

hydrochloric and sulfuric acid solutions promoted furfural formation at distillation temperatures, the yield being dependent on the acid concentration, the temperature and on the duration of the distillation. This is a first order reaction.

The behavior of mineral acids at distillation temperatures on furfural, arabinose, rhamnose, tetramethylene glycol, ketoxylose, xylonic acid, glycerol and erythritol was investigated. In the last four cases there was little or no reaction. The significance of these results on the mechanism of the pentose-to-furfural reaction has been discussed.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

SOME OBSERVATIONS ON THE FRIES REACTION¹

BY F. F. BLICKE AND O. J. WEINKAUFF

RECEIVED AUGUST 27, 1931

PUBLISHED JANUARY 7, 1932

We became interested in the Fries reaction² because it seemed possible that this reaction might play a role in the formation of hydroxydiarylphthalides such as phenolphthalein. Furthermore, we wished to determine whether or not diphenyl phthalate, as well as phenyl 2-(*p*-hydroxybenzoyl)-benzoate, under the influence of aluminum chloride, would yield 2-(4''-hydroxybenzoyl)-4'-hydroxybenzophenone.³

It has been stated by Rosenmund and Schnurr⁴ that phenyl benzoate, when heated with aluminum chloride, is converted quantitatively into 4-hydroxybenzophenone. Similar results were obtained by us. We found that the benzoate of 4-hydroxydiphenyl behaves in an analogous manner to yield a compound which was, undoubtedly, 4-(*p*-hydroxyphenyl)-benzophenone since the material obtained by the action of aluminum chloride on the ester, after methylation, was identical with the substance prepared by condensation of benzoyl chloride with the methyl ether of 4-hydroxydiphenyl.

Csanyi⁵ reported that diphenyl phthalate and aluminum chloride yield phenolphthalein but the amount of the latter which is produced and the experimental conditions which govern its formation were not recorded.

¹ This investigation was made possible by the establishment of the Michigan State Pharmaceutical Association Research Fund. We wish to express our appreciation for the aid which has been given us.

² A recent study of this reaction has been reported by Cox, *THIS JOURNAL*, **52**, 352 (1930).

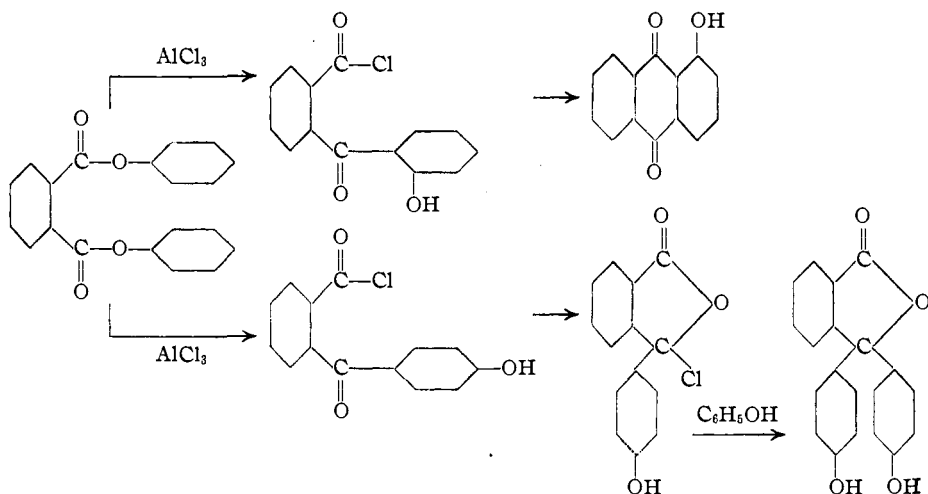
³ This substance is isomeric with phenolphthalein and is easily obtained from it. The preparation of this compound is described by the authors in an article which will be published in an early issue of *THIS JOURNAL*.

⁴ Rosenmund and Schnurr, *Ann.*, **460**, 89 (1928).

⁵ Csanyi, *Ber.*, **52**, 1792 (1919).

We carried out a series of experiments with diphenyl phthalate and aluminum chloride and obtained mixtures of phenolphthalein and 1-hydroxyanthraquinone but were unable to isolate any of the substituted benzo-phenone. Csanyi makes no mention of an anthraquinone as a reaction product. Although the formation of an anthraquinone in this reaction is not surprising it would seem that a 2-hydroxy instead of a 1-hydroxy compound should be produced. The only explanation which we can offer to account for the formation of the latter substance is that some 2-(2'-hydroxybenzoyl)-benzoyl chloride may have been produced as an intermediate reaction product.

Phenyl 2-(methoxybenzoyl)-benzoate was changed, practically quantitatively, into phenolphthalein.



Experimental Part

Preparation of Esters.—Phenyl benzoate was obtained in practically quantitative yield when benzoyl chloride and phenol, mixed in equivalent amounts, were allowed to remain at ordinary temperature for several hours. The ester was washed with alcohol and then recrystallized from the same solvent; m. p. 69–70°.

Diphenyl phthalate was prepared from phthalyl chloride and phenol in the manner described above. After recrystallization from alcohol it melted at 74–76°.

In order to obtain the benzoate of 4-hydroxydiphenyl, benzoyl chloride and 4-hydroxydiphenyl were mixed and kept in a molten state until no more hydrogen chloride was evolved. The ester melted at 150–151° after recrystallization from alcohol.

Phenyl 2-(*p*-methoxybenzoyl)-benzoate was prepared in the following manner. Forty-eight grams of 2-(*p*-hydroxybenzoyl)-benzoic acid was methylated with 160 cc. of 10% sodium hydroxide solution and 40 cc. of dimethyl sulfate. A portion of the methyl ester of 2-(*p*-methoxybenzoyl)-benzoic acid, which separated as a crystalline solid, was removed from the methylation mixture and recrystallized from methyl alcohol; m. p. 82–83°. Sixteen grams of sodium hydroxide was added to the reaction

⁶ Egerer and H. Meyer [*Monatsh.*, **34**, 80 (1913)] recorded the melting point as 83°.

mixture and the latter heated for three hours on a steam-bath in order to hydrolyze the methyl ester. When the mixture was cooled a crystalline precipitate formed, presumably the sodium salt of the substituted benzoic acid. The latter was removed by filtration and the precipitate and filtrate acidified separately. The 2-(*p*-methoxybenzoyl)-benzoic acid was recrystallized from dilute alcohol; m. p. 146–147°. ⁷

In order to prepare the acid chloride, 31 g. of the acid and 29 g. of thionyl chloride were mixed and allowed to remain at ordinary temperature for twelve hours. The excess thionyl chloride was removed under diminished pressure at ordinary temperature, the residue dissolved in absolute ether and the ether distilled under reduced pressure. The treatment with ether was continued until practically all of the thionyl chloride had been removed. The acid chloride was obtained in the form of a viscous oil.

Twenty-five grams of the crude chloride and potassium phenolate, prepared from 10.3 g. of phenol, 4.1 g. of potassium and 300 cc. of absolute ether, were heated for one hour on a steam-bath. After recrystallization from alcohol the phenyl 2-(*p*-methoxybenzoyl)-benzoate melted at 144–145°. The same ester was obtained from the acid chloride prepared with the aid of phosphorus pentachloride.

Anal. Calcd. for $C_{21}H_{16}O_4$: C, 75.88; H, 4.86. Found: C, 75.65; H, 4.86.

One and sixty-six hundredths grams of the ester was hydrolyzed and the phenol formed converted into tribromophenol. There was obtained 1.25 g. of 2-(*p*-methoxybenzoyl)-benzoic acid and 1.57 g. of tribromophenol; the calculated amounts of acid and tribromophenol are 1.28 g. and 1.65 g., respectively.

Reaction of Esters with Aluminum Chloride. Phenyl Benzoate.—Five grams of phenyl benzoate was heated with aluminum chloride according to the directions of Rosenmund and Schnurr.⁴ 4-Hydroxybenzophenone was obtained in quantitative yield; m. p. 135–136°.

Benzoate of 4-Hydroxydiphenyl.—Five grams of the ester, 3 g. of aluminum chloride and 25 cc. of tetrachloroethane were heated for one hour in a bath at 140°. The mixture was decomposed with ice and hydrochloric acid and then steam distilled to remove the solvent. The residue was boiled with sodium hydroxide solution, filtered and the filtrate acidified. The gummy precipitate was dried and dissolved in hot benzene. The crystals which were obtained from the solution were recrystallized from alcohol; m. p. 193–195°. This material, 4-(*p*-hydroxyphenyl)-benzophenone, was methylated with dimethyl sulfate. The methyl ether melted at 168–169° after recrystallization from alcohol.

4-(*p*-Methoxyphenyl)-benzophenone was synthesized in the following manner. Nine grams of 4-methoxydiphenyl,⁸ 7 g. of benzoyl chloride, 8 g. of aluminum chloride and 40 cc. of carbon disulfide were allowed to remain at ordinary temperature for twenty-four hours. The carbon disulfide was decanted, the mixture treated with ice and hydrochloric acid and then subjected to steam distillation. The residue was dissolved in benzene and shaken with sodium hydroxide solution a number of times. Upon evaporation of the benzene a yellow, crystalline product was obtained. After several recrystallizations from alcohol the compound was obtained in a colorless state; m. p. 168–169°. Mixed with the methylated product obtained from the Fries reaction the melting point was found to be that given above.

Diphenyl Phthalate.—Ten grams of diphenyl phthalate, 10 g. of aluminum chloride and 25 cc. of tetrachloroethane were heated at 100° for six hours. After the addition of hydrochloric acid the mixture was subjected to steam distillation. After all of the tetrachloroethane had been removed a small amount of yellow, crystalline material separated in the condenser. This substance was, undoubtedly, impure 1-hydroxy-

⁷ Meyer and Turnau [*Monatsh.*, **30**, 487 (1909)] recorded the melting point as 148°.

⁸ Werner, *Ann.*, **322**, 167 (1902).

anthraquinone; m. p. 180–200°. The residue in the steam distillation flask was treated with 120 cc. of 10% sodium hydroxide solution, the alkali-insoluble material, which weighed 3 g., removed by filtration and the filtrate acidified. The precipitated material was recrystallized from acetic acid. This proved to be phenolphthalein. The yield was 3 g., m. p. 253–255°. The alkali-insoluble product, after recrystallization from alcohol, was obtained in the form of yellow needles; m. p. 194–195°. This material was 1-hydroxyanthraquinone; mixed m. p. 196–198°. The hydroxyanthraquinone obtained as a reaction product was acetylated¹⁰ and mixed with pure acetylated 1-hydroxyanthraquinone. The mixed melting point, 185–187°, was that of pure acetyl-1-hydroxyanthraquinone.

In another experiment 10 g. of diphenyl phthalate, 10 g. of aluminum chloride and 25 cc. of tetrachloroethane were heated at 150° for thirty minutes. There were obtained 2.3 g. of 1-hydroxyanthraquinone and 6.3 g. of phenolphthalein.

Phenyl 2-(*p*-Methoxybenzoyl)-benzoate.—Two grams of the ester, 2 g. of aluminum chloride and 10 cc. of tetrachloroethane were heated for two hours at 90°. After decomposition and steam distillation of the reaction mixture the residue was dissolved in alkali and the solution acidified. After recrystallization from acetic acid the phenolphthalein obtained melted at 256–257°. The yield of pure material was 1.7 g.; the calculated amount is 1.9 g. The phenolphthalein is probably formed as a result of the formation of the following intermediate products: (a) 2-(*p*-methoxybenzoyl)-benzoyl chloride, *p*-methoxyphenylchlorophthalide or (b) *p*-methoxyphenylphenoxyphthalide. It is impossible to state at which stage during the process demethylation takes place.

Separation of Phenolphthalein from 2-Hydroxyanthraquinone.—Since it was considered possible that some 2-hydroxyanthraquinone might be formed from the action of aluminum chloride on diphenyl phthalate, the reaction products were carefully examined for this anthraquinone. However, we were unable to obtain any of the 2-hydroxy compound.

The separation of 1-hydroxyanthraquinone from phenolphthalein is not a difficult matter since the former substance does not dissolve readily in 10% sodium hydroxide solution. However, 2-hydroxyanthraquinone is readily soluble in aqueous sodium hydroxide, hence the following procedure was used in the case of reaction mixtures which we thought might consist of phenolphthalein and 2-hydroxyanthraquinone. The process is illustrated by the separation of a mixture prepared from 2.5 g. of phenolphthalein and an equal amount of 2-hydroxyanthraquinone. After the material had been dissolved in 60 cc. of 10% sodium hydroxide solution, 3 g. of zinc dust was added and the mixture heated for one hour on a steam-bath. The excess zinc was removed by filtration and the filtrate acidified with hydrochloric acid. The precipitated material was washed with water and then digested with 150 cc. of 5% sodium bicarbonate solution. The insoluble material, reduced hydroxyanthraquinone, was removed by filtration and the filtrate acidified. The precipitated material was dissolved in 25 cc. of hot alcohol and the solution mixed with 150 cc. of hot water. After some time phenolphthalein (4',4''-dihydroxytriphenylmethane-2-carboxylic acid) separated in the form of needles, m. p. 233–234°, yield 2.4 g. or 96% of the calculated amount. Phenolphthalin can be converted readily into phenolphthalein by oxidation.¹¹ The crude, re-

⁹ An unusually pure sample of 1-hydroxyanthraquinone which we prepared from 1-aminoanthraquinone melted at 200–201°. The highest melting point recorded for this compound in the literature is 193° [Ullmann, *Ber.*, **53**, 829 (1920)]. It was found that 2-hydroxyanthraquinone, prepared from 2-hydroxyanthrone-9, melts at 303–304°. Decker and Laube [*ibid.*, **39**, 113 (1906)] recorded the melting point as 306° (corr.).

¹⁰ Dimroth, Friedmann and Kämmerer, *ibid.*, **53**, 482 (1920).

¹¹ Baeyer, *Ann.*, **202**, 82 (1880).

