[Contribution from the Chemistry Department of Duke University]

EVIDENCE FOR THE INTERMOLECULAR MECHANISM OF THE FRIES REACTION. SOME EXCHANGE EXPERIMENTS[1]

CHARLES R. HAUSER and EUGENE H. MAN[2]

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It has long been debated whether the Fries conversion of phenyl esters to *o*- or *p*-hydroxy ketones with aluminum chloride or another acidic reagent involves the intermolecular Friedel-Crafts type of acylation or an intramolecular rearrangement (1). At the present time most workers appear to support an intermolecular mechanism, although one writer has recently proposed an intramolecular mechanism involving the *pi* electron concept (2). The intermolecular mechanism applied, for example, to the conversion of phenyl benzoate to *p*-hydroxybenzophenone would presumably involve first the formation of the benzoyl carbonium ion from the phenyl ester (equation 1) (3), or from benzoyl chloride which may be produced from the phenyl ester (4). The carbonium ion may then acylate either the phenol complex I from equation 1 (or its aluminum dichloride complex) to form directly a complex of the hydroxy ketone (II or III, equation 2) or unchanged phenyl benzoate to give ketone-ester IV as an intermediate (equation 3). Intermediate IV may be converted to the hydroxy ketone (as aluminum chloride complex II or III) either by an ester-phenol exchange (equation 4a) or by the C-acylation of phenol by the carbonium ion from intermediate IV (equation 4b).

Recently Schönberg and Mustafa (5) claimed to have established the intermolecular mechanism for the Fries reaction by the isolation of certain ketone-esters such as ketone-ester IV from the reaction mixture of phenyl benzoate and phosphorus pentoxide. However, these workers apparently did not show whether ketone-ester IV is converted to the hydroxy ketone under similar conditions, that is, whether it may be an intermediate in the Fries type of reaction. Moreover, phosphorus pentoxide might effect the reaction by a different mechanism from aluminum chloride which is the usual Fries reagent.

In the present investigation, ketone-ester IV was isolated from the reaction mixture of phenyl benzoate and aluminum chloride in ethylene chloride, and subsequently converted under similar conditions to *p*-hydroxybenzophenone (Fries product). Ketone-ester IV was obtained in 17% yield at 60° and in about the same yield, (18%) along with the hydroxy ketone (37%), at 84°. The hydroxy ketone was separated from ketone-ester IV by extraction with alkali; a blank experiment showed that the ketone-ester was not saponified appreciably during this extraction. The conversion of ketone-ester IV to the hydroxy ketone was effected in high yield in the presence of aluminum chloride and phenol which, presumably, first reacted with the reagent to form a complex. Since phenyl ben-

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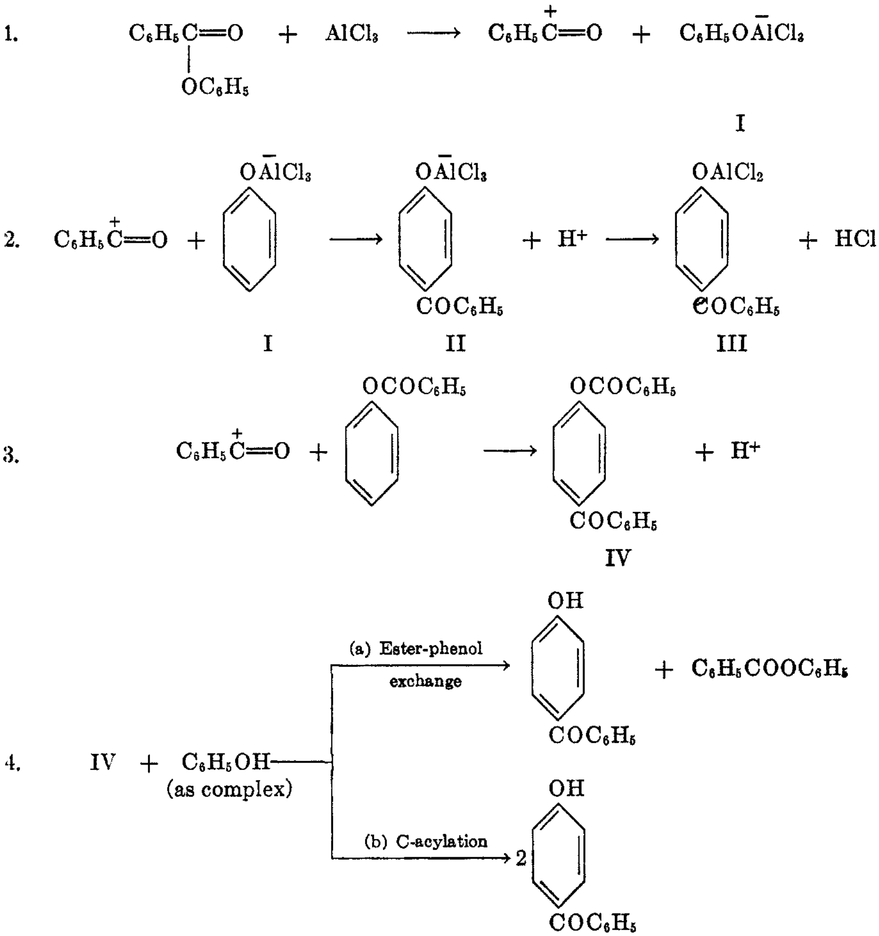
[2] DuPont Fellow, 1950–1951.

zoate was obtained as by-product, this conversion evidently involved the ester-phenol exchange represented by equation 4a. Thus ketone-ester IV could be, and probably is, a true intermediate in this Fries reaction which, on this basis,

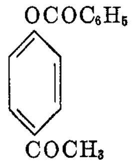


must involve the intermolecular mechanism. The fact that practically only ketone-ester IV was obtained at 60° whereas much of the hydroxy ketone also was isolated at 84° is in line with this conclusion, since relatively more of the ketone-ester should be converted to the hydroxy ketone at the higher temperature. It appears much less likely that ketone-ester IV was produced through the intermediate formation of the hydroxy ketone, which might arise either intermolecularly (equation 2) or intramolecularly. If this course were followed, ketone-ester IV could result from an ester-phenol exchange between the hydroxy ketone and phenyl benzoate. Such an exchange was realized in low yield between the hydroxy ketone and *p*-nitrophenyl benzoate, which itself does not undergo the Fries reaction. However, the formation of ketone-ester IV through the hydroxy ketone should have left relatively more of the hydroxy ketone at 60° than at

84° because, at the higher temperature, more of it would have been converted to ketone-ester IV. Actually, just the reverse result was obtained.

We have further found that a mixture of phenyl acetate, benzoyl chloride, and aluminum chloride in ethylene chloride at 40–50° yields ketone-ester V (23%), ketone-ester IV (3%), phenyl benzoate (16%), and benzoic acid (15%). This result seems best accounted for by an acyl exchange reaction to form phenyl benzoate and acetyl chloride (equation 5), followed by acetylation of part of the phenyl benzoate to form ketone-ester V (equation 6) and by benzoylation of part of the phenyl benzoate to form ketone-ester IV (equation 7). This larger proportion of acetylation is to be expected since acetyl chloride has been shown to be more reactive than benzoyl chloride in similar acylations (6). The benzoic acid resulted apparently from subsequent hydrolysis of the coordination complexes of the benzoic esters or benzoyl chloride, in both of which the benzoyl carbonium ion is potentially present (see equation 1). A partial exchange analogous to that represented in equation 5 has already been realized under similar conditions with benzoyl chloride and *p*-nitrophenyl acetate to form *p*-nitrophenyl benzoate and acetyl chloride (6). The reverse exchange has also been realized under similar conditions with acetyl chloride and phenyl benzoate to form benzoyl chloride (34%) and presumably phenyl acetate.

5. $$C_6H_5COCl + CH_3COOC_6H_5 \xrightleftharpoons{AlCl_3} C_6H_5COOC_6H_5 + CH_3COCl$$

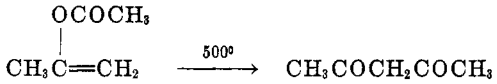
6. $CH_3COCl + C_6H_5COOC_{65}H \xrightarrow{AlCl_3}$  $+ HCl$

V

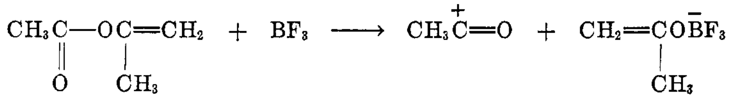
7. $$C_6H_5COCl + C_6H_5COOC_6H_5 \xrightarrow{AlCl_3} IV + HCl$$

Intramolecular rearrangements of the phenyl esters to form hydroxy ketone complexes followed by ester-phenol exchanges seem quite unlikely, especially since none of the hydroxy ketones were found. Moreover, phenyl benzoate itself was found to be unaffected by aluminum chloride under similar conditions and was recovered unchanged.

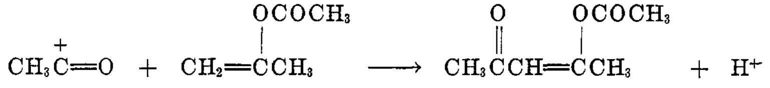
In this connection, it should be pointed out that ketone enol esters, such as isopropenyl acetate, which may be regarded as aliphatic analogs of phenyl esters, have been shown to be converted to β-diketones by intramolecular rearrangement at 500° (equation 8) (7), but by intermolecular self-acylation in the presence of boron trifluoride at 0–20° (equations 9, 10, 11) (7). Equations 9 and 10 of the latter reaction are analogous to equations 1 and 3 of the Fries intermolecular mechanism, ketone-ester VI corresponding to ketone-ester IV. Actually, ketone-ester VI, which is converted by boron trifluoride to boron difluoride complex VII (8) (equation 11), is more closely related to the *ortho* analog of ketone-ester IV which presumably would be converted by aluminum chloride to the corresponding aluminum dichloride complex sometimes postulated (9).

8. 

$$CH_3\overset{\overset{\textstyle OCOCH_3}{|}}{C}{=}CH_2 \xrightarrow{500^\circ} CH_3COCH_2COCH_3$$

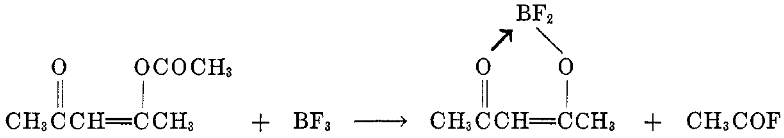
9. 

$$CH_3\underset{\underset{\textstyle O}{\|}}{C}{-}O\underset{\underset{\textstyle CH_3}{|}}{C}{=}CH_2 + BF_3 \longrightarrow CH_3\overset{+}{C}{=}O + CH_2{=}\underset{\underset{\textstyle CH_3}{|}}{C}O\overset{-}{B}F_3$$

10. 

$$CH_3\overset{+}{C}{=}O + CH_2{=}\overset{\overset{\textstyle OCOCH_3}{|}}{C}CH_3 \longrightarrow CH_3\overset{\overset{\textstyle O}{\|}}{C}CH{=}\overset{\overset{\textstyle OCOCH_3}{|}}{C}CH_3 + H^+$$

VI

11. 

$$\underset{\textstyle VI}{CH_3\overset{\overset{\textstyle O}{\|}}{C}CH{=}\overset{\overset{\textstyle OCOCH_3}{|}}{C}CH_3} + BF_3 \longrightarrow \underset{\textstyle VII}{CH_3\overset{\overset{\textstyle O\rightarrow BF_2}{\|}}{C}CH{=}\overset{\overset{\textstyle O-}{|}}{C}CH_3} + CH_3COF$$

VI VII

These results with ketone enol esters furnish further evidence by analogy that the Fries reaction with phenyl esters effected by acidic reagents involves an intermolecular mechanism, especially for those carried out at relatively low temperatures. Of course, it is possible that Fries reactions effected at relatively high temperatures, perhaps even at 140° at which phenyl benzoate has been converted quantitatively to *p*-hydroxybenzophenone (10), might involve an intramolecular rearrangement. Our evidence supporting the intermolecular mechanism was obtained at lower temperatures (60–84°) and may not necessarily be pertinent to the reaction under the more strenuous conditions. If the Fries reaction were effected by heat alone, it might be expected by analogy with the ketone enol ester to undergo an intramolecular rearrangement.[3]

EXPERIMENTAL[4]

Commercial acetyl and benzoyl chlorides, phenyl acetate, and phenyl benzoate were purified by distillation. *p*-Nitrophenyl benzoate (m.p. 140–141.5°) was prepared from *p*-nitrophenol and benzoyl chloride (6).

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[3] Dr. F. G. Young of the Carbide and Carbon Chemicals Corporation, South Charleston, West Virginia, has kindly informed us (private communication) that attempts to rearrange phenyl acetate and *p*-tolyl propionate at 500° (see ref. 7) were unsuccessful, the esters being recovered. This failure is not surprising since the *pi* electrons of the olefinic double bond, which appear to be involved in the thermal rearrangement of ketone enol esters, should be more available than the *pi* electrons in the aromatic system of a phenyl ester. It is of course possible that more reactive phenyl esters might be rearranged thermally.

[4] Melting points and boiling points are uncorrected. Analysis by Clark Microanalytical Laboratory, Urbana, Ill.

Reaction of phenyl benzoate with aluminum chloride. (a) At *84°*. In a 300 ml. round-bottom three-necked flask equipped with a sealed stirrer, reflux condenser, and thermometer, and protected from moisture with calcium chloride tubes, was placed a solution of 19.8 g. (0.1 mole) of phenyl benzoate and 17.3 g. (0.13 mole) of aluminum chloride in 50 ml. of ethylene chloride. After refluxing (84°) with stirring for 1½ hours, the reaction mixture was poured onto 500 g. of ice containing 20 ml. of hydrochloric acid to decompose the complexes, and the aqueous mixture was extracted with ether. The combined ether extracts were washed with saturated sodium bicarbonate solution (no benzoic acid being obtained on acidifying these extracts), and then with four 100-ml. portions of 10% sodium hydroxide solution.

The combined sodium hydroxide extracts were acidified to yield 7.3 g. (37%) of crude *p*-hydroxybenzophenone, m.p. 128–130° after one recrystallization from ethanol and one from ether-ligroin (b.p. 30–60°). Further purification gave the pure ketone, m.p. 132–133.5° (reported m.p. 135°) (11).

The ether solution was washed with water and dried over Drierite. After distilling the ether and ethylene chloride, there was obtained 5.4 g. (18%) of crude *p*-benzoylphenyl benzoate (IV), m.p. 102–107° after one recrystallization from ethanol-water. Two further recrystallizations from ether-ligroin (b.p. 30–60°) yielded the pure ketone-ester IV, m.p. 113–114° (reported m.p. 113–114°) (5).

Anal. Calc'd for $C_{20}H_{14}O_3$: C, 79.46; H, 4.67.
Found: C, 79.50; H, 4.58.

Ketone-ester IV was further identified by saponification with 10% sodium hydroxide solution (three-hours refluxing) to produce a good yield of *p*-hydroxybenzophenone, m.p. 132–133.5° after recrystallizing as described above. A small amount of benzoic acid was also obtained.

Ketone-ester IV (1.04 g.) was converted to the hydroxy ketone by refluxing four hours in ethylene chloride (30 ml.) with phenol (1.00 g.) and aluminum chloride (2.00 g.). The reaction mixture was decomposed with ice-hydrochloric acid and extracted with ether. The ether solution was extracted with 10% sodium hydroxide and the alkaline extracts acidified to give, after one recrystallization from ether-ligroin (b.p. 30–60°), 0.61 g. (91%) of *p*-hydroxybenzophenone, m.p. 132–133°. There was also isolated from the original ether solution 0.45 g. (67%) of phenyl benzoate, m.p. 64–67° after recrystallization from ethanol (reported m.p. 69–70°) (11).

Ketone-ester IV was found to be stable with aluminum chloride alone in ethylene chloride being recovered unchanged after refluxing 1½ hours.

(b). *At 60°*. Phenyl benzoate (19.8 g., 0.1 mole) dissolved in ethylene chloride (50 ml.) was heated at 60° for four hours with aluminum chloride (17.3 g., 0.13 mole) and worked up as described above in (a). The acidified sodium hydroxide extracts yielded about 2 g. of partially solid material from which no *p*-hydroxybenzophenone could be isolated.

The unextracted material in the ether solution was distilled with steam. The distillate yielded 12.1 g. (61%) of recovered phenyl benzoate, m.p. 67–69°. The residue yielded 5.3 g. (17%) of crude *p*-benzoylphenyl benzoate (IV), m.p. 110–113° after two recrystallizations from ethanol.

A similar solution of phenyl benzoate and aluminum chloride in ethylene chloride heated at 60° for one hour failed to produce any isolable amounts of either *p*-hydroxybenzophenone or ketone-ester IV. Phenyl benzoate was again recovered unchanged.

Ester-phenol exchange with p-hydroxybenzophenone and p-nitrophenyl benzoate. A solution of 4.00 g. of *p*-nitrophenyl benzoate and 2.69 g. of *p*-hydroxybenzophenone in 75 ml. of ethylene chloride was treated with 6.65 g. of aluminum chloride, and the resulting mixture was refluxed with stirring for four hours. The reaction mixture was decomposed with ice and hydrochloric acid and extracted with ether. After extracting with 10% sodium hydroxide to remove unreacted *p*-hydroxybenzophenone and the by-product, *p*-nitrophenol, the ether solution was washed with water, dried over Drierite, and the solvents distilled. The residue was recrystallized twice from ethanol, and once from ether-ligroin (b.p. 30–60°) to give 0.57 g. (14%) of crude *p*-benzoylphenyl benzoate (IV), m.p. 106–111°, which after one further recrystallization from ether-ligroin melted at 110–113° (mixture m.p., 110–113°).

Reaction of phenyl acetate and benzoyl chloride with aluminum chloride. In a 500-ml. round-bottom three-necked flask fitted as described above was placed 56.2 g. (0.4 mole) of benzoyl chloride in 100 ml. of dry ethylene chloride. To the stirred solution, occasionally cooled in a water-bath, 100 g. (0.75 mole) of aluminum chloride was added during 15 minutes, and, after stirring 25 minutes at 35°, 27.2 g. (0.2 mole) of phenyl acetate was added during 1¼ hours, keeping the temperature at 35–40°. The resulting mixture was heated at 45–55° an additional hour, then decomposed with ice and hydrochloric acid and extracted with ether. The ether solution was extracted with a saturated sodium bicarbonate solution, and then with cold 5% sodium hydroxide. There was recovered from the bicarbonate extracts 7.5 g. (15%) of benzoic acid, m.p. 121–122.5°, and from the sodium hydroxide extracts, a small amount of impure benzoic acid. The ether solution was dried over Drierite and the solvent distilled. The residue was distilled to give 16.3 g. (29%) of recovered benzoyl chloride and 6.3 g. (16%) of crude phenyl benzoate, m.p. 66.5–68° after two recrystallizations from ethanol. The solid residue remaining after the above compounds were distilled was fractionally crystallized from ethanol to yield two solid components. The first fraction yielded 11.0 g. (23%) of *p*-acetylphenyl benzoate (V), m.p. 131–134° after one recrystallization from methanol (reported m.p. 134°) (12). This product was further identified as V by saponification with 10% sodium hydroxide solution to give benzoic acid and *p*-hydroxyacetophenone, m.p. 107–109° after one recrystallization from ether-ligroin (b.p. 30–60°) (reported m.p. 109°) (11). The second fraction consisted of 2.0 g. (3%) of impure *p*-benzoylphenyl benzoate (IV), m.p. 101–107°, which was identified by saponification with 10% sodium hydroxide to give benzoic acid and *p*-hydroxybenzophenone, m.p. 130.5–132° after one recrystallization from ether-ligroin.

Exchange reaction with phenyl benzoate and acetyl chloride. This reaction, using 31.4 g. (0.4 mole) of acetyl chloride, 100 g. (0.75 mole) of aluminum chloride, and 39.6 g. (0.2 mole) of phenyl benzoate added as a solution in 50 ml. of ethylene chloride, was carried out in the same manner as that described above for phenyl acetate and benzoyl chloride. There were isolated 4.5 g. (18%) of benzoic acid, m.p. 121–122.5° (from the bicarbonate extracts); 9.5 g. (34%) of benzoyl chloride, b.p. 196–197°; and 13 g. (33%) of recovered phenyl benzoate, m.p. 64–66° after one recrystallization from ethanol. There was also obtained (from the sodium hydroxide extracts) about 6 g. of material which was not identified. Attempts to isolate from it *p*-hydroxyacetophenone or *p*-hydroxybenzophenone were unsuccessful.

SUMMARY

1. Evidence that the Fries conversion of phenyl benzoate to *p*-hydroxybenzophenone involves the intermolecular acylation of the phenyl ester has been obtained. *p*-Benzoylphenyl benzoate (IV) was isolated from the reaction mixture and shown to be probably an intermediate in the formation of the hydroxy ketone.

2. Certain acylations of phenyl esters with acid chlorides, and exchange reactions between phenyl esters and acid chlorides have been effected.

3. The analogy between the Fries reaction and the conversion of ketone enol esters to β-diketones has been considered.

DURHAM, NORTH CAROLINA

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(4) See Cox, *J. Am. Chem. Soc.*, **52,** 352 (1930); also, see Baltzly and Phillips, *J. Am. Chem. Soc.*, **70,** 4191 (1948).

(5) Schönberg and Mustafa, *J. Chem. Soc.*, 79 (1943).

(6) Man and Hauser, *J. Org. Chem.*, **17,** this issue.

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(12) Tanret, *Bull. soc. chim.*, [3] **11,** 949 (1894).