Anal. Calcd. for $C_{10}H_{11}ClO_2$: C, 60.5; H, 5.5. Found: C, 60.8; H, 5.7.

All acylureas were made by either of two methods which were used interchangeably with little difference in yield. In the first, an acid chloride was allowed to react with urea in the absence of solvent.[2] Reaction began spontaneously or upon brief warming and was completed by heating on the steam-bath. In the second method, due to Stoughton,[4] the acid chloride was added to urea in refluxing benzene. The trace of sulfuric acid used by Stoughton was found to be unnecessary in our work. An example of each procedure is given.

Isocaproylurea by the Dry Urea Method.—Twelve grams of urea was powdered and mixed with 11.8 g. of isocaproyl chloride. A vigorous reaction was initiated by cautious warming. When it had subsided the mixture was heated two hours on the steam-bath, cooled, triturated with water and separated by filtration. The solid was crystallized from alcohol to give 10.0 g., m. p. 182–184°, and a second crop of 1.5 g., m. p. 178–184°. Recrystallization brought the m. p. of the colorless blades to 183–184°.

2-Ethylvalerylurea by the Benzene Method.—To a boiling, stirred mixture of 10 cc. dry benzene and 7.5 g. of urea was added dropwise 9.2 g. of 2-ethylvaleryl chloride. Stirring and refluxing were continued for four hours. After cooling, the solid was removed by filtration, washed with petroleum ether, sucked dry, washed with sodium bicarbonate solution and again with water. Recrystallization from alcohol gave 8.0 g. of ureide melting at 204–206°.

Summary

A series of acylureas has been prepared and tested for anticonvulsant activity. In the aliphatic series the optimum effect upon experimental animals is reached with those derived from secondary and tertiary branched acids of about seven carbon atoms. In the aromatic series phenacetylurea is best; activity seems to diminish with any sort of aromatic substitution.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

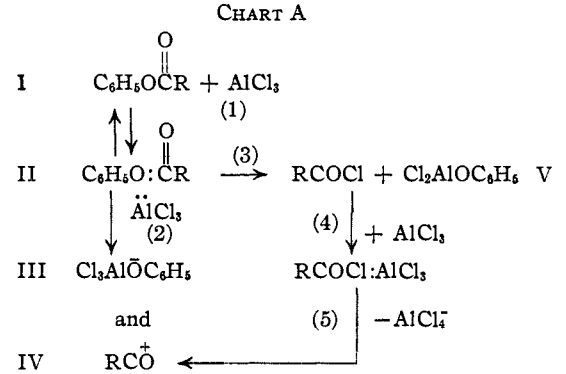
The Mechanism of the Fries Reaction[1]

BY RICHARD BALTZLY AND ARTHUR P. PHILLIPS

Three principal mechanisms have been advanced for the Fries reaction.[2] Fries and v. Auwers[3] regarded it as a true rearrangement. Cox[4] and Skraup believed the phenolic ester to be cleaved by aluminum chloride to liberate acyl chloride which then reacts as in the Friedel–Crafts synthesis. Rosenmund and Schnurr[5] wrote the reaction as a bimolecular acylation in which one molecule of ester serves as an acylating agent for another. All three mechanisms have been defended by their proponents on the basis of inconclusive evidence.

Examination of the Skraup–Cox and Rosenmund–Schnurr mechanisms in the light of present views on the nature of acid catalysis[6] shows them to be identical for practical purposes. In Chart A is shown what we believe to be the main line (Steps 1–2) in the formation of active fragments (III and IV). The oxo-carbonium ion,[7] IV, is the cationic intermediate in both schemes. Its attack on a molecule of ester, I, expresses Rosenmund's view, while its formation by the circuitous route of Steps 3–5 amounts to the Skraup–Cox mechanism. It is obvious that under the conditions of the reaction experimental discrimination among the possible basic fragments, I, III, V and the phenolate anion suggested by Luder and Zuffanti is impossible.[8]

CHART A



The remaining decision is whether the reaction is intramolecular or intermolecular.[9] While an intramolecular rearrangement of the acyl group to

(1) This paper was presented before the Organic Division of the American Chemical Society, New York Meeting, September, 1947.

(2) For reviews of the literature see Blatt, *Chem. Revs.*, **27**, 429 (1940), and "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1943, p. 342.

(3) v. Auwers and Mauss, *Ber.*, **61**, 1495 (1928); *Ann.*, **464**, 293 (1928).

(4) Cox, THIS JOURNAL, **52**, 352 (1930).

(5) Rosenmund and Schnurr, *Ann.*, **460**, 96 (1927).

(6) *Cf.* Luder and Zuffanti, "The Electronic Theory of Acids and Bases," John Wiley and Sons, New York, N. Y., 1946. Chart A of this paper is essentially similar to that shown by Luder and Zuffanti, p. 123.

(7) For this term see Newman and Gildenhorn, THIS JOURNAL, **70**, 317 (1948).

(8) As will be shown subsequently, it is probable that coördination of the ester (I) with aluminum chloride is essentially complete when the latter is in excess. Therefore, it is unlikely that free ester is available as an intermediate. The significant participation of phenolate anion is also improbable since it would require dissociation of aluminum chloride from a relatively strong base when it apparently combines extensively with the ester which is a weaker one.

(9) While the classical definition of a rearrangement implies nothing as to mechanism it is evident that Rosenmund in declaring that the Fries was not a *rearrangement* and v. Auwers in maintaining it to be a "true rearrangement" were using a more rigid definition, presumably that of an *intramolecular rearrangement*. Since, in the movement of a substituent from one position to another, this concept requires partial formation of the final bond before the initial bond is completely ruptured, steric as well as electronic conditions should be critical in determining the possibility of the shift. It has not been suggested hitherto that the ortho and para shifts proceed by different mechanisms, but this possibility is not excluded by existing evidence.

the ortho position should be sterically possible, a shift to the para position is at least unlikely.[9] The crux of Rosenmund and Schnurr's case is the occurrence of cross-products in a mixed Fries of 4-methylphenyl benzoate and 4-methyl-2-chlorophenyl acetate. This was discounted by v. Auwers as due to ester-interchange. But the most probable route of ester-interchange, if not the only possible one under the conditions, is an attack by the oxo-carbonium ion, IV, on a molecule of ester, I, forming a new cation, $C_6H_5\overset{+}{O}(COR)COR'$, capable of subsequent dissociation. If, however, IV is to be postulated for one purpose, it may as well be accepted for the other. Further, insofar as the ester is coördinated with aluminum chloride, it is not available for ester-interchange.[8] The conclusion appears inevitable that the reaction is not intramolecular although the oxo-carbonium ion, IV, as a free substituting agent capable of attacking any susceptible particle it encounters may also attack the fragment from which it had separated. The extent to which this process, which simulates an intramolecular rearrangement but is not one, would occur should depend on the reactivity of the former partner compared to available competitors and their relative availability in space. Thus increasing dilution should favor the recombination of former partners.

In hope of clarifying the situation further it was decided to make a preliminary study of reaction kinetics in the Fries. It is apparent that while demonstration of a rate second order in respect to ester concentration would eliminate intramolecular rearrangement as a possibility, the existence of first-order kinetics is consistent also with the scheme shown in Chart A since Step 2 could be rate-determining. Experiments were undertaken to discover (a) whether a kinetic study would be feasible and (b) what periods of reaction and what concentrations of reactants would be suitable.[10]

In Table I are shown the results of four exploratory runs that served to fix the optimum conditions for the reaction and incidentally to make more precise operations pointless. Losses in isolation did not exceed two millimoles. It is evident that there is no significant difference between the yields in the last three runs.[11] A maximum rate is obtained with 100% excess aluminum chloride and this rate is independent of the actual concentrations in the range studied.[12]

Another means of attack on the problem lies in conducting the reaction in the presence of a competing substance at different concentrations. If the competitor is of activity comparable to that of the cleavage-fragments of II, a mixture of ketones should be produced. The ketone formed by acylation of the competitor would be the result solely of attack by IV on fragments not previously associated with it. Since the normal product of isomerization of the ester could be formed *both* by the attack of oxo-carbonium ions on their former partners and on other fragments of the same type, this product should be formed in greater proportion when the reaction proceeds in a more dilute solution—if the recombination of former partners makes any significant contribution to the over-all reaction.

It seemed likely that 2-hydroxybiphenyl would be a suitable competitor both from the standpoint of activity and ability to afford a separable product. Accordingly two runs were made, using in each 0.2 mole of *o*-cresyl acetate, 0.2 mole of 2-hydroxybiphenyl and 0.6 mole of aluminum chloride. The other reagents were dissolved in the nitrobenzene considerably before addition of the ester in the expectation that the phenol would thus be coördinated completely with aluminum chloride and that ester exchange would be discour-

TABLE I

RESULTS OF EXPLORATORY EXPERIMENTS

0.1 MOLE OF *o*-CRESYL ACETATE IN NITROBENZENE AT 26°

TIME OF REACTION, SEVEN HOURS

Experiment	Volume, cc.	$AlCl_3$, mole	4-Hydroxy-3-methylacetophenone isolated, moles
I	500	0.11	0.026
II	500	.2	.049
III	500	.5	.048
IV	1000	.2	.047

TABLE II

RESULTS OF COMPETITIVE FRIES REACTIONS

Experiment	Volume of $C_6H_5NO_2$, cc.	Products, moles: 4-Hydroxy-3-methylacetophenone	Products, moles: 4-Hydroxy-3-phenylacetophenone
V	500	0.08	0.05
VI	2000	.093	.026

(10) Initially it was obvious that only the low-temperature reaction could be studied usefully; the high-temperature reaction (baking procedure) proceeds too rapidly to permit temperature control. Since, therefore, *p*-hydroxy ketones must constitute the bulk of the product a phenol, *o*-cresol was chosen whose esters under any conditions have little tendency to give an ortho shift. Although nitrobenzene does not give so clean a reaction as some other solvents, it is virtually the only one capable of dissolving the necessary quantities of aluminum chloride. Nitro-ethane, suggested by Dr. Newman, produces a tarry product.

(11) The apparent discrepancy in the much lower yield in Experiment I might be due to one or both of two causes. The extent to which "anhydrous aluminum chloride" is really anhydrous is uncertain. It is possible, though unlikely, that all aluminum chloride concentrations were lower than given, and this would affect the first run most. A more probable cause is that since the product should be able to coördinate two mols of acid, up to two equivalents may be necessary to give a maximum rate. This may have some correlation with the observation of Ralston and co-workers (*J. Org. Chem.*, **5**, 645 (1940); **6**, 750 (1941)) that esters of phenol yielded more *p*-hydroxy ketone in the presence of larger excesses of aluminum chloride. The *o*-hydroxy ketone would probably coördinate only one mol of acid.

(12) Kästner (Thesis, Marburg, 1937, reported in some detail in "Newer Methods of Preparative Organic Chemistry," 1st American Ed., Interscience Publishers, New York, N. Y., 1948, pp. 284–291) has carried out kinetic studies with the boron fluoride complexes of phenolic esters in several solvents. His general conclusions are in agreement with ours, namely, that the rate-determining step is first order with respect to ester concentration. Irregular results obtained in certain solvents or in more dilute solution could be due to dissociation of the boron fluoride–ester complex.

aged or prevented. Since the proportion between the products rather than the formal kinetics of the reaction was important, the reaction was allowed to proceed nearly two days in order that larger yields could be obtained. The results are shown in Table II.

Run V, by itself, showed that the choice of 2-hydroxybiphenyl as a competitor was a fortunate one. The quantities of the two products obtained were comparable and the separation was not difficult. The combined yield, 65%, is normal for a Fries run in nitrobenzene. Since in Run VI, at the higher dilution, the proportion of biphenyl derivative obtained was much less, it is clear that the Fries reaction can proceed to a considerable extent through return of the oxo-carbonium ion to the fragment from which it seceded when the conditions of the reaction are favorable therefor (still, however, by an intermolecular process). As usually carried out this phenomenon would be of subsidiary importance.

The above remarks have *direct application* only to the Fries at low temperatures leading to a para shift. It is obvious that in the usual procedure for effecting an ortho shift (high temperature, no solvent) the environment would favor intermolecular reaction even more strongly. While the observations reported here do not exclude intramolecular rearrangement as a possible concurrent route of reaction they are completely consistent with the inherently more probable formulation in Chart A.

Experimental

Exploratory Runs (Table I).—In Runs I–III the required amounts of aluminum chloride were dissolved in 400 cc. of nitrobenzene in 500-cc. volumetric flasks. These solutions were allowed to stand overnight to dissipate the heat of solution. One-tenth mole (15 g.) of *o*-cresyl acetate was added to each, the solutions were made up to volume with nitrobenzene and transferred to round-bottom flasks immersed in a tank of water. Both the reaction flasks and the tank-water were stirred. The temperature of the reactions rose initially to about 35° but had fallen to 26° within fifteen minutes. Although precise thermostating was not deemed important at this stage of the study, the reaction temperature did not vary more than 0.2°. Run IV differed in that the aluminum chloride was dissolved in 800 cc. of nitrobenzene and the solution was made up to 1 l. after addition of the ester.

All these runs were worked up similarly. After seven hours, ice and hydrochloric acid were added and the nitrobenzene was steam-distilled off. The steam-distillates were examined for the presence of *p*-hydroxy ketone. This was not detected although both cresol and cresol ester were present. The residues from the steam-distillations were taken into ether, dried over a little calcium chloride and evaporated to small volume. On addition of hexane, 2-methyl-4-hydroxyacetophenone crystallized, m. p. 106–108° (lit., 104°). The mother liquors from the first crops of solid usually yielded smaller second crops of about the same degree of purity. Final evaporation of the mother liquors gave oily residues weighing about 0.1 g. and consisting mainly of *o*-cresol or nitrobenzene. The products isolated from Runs I to IV, respectively, weighed 3.9, 7.3, 7.2 and 7.0 g.

Competitive Runs (Table II).—Two portions of 70 g. (0.6 mole) each of aluminum chloride were dissolved in 500 cc. of nitrobenzene. The solutions were cooled approximately to room temperature and to each was added 34 g. (0.2 mole) of *o*-hydroxybiphenyl. There was no considerable development of heat and no evolution of hydrogen chloride. To each was then added 30 g. of *o*-cresyl acetate. Run VI was further diluted by addition of 1500 cc. of nitrobenzene. Each was then stirred for forty-seven and one-half hours. Since the proportion rather than the precise quantity of the products was important, the temperature was not controlled, however, in both cases it was very close to 26°.

The reaction-mixtures, after decomposition with ice and hydrochloric acid, were steam-distilled to remove nitrobenzene and the residues were taken into ether. By fractional crystallization from ether–hexane mixtures and from dilute methanol, combined with fractional distillation *in vacuo* the expected products were separated without great difficulty. The quantities of 4-hydroxy-2-methylacetophenone and 4-hydroxy-2-phenylacetophenone[13] isolated are shown in Table II. About 1 g. of 2-hydroxy-3-methylacetophenone semicarbazone was isolated by appropriate treatment of the mother liquors from Run VI and a trace of the same substance from Run V.

Summary

1. It is proposed that the Fries reaction proceeds through coördination of acid (aluminum chloride) with the phenolic ester, followed by cleavage of the complex to yield an oxo-carbonium ion which then attacks any susceptible particle it encounters. In very dilute solutions a significant amount of the product is formed by the chance attack of the oxo-carbonium ion upon the fragment from which it seceded.

2. The cleavage of the ester–acid complex is probably the rate-determining step of the reaction.

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(13) Auwers and Wittig, *J. prakt. Chem.*, **108**, 99 (1924).