on minute changes in experimental conditions.

[25] D. S. Tarbell and P. E. Fanta, THIS JOURNAL, **65**, 2169 (1943).

[26] G. Wittig, A. Oppermann and K. Faber, *J. prakt. Chem.*, **158**, 61 (1941).

[27] G. Baddeley, *J. Chem. Soc.*, 273 (1943).

[28] *Cf.* M. T. O'Shaughnessy and W. H. Rodebush, THIS JOURNAL, **62**, 2906 (1940).

methyl-, 2-hydroxy-4-methyl- and 4-hydroxy-2-methylbenzophenones and of their methyl ethers were determined. The more prominent data are shown in Table V. It is evident that the spectrum of 2-hydroxy-4,6-dimethylbenzophenone entirely lacks the chelate band at 276 mμ shown by the 2-hydroxy-4-methyl analog. In fact, its absorption resembles a rough summation of that of a simple phenol with that of a simple benzoyl derivative. (Such interference with conjugation also would be expected of 4-hydroxy-2,6-dimethylbenzophenone which was not available for study.)

The *p*-hydroxy ketones would be expected to be, and are, somewhat more acidic than simple phenols. The chelate *o*-hydroxy ketones appear to be rather less acidic, since the higher isomer pairs are separable by extraction with 0.5–1 *N* alkali from ethereal solutions. (Obviously the solubilities of the unionized compounds also are involved here.) In the case of 2-hydroxy-4-methylbenzophenone, calculations based on the extinction coefficients at *p*H 11 and 13 for λ 390 and 240 mμ, indicate the presence of 16–25% of free phenol at *p*H 11. This corresponds to values of pK_a from 10.3 to 10.5.

Experimental

The methods employed followed a general scheme which was varied in detail to allow for the physical properties of the compounds expected.

The aluminum chloride first was dissolved with stirring in slightly more nitrobenzene than was necessary. Stirring was continued until the heat of solution was dissipated and the ester (and competitor if any) then was added. This addition tended to cause a slight rise in temperature (not over 5°). After stirring to ensure mixing, the solutions were allowed to stand for the stated periods and then hydrolyzed by addition of cracked ice and hydrochloric acid. The total mixtures were then steam distilled.

With the higher aliphatic esters, from which the products of interest would not be readily volatile with steam, the steam distillation was interrupted when the bulk of the nitrobenzene had come over. The residue was cooled, taken into ether and the ether was evaporated. A considerable quantity of methanol then was added and hydrogen chloride gas was run in to give a strongly acid solution which was allowed to stand overnight. This step was designed to ensure cleavage of any phenol esters remaining. The methanol then was boiled off on the steam-bath and the residue was partitioned between ether and water. The ethereal layers were washed with water to remove any inorganic material and dried over small amounts of calcium chloride, usually with addition of petroleum ether. After drying, the solvents were evaporated and the residual oils subjected to vacuum distillation.

When the bulk of the *o*-hydroxy ketone had been distilled, the residues were removed, dissolved in ether and extracted with portions of 0.5–1.0 *N* alkali. This process removes *p*-hydroxy ketone but not the *ortho* compounds. The crude *p*-hydroxy ketones, precipitated on acidification of the alkali extracts, gave no color with ferric chloride solution in alcohol but did contain considerable amounts of tar (and the greater part of the colored by-products of the reaction). The materials not extracted with alkali were fractionated further to obtain the products in pure form.

In the experiments with *m*-cresyl acetate and propionate the steam distillations were prolonged until a small portion of the distillate was negative to ferric chloride. The *o*-hydroxy ketone then was isolated from the steam distillate.

In the runs with benzoic esters none of the products of interest were volatile with steam so the nitrobenzene was steam distilled off completely and discarded.

Detailed procedures for typical runs follow.

Purification of *m*-Cresol.—Toward the end of this work *m*-cresol of apparently considerable purity became available. In the earlier period the source was Eastman Kodak Co. "practical grade" material which is of rather uncertain purity. The most obvious contaminant is, of course, *p*-cresol. Most of the *m*-cresyl esters made in this period were prepared from purified *m*-cresol obtained in the following general fashion.

A large quantity of *m*-cresol was dissolved in glacial acetic acid and brominated by about half of an equivalent amount of bromine in glacial acetic acid. From the product, after distillation of acetic acid, fractional distillation *in vacuo* permitted isolation of the bromocresol fraction and from this 4-bromo-*m*-cresol was separated by crystallization from hexane.

The bromine can be removed by the action of hot hydriodic acid and red phosphorus or, more smoothly, by hydriodic and hypophosphorous acids.

Debromination of 4-Bromo-*m*-cresol.—In a 2-l. 3-necked flask with stirrer and reflux condenser was placed 200 cc. of glacial acetic acid, 130 cc. of hypophosphorous acid (52%) and 100 cc. of constant-boiling hydriodic acid. The reaction mixture was stirred and heated until refluxing began and 198 g. of 4-bromo-*m*-cresol dissolved in 250 cc. of glacial acetic acid was admitted gradually through a dropping funnel. When all the bromocresol had been added, refluxing was continued for one hour. The solution was distilled at atmospheric pressure until layers formed, cooled and diluted with water. The cresol was taken into ether, washed with water, bicarbonate solution and again with water and dried over a little calcium chloride. On distillation, 84.5 g. of *m*-cresol boiling at 198–201° was obtained together with 10 g. boiling slightly outside that range. The residue was very small.

Fries Reaction of *meta*-Cresyl Acetate (Experiment XIII).—Thirty grams (0.224 mole) of anhydrous aluminum chloride was dissolved with stirring in 150 cc. of nitrobenzene. Stirring was continued until the temperature had fallen to about 30° and 30 g. (0.2 mole) of *m*-cresyl acetate together with 50 cc. more nitrobenzene was added. Stirring was continued for a few minutes and the solution was allowed to stand while protected from the air for 92 hours. Cracked ice and hydrochloric acid then were stirred in and the flask was set up for steam distillation. Distillation was suspended when no more material positive to ferric chloride was coming over. The distillation flask was cooled and the precipitated solid was filtered off. The filtrate was extracted with ether which was used to dissolve the crude precipitate (*p*-hydroxy ketone). The ethereal solution was filtered and boiled down to small volume with addition of hexane. The main crop of *p*-hydroxy ketone so obtained weighed 7 g. and melted at 126.5–128°. A second crop of 0.5 g. was obtained from the mother liquors.

The steam distillate was separated into layers, and the aqueous portion was extracted with ether which was added to the main nitrobenzene layer. After drying over a little calcium chloride, ether was evaporated and the solution was concentrated under a fractionating column. Two fractions were collected boiling at 98–99° (I) and 99–101° (II). The residue was dissolved in about 500 cc. of methanol and hydrogen chloride was run in until the temperature had risen to about 50°. This solution (III) was allowed to stand for about 40 hours and the solvent was then evaporated.

Fraction I was redistilled under a fractionating column, the nitrobenzene obtained being discarded. Fraction II was added and a further quantity of nitrobenzene separated, after which III was admitted. Fractions I' (b. 98–99° at 18 mm.), II' (b. 99–103°), III' (b. 105–124°) and IV (b. 124–127°) were taken. Fraction IV weighed 7.5 g. and was identified as 2-hydroxy-4-methylacetophenone by conversion of a portion to the phenylhydrazone. The intermediate fractions I'–III' were refractionated in series, the mother liquor from crystallization of the *p*-hydroxy ketone being added with III'. A further quantity (6 g.) of *o*-hydroxy ketone was obtained and from the residue 1.5 g. more *p*-hydroxy ketone. The total of *o*-hydroxy ketone was thus 13.5 g. and of *p*-hydroxy ketone, 9 g.

Competitive Fries Reactions of *m*-Cresyl Acetate and Diphenyl Ether (Expt. XXIV).—Fifty-four grams (0.4 mole) of aluminum chloride was dissolved in 350 cc. of nitrobenzene with stirring. When the solution had cooled to 30°, 45 g. (0.3 mole) of *m*-cresyl acetate, 65 cc. (0.4 mole) of diphenyl ether and 50 cc. more nitrobenzene were added. The solution, which assumed a deep brown color (as distinguished from the brown-olive shade of Fries reactions without the diphenyl ether) was allowed to stand for 257 hours. After hydrolysis, the solution was steam distilled until a sample of distillate gave a very weak ferric chloride test.

The steam distillate was separated into layers, the aqueous layer was extracted with ether and added to the nitrobenzene layer (which also contained most of the *o*-hydroxy ketone and unreacted diphenyl ether). After drying over a little calcium chloride the ether was evaporated and the residual oil was concentrated *in vacuo* under a fractionating column until the b.p. reached 92° at 11 mm. pressure. This distillate was negative to ferric chloride and was discarded. The undistilled residue was subjected to methanolysis as in the preceding experiment and fractionated *in vacuo*, the mother liquors from crystallization of the *p*-hydroxy ketone being added near the end. Five fractions were taken, the first boiling at 92–95° at 11.5 mm. and the last at 119.5–122° at 8 mm.

The steam-involatile fraction yielded 8 g. of pure *p*-hydroxy ketone as the first crop of crystals from ether–hexane. Four grams more was obtained from the mother liquors and by alkali extraction of the residue from the fractional distillation. The total yield of *p*-hydroxy ketone was thus 12 g.

The high-boiling residues from the fractional distillation, after alkali extraction were dissolved in hexane, charcoaled and cooled in the refrigerator. Two crops (9.5 g. and 2.5 g.) of *p*-acetyldiphenyl ether were obtained, the first melting at 49°.

Repeated refractionation of the ferric chloride positive distillates gave no effective separation of *o*-hydroxy ketone from the slightly less volatile diphenyl ether. These fractions were combined, dissolved in 100 cc. of methanol and 24 g. of phenylhydrazine was added together with 1 cc. of acetic acid. The solution was warmed three hours on the steam-bath. A first crop of 20.3 g. of phenylhydrazone was collected and a second of 8.7 g. after diluting the filtrate with a little water. The filtrate from this second crop was evaporated and partitioned between ether and dilute hydrochloric acid. The ethereal layer was evaporated and steam distilled to remove diphenyl ether. The residue was crystallized from ether–hexane giving 3.8 g. more of phenylhydrazone (total 32.8 g., 0.137 mole).

Experiment XXV.—The quantities were the same as in the previous experiment except that 2 l. of nitrobenzene was used. After standing 429 hours, cracked ice and hydrochloric acid were stirred in and steam distillation was commenced. The steam distillation was continued during two days at the end of which time some *o*-hydroxy ketone and diphenyl ether still remained behind. After this prolonged treatment a separate methanolysis was judged unnecessary.

The nitrobenzene layer and the ether extract of the aqueous steam distillate were united and fractionated *in vacuo*. The material boiling from 90–134° at 16 mm. reacted in methanol with excess (0.3 mole) phenylhydrazine.

The residue from the steam distillation was taken into ether, washed with dilute acid, water and then extracted with 100 cc. of *N*/5 alkali. The alkaline extract on acidification gave a positive ferric chloride test indicating that this alkali was too strong for a clean separation. Extraction was continued with 2 *N* alkali leaving a neutral fraction with a weak ferric chloride test. It was added to the residue from fractionation of the steam distillate and a further ferric–chloride positive distillate obtained which was added to the phenylhydrazine reaction mixture.

Further distillation at 1 mm. of the least volatile material afforded 3 g. of oil not free from diphenyl ether. Reckoned as *p*-acetyldiphenyl ether this would be 15 mmoles (6%). It was converted to the 2,4-dinitrophenylhydrazone,[29] m.p. 215–216°, of which 2.3 g. was collected. This corresponds to 6 mmoles or a 2% yield which is obviously the minimum, whereas the crude yield of 6% is a rather high maximum.

The alkali-soluble material afforded 3 g. (20 mmoles) of 4-hydroxy-2-methylacetophenone after removal of about 0.5 g. of tar. The mother liquors (in hexane) were distilled and the distillate added to the phenylhydrazine reaction mixture.

The phenylhydrazine reaction mixture on dilution with water and hexane (giving layers) afforded 18 g. of 2-hydroxy-4-methylacetophenone phenylhydrazone melting at 105–106° after washing with hexane. The filtrate was steam distilled to remove the nitrobenzene and the bulk of the diphenyl ether. A second crop of phenylhydrazone was then collected weighing 17.5 g. and melting at 103.5–105.5°. After steam distillation of the mother liquors a third crop of 1.5 g. was obtained. This gives a total of 37 g. (154 mmoles) or 51%.

Fries Reaction with *m*-Cresyl Butyrate. Expt. XVI.—Fifty-four grams (0.4 mole) of aluminum chloride was dissolved in 350 cc. of nitrobenzene and 35.6 g. (0.2 mole) of *m*-cresyl butyrate together with 50 cc. more nitrobenzene was added. After stirring for a few minutes the solution was allowed to stand 66 hours and hydrolyzed. Steam distillation was continued until about 330 cc. of nitrobenzene had come over. The distillation flask was cooled and the contents were partitioned between ether and water. The ethereal layers were washed thoroughly, evaporated and subjected to acid-catalyzed methanolysis overnight. The methanol was evaporated and the residual material distilled *in vacuo* with fractionation. A main fraction of 19.5 g. (b.p. 92–93° at 1 mm.) was identified as 2-hydroxy-4-methylbutyrophenone by conversion of a portion to the phenylhydrazone. Two small intermediate fractions (b. 99.5° at 18 mm. to 87° at 1 mm. and 87–92° at 1 mm.) were refractionated and 2 g. more of *o*-hydroxy ketone isolated.

The distillation residue from the first fractionation was dissolved in hexane, charcoaled and allowed to cool. Four grams of 4-hydroxy-2-methylbutyrophenone[6] was collected. The mother liquors afforded 1.5 g. more of the *o*-hydroxy isomer giving a total of 23 g. of that substance.

Fries Reaction with *m*-Cresyl Heptoate (Expt. XXII).—A solution was prepared from 54 g. (0.4 mole) of aluminum chloride and 350 cc. of nitrobenzene. To this was added 42 g. (0.19 mole) of *m*-cresyl heptoate and 50 cc. of nitrobenzene. After standing 66 hours the solution was hydrolyzed. Steam distillation removed 270 cc. of nitrobenzene and the residual material was treated in the same fashion as in experiment XVI. Fractional distillation afforded 34.5 g. of the *o*-hydroxy ketone, identified as the phenylhydrazone.[7] From the distillation residues was obtained 4 g. of *p*-hydroxy ketone, m.p. 67–67.5° after crystallization from ether–hexane and sublimation in a high vacuum.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.3; H, 9.1. Found: C, 75.9; H, 9.1.

Competitive Fries Reaction of *m*-Cresyl Caproate and Diphenyl Ether (Expt. XXVII).—Eighty grams (0.6 mole) of aluminum chloride was dissolved in 500 cc. of nitrobenzene. The solution was allowed to cool and 41 g. (0.2 mole) of *m*-cresyl caproate, 35 cc. of diphenyl ether and 50 cc. of nitrobenzene were stirred in. The solution was allowed to stand 66 hours, hydrolyzed and steam distilled as usual. When 525 cc. of nitrobenzene had come off, the residue was cooled, then taken into ether, washed, evaporated and let stand overnight in methanolic hydrogen chloride. In the fractional distillation, after removal of a nitrobenzene fraction, two cuts were taken: II, b. 91–122° at 1 mm., and III, b. 122–137°. The residue was cooled, dissolved in ether and extracted with *N* potassium hydroxide solution. Most of the color went into the aqueous layer from which a solid precipitated on acidification. This solid was filtered off, dissolved in ether–hexane, charcoaled and allowed to crystallize. The precipitate weighed 4.5 g. and melted at 76–76.5° after crystallization from hexane.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.7; H, 8.8. Found: C, 75.9; H, 8.8.

Since *o*-cresol is a conceivable impurity in the *m*-cresol used for this preparation, 4-hydroxy-3-methylcaprophenone, reported by Coulthard, Marshall and Pyman[6] to melt at 79–80°, was prepared for comparison. The mixture of the two specimens showed a much lower melting point so there is little doubt that the 76° melting compound is 4-hydroxy-2-methylcaprophenone. The mother liquors from the crystallization of this material were found to contain only 0.3 g. of oily material which was discarded.

The ethereal layer from the alkali extraction was again evaporated and distilled without a fractionating column. Fractions IV, b. 149–158° (6.5 g.), V boiling at 158–170° at 1 mm. (4.5 g.) and VI boiling at 170° (11 g.) were taken. Fraction VI solidified and was identified as *p*-caproyldiphenyl ether.

Fractions II–V were refractionated in series. There were obtained I′, 9.5 g. b.p., 126–130° at 13 mm., mainly diphenyl ether (faint ferric chloride test) which was discarded; II′, 6 g., b.p. 103–119°, III′, 16 g., b.p. 119–121° (2-hydroxy-4-methylcaprophenone[6]), and IV′, 1 g., b.p.

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[29] H. H. Szmant and H. V. Planinsek, This Journal, **72**, 4042 (1950).

121–130°, all at 1 mm. The residue solidified on cooling and was found to be mainly caproyldiphenyl ether. A total of 20 g. of this substance was isolated. Refractionation of II′ and IV′ gave 2.5 g. more (a total of 18.5 g.) of *o*-hydroxy ketone. The caproyldiphenyl ether (presumably 4-phenoxycaprophenone) crystallizes from hexane in long prisms, m.p. 48–49°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5. Found: C, 80.2; H, 7.3.

Experiment XXIX.—Forty grams (0.3 mole) of aluminum chloride was dissolved in 270 cc. of nitrobenzene, cooled to room temperature and 48 g. (0.23 mole) of *m*-cresyl caproate, 50 cc. of diphenyl ether and 30 cc. of nitrobenzene were added. The solution was allowed to stand 330 hours and was then hydrolyzed as usual. About 260 cc. of nitrobenzene was steam distilled off and the residual material was treated as in the preceding experiments. On distillation there was obtained, after a forerun fraction, a main portion of *o*-hydroxy ketone weighing 31.5 g. The residue (14.5 g.) was partitioned between ether and *N* alkali. The alkaline extract gave only a little solid on acidification and from this 1.5 g. of *p*-hydroxy ketone was separated. The foreruns and neutral material from this extraction were refractionated in series giving 4 g. more *o*-hydroxy ketone and 10–10.5 g. of caproyldiphenyl ether.

Fries Reaction of *m*-Cresyl *m*-Chlorobenzoate (Expt. XXXVII).—To a solution of 27 g. (0.2 mole) of aluminum chloride in 300 cc. of warm (*ca.* 50°) nitrobenzene was added 24.7 g. (0.1 mole) of *m*-cresyl *m*-chlorobenzoate.[30] The flask was protected by a soda-lime tube and set in a 63° oven for 72 hours. It was then cooled, hydrolyzed and steam distilled, about 250 cc. of nitrobenzene being taken off. The residual material was taken into ether and washed with water until the washings were neutral. A small black precipitate was filtered off and the filtrate was extracted twice with 5% sodium carbonate solution. Acidification of the extract gave 1.1 g. of *m*-chlorobenzoic acid (7 mmoles). The ethereal layer was then extracted with 2 *N* sodium hydroxide solution. There was a tendency to formation of a third layer so the third portion of alkali was diluted to about 1.2 *N*. The alkali extracts gave a black oil on acidification. This was taken into ether, a black sludge was filtered off and the solution was dried briefly over calcium chloride. The ethereal solution was decanted and evaporated down with hexane. The brown residue was crystallized from ether–hexane affording two crops (9 g. and 1 g.) of brownish crystals. From later-distilled fractions 0.5 g. more was obtained giving a total of 10.5 g. of *p*-hydroxy ketone. This material was fairly pure as judged by the melting point, but was not readily freed of color. For analysis, a portion was distilled at 0.05–0.10 mm. and was thus recovered as a colorless solid melting at 125–125.5°. This is undoubtedly 4-hydroxy-2-methyl-3′-chlorobenzophenone.

Anal. Calcd. for $C_{14}H_{11}ClO_2$: C, 68.2; H, 4.5. Found: C, 68.2; H, 4.6.

The ethereal layer from the original alkali extractions was distilled giving, after nitrobenzene had come over, 4.7 g. in three fractions which were examined separately. The mother liquors from the crystallization of the *p*-hydroxy compound also were distilled at 0.1 mm. The distillate came over in the range of 120–155° but mainly at 147°. It weighed 6 g. and, when dissolved in hexane, deposited the 0.5 g. of *p*-oxyketone mentioned above. The various distilled fractions were saponified in methanolic alkali. The alkali-soluble portion (all except a small neutral residue) was taken into ether–hexane, washed with carbonate solution and crystallized from hexane. Several crops of crystals were obtained and a final solid residue (6 g.), which was largely inseparable by recrystallization. There was obtained pure 3 g. of yellow needle-prisms melting at 89.5–90.5°, giving a strong ferric chloride test and identified as 2-hydroxy-4-methyl-3′-chlorobenzophenone.[31]

Anal. Calcd. for $C_{14}H_{11}ClO_2$: C, 68.2; H, 4.5. Found: C, 68.1; H, 4.5.

A small portion of another compound melting at 88–89° also was isolated and this proved to be *m*-dinitrobenzene, presumably present in the original nitrobenzene used.

The "inseparable" material was estimated as containing 70% of *o*-hydroxy ketone by two methods. One gram was chromatographed on alumina from hexane giving 700 mg. of pure *o*-hydroxy ketone. The remaining 5 g. was dissolved in alcohol and added to a solution of stannous chloride and hydrochloric acid. From this reduction mixture 3.5 g. of *o*-hydroxy ketone was isolated. Thus a total of 7 g. of this substance was accounted for.

Fries Reaction with 3,5-Dimethylphenyl Benzoate (Expt. XXXVIII).—One-tenth mole (22.6 g.) of this ester was added to a solution of 27 g. (0.2 mole) of aluminum chloride in 300 cc. of warm nitrobenzene. The flask was protected with a soda-lime tube and set in an oven at 62–63° for 18 hours. The solution was then hydrolyzed and most of the nitrobenzene steam distilled off. (On redistillation, the nitrobenzene was found to contain no significant amount of higher-boiling material.) The residue from the steam distillation solidified to a dark mass when cooled. This was filtered off; it weighed 19.5 g. The material was dissolved in ether, charcoaled to remove a dark green contaminant, and evaporated to small volume with hexane. There was obtained 15.5 g. of a light yellow-brown solid that melted at 142.5–143.5°. This material was recrystallized from ethyl acetate and ethyl acetate–hexane mixtures giving 12.5 g. of material in four fractions all having essentially the same melting point. From the mother liquors and those from the first crop 5.5 g. more of the same solid of the same degree of purity were obtained, giving a total of 18 g. (80%). The mother liquors were not entirely free of nitrobenzene and after removal of that no further products could be isolated save a small amount (100–200 mg.) of *m*-dinitrobenzene. It thus appears that the main product is also the only one present in appreciable amount.

The highest melting point observed for this compound was 143–143.5°. It is colorless when sublimed in *high vacuum* and gives a negative test with ferric chloride in alcohol. There was no m.p. depression with the known 2-hydroxy-4,6-dimethylbenzophenone[26] and its analysis was correct for that compound.

A similar experiment run at 25–30° for 66 hr. afforded the same compound in about 55% yield. There was no evidence of a *p*-hydroxy isomer.

Under the same conditions as those of experiment XXXVIII except that 0.15 mole of diphenyl ether was added with the ester, the *o*-hydroxy ketone was isolated in 60% yield and *p*-benzoyldiphenyl ether in 40%. These compounds are separated easily through the fact that *this* *o*-hydroxy ketone, unlike the chelate types, is readily extracted from ethereal solution by *N* alkali.

Experiments with Pivalic Esters

The cresyl esters of pivalic acid were prepared by warming pivaloyl chloride with *m* and *p*-cresol. The *m*-cresyl ester boiled at 116–117° at 14 mm., the *p*-cresyl ester at 103–104° at 7 mm.

High Temperature Fries with *m*-Cresyl Pivalate.—One-tenth mole (19.2 g.) of *m*-cresyl pivalate and 15 g. (0.112 mole) of aluminum chloride were mixed in a 500-cc. round-bottomed flask. A watch-glass was placed on the top of the flask and it was immersed in a metal-bath initially at 100°. This temperature was raised during the next half-hour to 140°. A vigorous evolution of gas took place, gradually subsiding. The gas could be ignited, burning with a partly green and partly luminous flame (to be expected of a mixture of carbon monoxide and isobutylene). After the usual working-up and distillation a 2-g. fraction boiling 122–127° at 7.5 mm. was obtained, giving a positive ferric chloride reaction. The fractions boiling 85–122° and 127–153° weighed 2 and 3 g., respectively, and gave weak ferric chloride reactions. From the main fraction about 1 g. of crude phenylhydrazone was obtained.

Low Temperature Fries of *m*-Cresyl Pivalate.—In 150 cc. of nitrobenzene was dissolved 18 g. (0.134 mole) of aluminum chloride. The solution was stirred until it had returned to room temperature and 24 g. (0.125 mole) of *m*-cresyl pivalate was added and washed in with 10 cc. of nitrobenzene. There was no visible evolution of gas. The solution was stirred briefly and allowed to stand 142 hours. After hydrolysis with ice and hydrochloric acid, the material was subjected to steam distillation, 110 cc. of nitroben-

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(30) E. Monroe and C. R. Hand, THIS JOURNAL, **73**, 487 (1951).

(31) S. Skraup and K. Poller (*Ber.*, **57**, 2033 (1924)) have assigned this structure to a colorless compound, m.p. 147°, isolated in very small yield from a reaction of *m*-chlorobenzoyl chloride, zinc chloride and *m*-cresyl acetate. The quantity of their material was insufficient for analysis and their melting point is most improbable for a chelate 2-hydroxybenzophenone.

zene being removed. The residue was cooled, partitioned between ether–hexane mixture and water and washed with water. The ethereal layer was evaporated and distilled *in vacuo* under a fractionating column. Several fractions were taken of which the most promising weighed 5 g. and boiled at 121–126° at 7.5 mm. Refractionation gave two other fractions weighing together 3.5 g. These portions of material were treated separately with excess phenylhydrazine (in alcohol with a little acetic acid). There was obtained in all 8 g. (0.028 mole) of a phenylhydrazone melting at 124–125°.

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.5; H, 7.9. Found: C, 76.2; H, 7.7.

Low Temperature Fries of *p*-Cresyl Pivalate.—The same quantities and procedure were employed as with *m*-cresyl pivalate except that the reaction time was 162 hours. On working up, only 2 g. of material boiling over 80° at 7 mm. was obtained. This gave a positive ferric chloride test and was treated with phenylhydrazine as in the previous experiment, but the phenylhydrazone could not be crystallized. The material was taken into ether, washed with dilute acid and the solvent was evaporated. The residue was allowed to evaporate at $^1/_3$ mm. pressure (furnace temperature 130°). The residue weighed about 0.8 g. and could now be crystallized from pentane, m.p. 107–108°.

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.5; H, 7.9. Found: C, 76.3; H, 8.1.

Friedel–Crafts Reaction of Pivaloyl Chloride and Diphenyl Ether.—One-fifth mole (27 g.) of aluminum chloride was added gradually to a stirred solution of 34 g. (0.2 mole) of diphenyl ether and 24 g. (0.2 mole) of pivaloyl chloride in 200 cc. of nitrobenzene. There was a vigorous frothing (evolution of CO ?) as the first portions of aluminum chloride were added. The reaction mixture was stirred for an hour and allowed to stand three days. After hydrolysis in the usual way, 160 cc. of nitrobenzene was distilled off. The residue was cooled and partitioned between ether and dilute acid. A considerable amount of whitish polymeric material was discarded. The ethereal extract was washed with water and boiled down with hexane. On distillation *in vacuo* a considerable polymeric residue remained. This was insoluble in ether and water but soluble in methanol; it was discarded. No portion of the distillate boiled sharply. Redistillation gave 5 g. boiling at 148–151° at 1 mm. This did not solidify but analysis indicated the presence of material containing two oxygen atoms. Treatment with Girard reagent[32] gave a ketonic fraction weighing 3 g. This was not homogeneous but a poor yield of a semicarbazone was isolated melting at 150–152°.

Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.4; H, 6.8; N, 13.5. Calcd. for $C_{22}H_{29}N_3O_2$: C, 70.0; H, 7.7; N, 11.1. Found: C, 70.1; H, 7.6; N, 11.4.

Mixed Fries Reaction of *m*-Cresyl Caproate and 2,6-Dimethylphenyl Acetate.—The technique used was intended to accomplish complete coördination of ester with catalyst in a liquid phase before initiation of the Fries itself, thereby minimizing the likelihood of ester exchange.[33] Aluminum bromide was employed as catalyst because of its greater solubility.

In a preliminary model experiment, 73 g. (0.27 mole) of aluminum bromide was dissolved in 200 cc. of carbon disulfide, cooled (with stirring and protection against moisture) to 10° and kept below 10° while 43 g. (0.21 mole) of *m*-cresyl caproate was added through a dropping funnel. The solvent was then removed *in vacuo* while below 25° and the flask was immersed in a metal-bath kept at 130°. The vigorous reaction was over in about five minutes. The flask was kept in the metal-bath for 15 minutes further and then removed and allowed to cool to about 60°. The reaction mixture then was hydrolyzed in the usual way with warm hydrochloric acid whose temperature was moderated by adding cracked ice at intervals. When the hydrolysis was complete (as shown by complete conversion of the orange-colored organic glass to a yellow mobile oil) the material was cooled, taken into ether and washed with water until the aqueous layers were no longer acid to congo paper. The ethereal layers were evaporated and the residue was dissolved in 200 cc. of methanol. Hydrogen chloride gas was passed in until the solution was strongly acid and the whole was allowed to stand for two days. The solvent was then evaporated and the residue distilled at 1 mm. pressure. A low-boiling forerun weighed 2 g. and afforded 1 g. of phenylhydrazone[6] (=0.7 g. of ketone). The main run of ketone weighed 39.3 g. while a residue of 1.5 g. remained in the flask. No phenylhydrazone was obtained from the residue. The yield of 6-caproyl-*m*-cresol was thus over 90%.

Aluminum bromide then was dissolved in carbon disulfide to give 168 g. (0.63 mole) of solute in 410 g. of solution. This was diluted by 200 cc. of carbon disulfide and a solution of 56 g. (0.27 mole) of *m*-cresyl caproate and 41.5 g. (0.254 mole) of 2,6-dimethylphenyl acetate (b.p. 116–117° at 17 mm.) in 100 cc. of carbon disulfide was run in under the same conditions as described above. The baking was also as previously described except that reaction appeared to take place in two waves, each of diminished vigor, and separated by about a 5-minute interval.

The reaction product was hydrolyzed and washed as above, but subsequent treatment differed. The ethereal layers were washed with seven 50-cc. portions of *N* sodium hydroxide and one 50-cc. portion of 0.5 *N*, the last two washings being combined. The alkaline extracts were acidified separately: I, II and III gave light-colored solid precipitates, IV a darker solid, V and VI darkish, partly crystalline precipitates, and VII a dark oil. Fractions I, II and III melted at 148–151, 150–152 and 149–151.5°, respectively. They were united and recrystallized from alcohol, affording 16 g. of material melting at 151.5–152.3°. By crystallization of IV from the mother liquors of the three first, there was obtained 5.5 g. of material of the same melting point. A further crop of 5.5 g. melting at 148–151° was collected after partial evaporation of the mother liquors.

Fractions V and VI were filtered and the solid portions washed with hexane. The filtrates were united with VII and extracted with ether. The solid portions from V and VI were united and crystallized several times from ether–hexane, m.p. 95–98°, negative ferric chloride test. The filtrates from these solids were united with the alcoholic mother liquors of fractions I–IV and afforded 2.5 g. of the 151–152° melting substance. This is undoubtedly 4-acetyl-2,6-dimethylphenol reported as melting at 150–151°.[34] The total amount weighed 29.5 g. or 0.18 mole.

The final mother liquors from the above crystallizations were added to the hexane-soluble portions of fractions V–VII and distilled *in vacuo*.

The solid material from fractions V–VI was further recrystallized from methanol without much improvement and was then distilled at 1 mm. pressure. Six grams came over in the range 182–200° leaving 1 g. of tarry residue. The distillate solidified and melted at 97–99° after crystallization from hexane.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.3; H, 9.2. Found: C, 76.0; H, 9.4.

The 97–99° melting compound is therefore 4-caproyl-2,6-methylphenol. Allowing for major losses falling on this fraction, it is reasonable to equate it to 0.03 mole in the accounting.

The ethereal solution of material not extracted by the alkali wash was evaporated and fractionated *in vacuo*. There was obtained a main portion of 39.5 g. boiling at 125–130° at 1 mm. The highs and lows were refractionated with the hexane-soluble material from the crystallization of *p*-hydroxy ketones affording 7 g. more of the same material which was 6-caproyl-*m*-cresol, identified as the phenyl hydrazone. The more volatile fractions were converted to the phenylhydrazones (total yield, 0.226 mole). There was obtained 5.6 g. (0.023 mole) of phenylhydrazone melting at 104–105° which is the recorded m.p. of the phenylhydrazone of 6-acetyl-*m*-cresol. A reasonable apportion-

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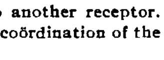
[32] A. Girard and G. Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936).

[33] It is supposed that ester exchange occurs by transfer of a positive acyl moiety from a coördinated ester molecule to an uncoördinated one, giving a form which could be written as



$R-C(=O)-\overset{+}{O}(Ph)-C(=O)-R'$.

One of these acyl moieties could then pass on to another receptor. Such a process should be minimized by complete coördination of the ester at low temperature.

[34] K. v. Auwers and H. Mauss, *Ann.*, **460**, 266; **464**, 305 (1928).

ment of small intermediate fractions raises this figure to 0.04 mole.

Bromination Experiments

These were performed as much as possible under identical conditions. For the experiments without aluminum chloride about 0.4 mole of *m*-cresol or of *m*-cresyl acetate was dissolved in 200 cc. of nitrobenzene and 0.2 mole of bromine in 250 cc. of nitrobenzene was added rapidly with stirring. In the *m*-cresol bromination, the entire material was distilled *in vacuo* and the bromo-*m*-cresol fractions (b.p. 118–120° at 6.5 mm.) were crystallized from hexane. The known 4-bromo-*m*-cresol[35] was obtained in over 90% yield (from the distillate fraction) and working up of the mother liquors disclosed no appreciable amount of isomeric material. The same result was obtained in the presence of aluminum chloride (dissolved in the nitrobenzene before addition of the *m*-cresol).

The bromination of *m*-cresyl acetate also was performed as above but the working up was complicated apparently by incompleteness of a methanolysis step designed to convert all the ester to phenol. As a result the initial crops of 4-bromo-*m*-cresol were relatively small, but as the mother liquors were subjected to further treatment it became apparent that little or no isomeric material was present.

The brominations of *m*-cresyl acetate and 3,5-dimethylphenyl acetate were done in the presence of aluminum chloride in a similar fashion except in regard to timing. In each case the ester was added to the solution of aluminum chloride in nitrobenzene (at *ca.* 30°) and after stirring for one minute the bromine solution was added. Two minutes later the solutions were free of bromine (starch–KI paper) and were hydrolyzed at once with ice and hydrochloric acid. Despite these precautions Fries products were formed in small amount. Separation of non-chelate ketones presented no serious problem. The small amounts (*ca.* 0.5 g. in each case) were removed from fractions containing them by treatment with phenylhydrazine (followed by acid extraction and steam distillation of non-hydrazone material). In the experiment with *m*-cresyl acetate the distillate fractions assumed to contain all the bromo-*m*-cresol weighed 33.5 g. Of this about 0.5 g. was *o*-acetyl-*m*-cresol. Twenty-two grams of pure 4-bromo-*m*-cresol was isolated as such and the equivalent of 3 g. more as its *p*-nitrobenzoate.[36] The remaining fractions at this stage of manipulation were small and as they still gave small crops of 4-bromo-*m*-cresol when cooled to −70° were considered incapable of containing substantial amounts of isomeric bromocresols.

From the bromination of 3,5-dimethylphenyl acetate about 50% of the starting ester was recovered as 3,5-dimethylphenol, about 30% as 4-bromo-3,5-dimethylphenol[37] and 6–7% as 2,4-dibromo-3,5-dimethylphenol.[38] Ketonic material corresponded to 1–2% of the starting ester.

Friedel–Crafts Reaction of Acetyl Chloride on Diphenyl Ether and *m*-Cresyl *m*-Chlorobenzoate.—Forty grams (0.3 mole) of aluminum chloride was dissolved with stirring in 300 cc. of nitrobenzene. When the solution had cooled to 30°, 18 g. (0.1 mole) of diphenyl ether was added and then, in rapid succession, 22.5 g. (0.09 mole) of *m*-cresyl *m*-chlorobenzoate, 8 g. of acetyl chloride and 50 cc. more nitrobenzene. The temperature rose to 40° and stirring was continued for an hour. Eighteen hours after addition of the acetyl chloride, the reaction mixture was hydrolyzed by addition of ice and hydrochloric acid. The material in the reaction flask was subjected to steam distillation, the distillate containing the first 300 cc. of organic material (nitrobenzene) was discarded, the later portions were retained, distillation being continued as long as an oil layer came over. This steam-volatile material was taken into ether, washed with sodium carbonate, dried and evaporated, weight 57 g.

The residue from the steam distillation was taken into ether and washed in succession with dilute hydrochloric acid, water and sodium carbonate solution. The ethereal layer (about 700 cc.) was then added to a solution of 20 g. of potassium hydroxide in about 150 cc. of methanol and let stand 41 hours. It was then diluted with cold water and the ethereal and aqueous layers were separated. The latter was extracted with ether and the combined ethereal layers were washed with water, dried and evaporated, weight 22 g. (neutral fraction). The aqueous alkaline layer was brought to *p*H 8 by addition of acid and bicarbonate and again extracted with ether. The ethereal layer was evaporated (phenolic fraction, 10 g.).

The bicarbonate solution was strongly acidified and the precipitated solid was collected and dried. It melted sharply at 154–155° and was identified as *m*-chlorobenzoic acid. This material weighed 11 g. (70 mmoles).

The steam-volatile fraction was distilled *in vacuo* and the material boiling below 104° at 20 mm. was discarded. The main neutral fraction was added to the residue and distillation was continued at 1 mm. The fractions taken were C (5 g.), boiling 60–134°; D (14.3 g.), 134–138°; and E (2 g.), 138–161°. The residue weighed 4 g. Redistillation of C and E gave D′, 3 g., similar to D. D and D′ solidified and were remelted by 49°. They were combined and crystallized from pentane. A fraction was obtained at room temperature weighing 10 g. and melting at 50–51°.[39] In the refrigerator 5 g. more separated, m.p. 48–50°. The residue on evaporation of the mother liquors smelled of diphenyl ether and gave a faint ferric chloride test but still solidified. The 17.3 g. of distillate amounts to 82 mmoles, the 15 g. of crystalline solid to 71.

The neutral residue could not be induced to crystallize; it was distilled at 0.06 mm. pressure (bath temp. 140–175°) and the distillate (2.5 g.) was crystallized from pentane. There was obtained, after two crystallizations, 1 g. of glossy platelets melting at 70–71°.

Anal. Calcd. for $C_{19}H_{13}ClO_2$: C, 73.9; H, 4.2. Found: C, 73.9; H, 4.5.

The crude and purified quantities of this material amount to 9 and 6 mmoles, respectively. It is presumed to be 3-chloro-4′-phenoxybenzophenone.

The phenolic fraction was distilled at 20 mm. pressure, 6 g. boiling at 99–103° being obtained (*m*-cresol). The residue weighed 2.5 g. and was distilled separately at 0.06 mm. pressure. A small forerun appeared before that pressure was attained and evaporated as the pressure fell. The tarry residue weighed 0.5 g. The distillate, on crystallization from ether–hexane mixture, disclosed two crystalline types. By extraction with hot water one type was removed and identified as 4-hydroxy-2-methylacetophenone (0.2 g., 1 mmole). The material insoluble in hot water melted at 120–123° and was identified as 4-hydroxy-2-methyl-3′-chlorobenzophenone, weight 1 g., 4 mmoles.

Since the phenolic fraction before distillation at 0.06 mm. amounted to 2.5 g. and 1.5 g. of this consisted of tar and of benzophenone derivative it is evident that while the 4-hydroxy-2-methylacetophenone probably exceeded the 0.2 g. isolated, not over 1 g. could have been present.

Several fractions during the working up gave faint to weak ferric chloride tests and it is evident that traces of *o*-hydroxy ketones had been formed. In no case was a ferric chloride test sufficiently strong as to encourage an attempt at isolation.

Ultraviolet absorption spectra were determined on a Beckmodel DU quartz spectrophotometer, cell length 1 cm., concentrations 10 mg. per liter.

Acknowledgment.—The authors wish to express their gratitude to Mr. Samuel W. Blackman who performed the analyses here reported and to Dr. Peter B. Russell, Mrs. Bernadine Pera and Miss Frances Smith for assistance at various stages of the work.

Appendix (Received January 6, 1955).—One question that is not touched upon in the preceding discussion is why *m*-cresyl acetate affords so much more *p*-hydroxy ketone than do the higher esters of *m*-cresol. This must be due to the operation of at least one of two effects: (a) the intermolecular reaction is favored in an absolute sense with the acetate, or (b) the rearrangement is similarly favored with the higher esters.

These effects might show up in the rates. The first pos-

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[35] R. F. Walther and W. Zipper, *J. prakt. Chem.*, [2] **91**, 364 (1915).

[36] G. V. Jadhan and Y. I. Rangwah, *Proc. Ind. Acad. Sci.*, **1A**, 616 (1935).

[37] K. v. Auwers, *et al.*, *Ann.*, **421**, 72 (1920); *Ber.*, **48**, 1715 (1916); **54**, 1296, 1310 (1922).

[38] K. v. Auwers and E. Borsche, *ibid.*, **48**, 1698 (1916).

[39] H. Kipper (*Ber.*, **38**, 2490 (1905)) gives 45° as the melting point of *p*-phenoxyacetophenone. A. W. Ingersoll, *et al.* (This Journal, **58**, 1808 (1936)) give 50° as the melting point.

sibility could be rationalized on the basis that reaction of a polarized ester complex with a second aromatic molecule can be viewed either as an electrophilic attack on the latter, or a nucleophilic attack on the former.

From the second viewpoint, one would expect that an acetate would react more rapidly than a higher ester, as is generally the case.[40] Accordingly, o-cresyl acetate and butyrate (selected as yielding preponderantly *p*-hydroxy ketones) were allowed to react under identical conditions. The results are shown in Table VI. It is apparent that there is no significant difference in the rates of the *para* shift. Consequently, if the consideration (a) does operate at all it is without effect on the rate. On the other hand, the *ortho* shift is clearly proceeding faster with *o*-cresyl butyrate than with the acetate. In fact, the *ratio* of *o*-hydroxy ketones formed in the two cases is comparable to that in the *m*-cresyl series (*cf.* Table II, reactions XII and XVI).[41,42]

TABLE VI

FRIES REACTIONS OF *o*-CRESYL ESTERS

In both cases 0.2 mole of ester and 0.4 mole of aluminum chloride reacted in 350 cc. of nitrobenzene for 7 hours

	Yield, %	
Ester	*p*-Hydroxyketone	*o*-Hydroxyketone
Acetate	38	<1
Butyrate	37	4

It thus seems likely that the tendency of aliphatic esters of phenols to rearrange to *o*-hydroxy ketones is *generally* greater with the higher esters. The fundamental reason for this is not deduced readily. It is tempting to assume that the increased chain-length with the higher esters favors a spatial arrangement more suitable to an intramolecular shift, but calculations to support this assumption are not feasible in the absence of reliable data on oxygen bond-angles or of any data on the bond-angles of tricovalent oxygen.

Experimental.—Two solutions were prepared, each containing 54 g. (0.4 mole) of anhydrous aluminum chloride. These were protected from the air and set in a single large tank of water overnight. In the morning there was added to flask A, 30 g. (0.2 mole) of *o*-cresyl acetate, and to flask B, 35.6 g. (0.2 mole) of *o*-cresyl butyrate. Both flasks were swirled to mix and allowed to stand 7 hours. The temperature of the water tank was 25–26° throughout. At the end of the 7 hours, the reactions were stopped by addition of cracked ice and hydrochloric acid. About 250 cc. of methanol was added to each and the resultant mixtures allowed to stand three days.

Ketones from *o*-Cresyl Acetate.—The reaction mixture of flask A was steam distilled until all volatile material had come over. The residue was cooled, filtered, and the filtrate was extracted with ether. This extract was used to dissolve the solid *p*-hydroxy ketone which was purified by crystallization from ether–hexane mixture (after charcoaling). Four crops of crystals amounting to 11.5 g. (38%) were collected. The first two crops, weighing 9 and 1 g., respectively, melted at 106.5–108° and 106.5–107.5°. The small final mother liquor which gave a positive ferric chloride test was added to the residue from the steam-volatile fraction.

The steam distillate was partitioned and the aqueous layers were extracted with ether–hexane before being discarded. The non-aqueous material was fractionated *in vacuo*. The highest-boiling material, which was still not free of nitrobenzene, weighed 3 g. No earlier fractions contained more than traces of *o*-hydroxy ketone. This 3-g. sample, to which was added the hexane-soluble material from the *p*-hydroxy ketone mother liquors, was treated with excess phenylhydrazine in alcohol. As no solid separated, the material was taken into ether, washed with dilute acid, and steam distilled. The residue weighed about 0.5 g. and did not readily crystallize. The amount of *o*-hydroxy ketone could not have exceeded 2 mmoles and was presumably somewhat less than that figure.

Ketones from *o*-Cresyl Butyrate.—The reaction mixture in flask B was steam distilled until most of the nitrobenzene had come over. The residue solidified on cooling and was purified by crystallization from ether–hexane and from ethyl acetate. The first crop of crystals weighed 7.5 g. and melted at 133–133.5° (Coulthard, Marshall and Pyman[6] give 132–133°). Successive crops of 4.5, 1.8, 1 and 0.2 g. were obtained, totaling 15 g. (37%). The final mother liquor weighed 1 g. and was added to the highest-boiling fraction from the distillation of the steam-volatile material. This last fraction, giving a positive ferric chloride reaction, was treated with phenylhydrazine and yielded 2 g. of phenylhydrazone, melting at 153–155° and at 156–157° after one crystallization from alcohol (Coulthard, Marshall and Pyman[6] give 157–158° for the m.p. of 2-hydroxy-3-methyl butyrophenone phenylhydrazone). The isolated phenylhydrazone amounts to 7.5 mmoles or about 4%.

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(40) No data are available for a *series* of phenyl esters. The rates of saponification, amidification, etc., of acetates are generally about 1.5 times those of corresponding propionates (*cf.* Landolt-Börnstein, "Physikalische Chemische Tabellen," 5th ed., 2nd Suppl., Berlin, Springer, 1931, pp. 1397, 1401; also, M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **70**, 1946 (1948)).

(41) To our knowledge the occurrence of *o*-hydroxy ketones in Fries reactions of *o*-cresyl esters at room temperature had not been reported until recently. N. M. Cullinane, E. T. Lloyd and J. K. Tudball (*J. Chem. Soc.* 3894 (1954)) have described experiments with titanium tetrachloride catalyst in which 1–3% of *o*-hydroxy ketone was obtained from *o*-cresyl acetate at 30°.

(42) Although the significance is doubtful, it may be of interest to point out that if the yield of product in this *o*-cresyl acetate experiment is used to calculate a first-order rate constant and this constant is applied to a 24-hour run, the predicted yield is 80.5%. In run XIX of Table II, the only earlier experiment under approximately comparable conditions that may not have gone for an excessive time, the total yield of ketones was 83%. (Neither experiment was actually thermostated but they were carried out at nearly the same time of year (December and January) and must have been at about the same temperature.)