

Summary

1. Triethyl ortho-acetate condensed only with difficulty with either ethyl acetoacetate or diethyl malonate in the presence of acetic anhydride, forming the methyl homologs of ethoxymethylene esters. They were unstable liquids, decomposing partially on distillation. They formed, however, characteristic copper salts which could be purified and identified.

2. Triethyl ortho-benzoate condensed easily with either ethyl acetoacetate or diethyl malonate, forming very stable phenyl analogs of ethoxymethylene esters with definite physical properties. Their copper salts were also made and analyzed.

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STUDIES IN THE 3-NITROPHTHALIC ACID SERIES

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I. Phenol-3-nitrophthalein and Resorcinol-3-nitrophthalein.—This paper gives an account of the preparation of phenol-3-nitrophthalein and resorcinol-3-nitrophthalein and a comparison of the properties of these compounds with those of phenolphthalein and fluorescein. In previous contributions² dealing with derivatives of phthalic and diphenic acids, it was pointed out that the groups in diphenic anhydride give the sodium salt of phenoldiphenic a light yellow instead of a red color and that an alkaline solution of resorcinoldiphenic does not show fluorescence.

Discussion of Experiments

All of the temperatures given are uncorrected.

Phenol-3-nitrophthalein.—Fifteen grams of 3-nitrophthalic anhydride, 16.1 g. of phenol (calcd. amt. $\times 1.1$) and 3 g. of concd. sulfuric acid (d 1.84) were placed in a loosely stoppered Erlenmeyer flask and heated in an oil-bath which was rapidly raised to 170°, maintained at this temperature for about two and one-half hours and then at 215–220° for three hours longer. After the reaction product had cooled, it was powdered and added to about 600 cc. of water in a beaker. The mixture was boiled for four hours to remove the excess of phenol; the water lost by evaporation was replaced from time to time. The insoluble solid was collected on a filter, transferred to a beaker and stirred with three 60-cc. portions of 3.5% sodium hydroxide solution. Acidification of the combined, filtered alkaline liquids yielded a dark colored precipitate. This material was collected on a filter, dried for forty-eight hours at room temperature and then ground with six 100-cc. portions of ether in a mortar. The ether

¹ Some of the experimental results described in this paper are taken from a thesis submitted to the Faculty of the Massachusetts Institute of Technology by R. L. Wakeman in partial fulfilment of the requirements for the degree of Bachelor of Science.

² Underwood and Kochmann, *THIS JOURNAL*, **45**, 3071 (1923); **46**, 2069 (1924).

extract was filtered, and the solvent was removed by distillation on a water-bath. Phenol-3-nitrophthalein was obtained in the form of long yellow needles, m. p. 204–205°, by crystallization from acetone, with the use of decolorizing carbon. The crystals weighed 0.6 g. (2.1% yield). The compound dissolves in sodium hydroxide solution with the development of a violet color. A very dilute solution of the sodium salt of phenol-3-nitrophthalein becomes practically colorless upon the addition of a large excess of concd. sodium hydroxide solution. Apparently the nitro group in 3-nitrophthalic anhydride gives a violet instead of a red color to the sodium salt of the phenol condensation product.

Anal. Calcd. for $C_{20}H_{13}O_6N$: C, 66.10; H, 3.61; N, 3.86. Found: C, 65.91, 65.73; H, 3.80, 3.85; N, 4.01, 4.12.

Resorcinol-3-nitrophthalein.—An intimate mixture of 5 g. of 3-nitrophthalic anhydride and 6.3 g. of resorcinol (calcd. amt. $\times 1.1$) was placed in a large test-tube, and heated at 195–200° for one and one-fourth hours. After the melt had cooled, it was powdered and boiled with 150 cc. of water for half an hour. The solid reaction product was collected on a filter, and then stirred with two 60-cc. portions of 2% sodium hydroxide solution. The filtered alkaline solution was acidified with 6 *N* sulfuric acid and shaken with three 80-cc. portions and one 40-cc. portion of ether. The ether extract was filtered, and the solvent was removed by distillation on a water-bath. The solid residue was extracted with 40 cc. of boiling alcohol, and water was added to the hot filtered solution, with stirring, until it became turbid. The mixture was heated to its boiling point and then allowed to cool slowly to room temperature. The precipitated resorcinol-3-nitrophthalein was collected on a filter, dried in the air and for a short time at 105°. Another lot of resorcinol-3-nitrophthalein was obtained by concentrating the filtrate to approximately one-half its volume. The product was dissolved in a small amount of boiling alcohol, precipitated by the addition of water, collected on a filter and dried at 105°. The yield of resorcinol-3-nitrophthalein, m. p. 260°, was 1.7 g. (17.4%). The product formed red crystalline granules, which dissolved in sodium hydroxide solution with the development of a brownish-yellow color. A dilute alkaline solution of resorcinol-3-nitrophthalein exhibited a green fluorescence, but not nearly to the same extent as a solution of fluorescein.

Anal. Calcd. for $C_{20}H_{11}O_7N$: C, 63.65; H, 2.94; N, 3.71. Found: C, 63.54, 63.30; H, 3.20, 3.11; N, 3.95, 3.88.

II. Reactions of Derivatives of 3-Nitrophthalic Acid with Acetic Anhydride.—Investigations dealing with the removal of alcohol, water and ammonia from derivatives of phthalic and diphenic acids have been previously described. It was noted that monomethyl diphenate and monoethyl diphenate, as well as the dimethyl and diethyl esters of diphenic and phthalic acids, remain unchanged when heated with acetic anhydride, but monomethyl and mono-ethyl phthalates yield phthalic anhydride. Under similar conditions diphenamic acid is dehydrated in two different ways, giving diphenimide and 2-cyanobiphenyl-2'-carboxylic acid; the diamide of diphenic acid is transformed into 2,2'-dicyanobiphenyl, through the loss of two molecules of water. Phthalamic acid is converted into phthalimide and phthalic anhydride by treatment with acetic anhydride, and phthalamide gives *o*-cyanobenzamide and phthalimide.³

³ Underwood and Clough, *THIS JOURNAL*, **51**, 583 (1929); Underwood and Barker, *ibid.*, **52**, 4082 (1930).

Discussion of Experiments

The methyl esters and the amides of 3-nitrophthalic acid have been previously prepared. We used dry hydrogen chloride instead of concd. sulfuric acid as a catalyst in the synthesis of dimethyl 3-nitrophthalate. The procedures given in the literature for the preparation of 3-nitrophthalimide and 3-nitrophthalic acid monoamide (1) involve the dehydration of mono-ammonium 3-nitrophthalate by heat alone and the treatment of 3-nitrophthalimide with barium hydroxide solution, respectively.⁴ We found that it was advantageous to employ a mixture of the mono-ammonium salt and anhydrous zinc chloride and to use sodium hydroxide instead of barium hydroxide; typical experiments are described below.

Monomethyl 3-Nitrophthalates.—Five grams of each ester was heated with 5 g. of glacial acetic acid and 8 g. of acetic anhydride for six hours at 145°. Practically all of the liquid was then removed by distillation, and the residue was cooled in ice. The product was crystallized from a small amount of glacial acetic acid. 3-Nitrophthalic acid methyl ester (1) was recovered unchanged. Two grams of 3-nitrophthalic anhydride was obtained from the 3-nitrophthalic acid methyl ester (2).

Dimethyl 3-Nitrophthalate.—After a mixture of 5 g. of dimethyl 3-nitrophthalate, 5 g. of glacial acetic acid and 8 g. of acetic anhydride had been refluxed for six hours at 145°, the liquid was removed by distillation, and the residue was cooled in ice. Practically all of the ester was recovered unchanged.

3-Nitrophthalimide.—A solution of the mono-ammonium salt of 3-nitrophthalic acid, prepared by the addition of the acid to the calculated amount of concd. ammonium hydroxide, was evaporated practically to dryness. The product was collected on a filter and dried. An intimate mixture of 15 g. of powdered mono-ammonium 3-nitrophthalate and 5 g. of powdered anhydrous zinc chloride was placed in a large test-tube and heated at 225–230° for four and one-half hours. The melt was allowed to cool, transferred to a mortar, reduced to a powder and extracted with four 15-cc. portions of boiling acetone. The filtered acetone solution was refluxed with 0.3 g. of decolorizing carbon for several minutes and filtered; this treatment was repeated. About two-thirds of the solvent was removed by distillation on a water-bath, and the residue was cooled in ice. The 3-nitrophthalimide was collected on a filter and dried for half an hour at 100°. The yield of 3-nitrophthalimide, m. p. 214–215°, was 5.05 g. (40%).

3-Nitrophthalamic Acids.—Five grams of 3-nitrophthalic acid monoamide (2) was refluxed with 5 g. of glacial acetic acid and 8 g. of acetic anhydride for six hours at 145°. The crystals deposited when the solution was cooled in ice were collected on a filter and recrystallized from alcohol. Two and one-tenth grams of 3-nitrophthalimide was obtained.

When 10 g. of 3-nitrophthalimide was heated with 25 cc. of 10% sodium hydroxide solution (calcd. amt. $\times 1.34$) and 35 cc. of water for an hour at 80–85°, most of the solid gradually dissolved. 3-Nitrophthalic acid monoamide (1) was precipitated by acidification of the hot filtered solution with concd. hydrochloric acid. After the reaction mixture had been cooled in ice, the solid was collected on a filter, washed with 20 cc. of water and dried in a vacuum desiccator over anhydrous calcium chloride. The yield of 3-nitrophthalic acid monoamide (1) was 7.5 g. (68.6%). The product softened at 144–146°, solidified as the temperature was raised and remelted at 214–215°.

A solution of 5 g. of the monoamide in 5 g. of glacial acetic acid and 8 g. of acetic anhydride was refluxed for six hours at 145°, and then allowed to stand for twelve hours. The solid which formed was collected on a filter. The filtrate was diluted

⁴ Bogert and Boroschek, *THIS JOURNAL*, **23**, 740 (1901).

with 40 cc. of ether and filtered again. The reaction product, which weighed 2.9 g. after crystallization from a small amount of a mixture of equal volumes of alcohol and acetone, was identified as 3-nitrophthalimide.

3-Nitrophthalimide.—By use of the procedure described above, we obtained 2.1 g. of 3-nitrophthalimide by heating 5 g. of 3-nitrophthalimide with 5 g. of glacial acetic acid and 8 g. of acetic anhydride for six hours at 145°. A small amount of impure acetamide was secured by fractionation of the distillate.

Summary

Phenol-3-nitrophthalein and resorcinol-3-nitrophthalein are formed by the condensation of 3-nitrophthalic anhydride with phenol and resorcinol respectively. Phenol-3-nitrophthalein dissolves in sodium hydroxide solution with the development of a violet color. A dilute alkaline solution of resorcinol-3-nitrophthalein exhibits a green fluorescence, but not nearly to the same extent as a solution of fluorescein.

When 3-nitrophthalic acid monomethyl ester (1) and dimethyl 3-nitrophthalate are heated with acetic anhydride, each ester remains unchanged. Under similar conditions 3-nitrophthalic acid monomethyl ester (2) yields 3-nitrophthalic anhydride. The isomeric 3-nitrophthalamic acids and 3-nitrophthalamide are converted into 3-nitrophthalimide by treatment with acetic anhydride.

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A NEW MODIFICATION OF THE REFORMATSKY REACTION

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Reformatsky published a new method for making β -hydroxy acids from ketones or aldehydes by condensing them with α -iodo esters in the presence of zinc.¹ Later, he and his associates and others² published records of reactions in which bromo acid esters had been substituted for iodo esters. Reformatsky also made the statement that chloro esters react with ketones in a manner analogous to bromo and iodo esters but do not react with aldehydes.³

Although β -hydroxy acids have been made from chloro esters by the use of sodamide,⁴ with an aldehyde or ketone, there is no record in the literature to show that it has been done with zinc as a condensing agent.

We have found that chloro esters do not condense with ketones or aldehydes in the presence of zinc alone, but that the reaction can be effected

¹ Reformatsky, *J. Russ. Phys.-Chem. Soc.*, **22**, 44 (1890).

² Reformatsky, *J. prakt. Chem.*, **54**, 469 (1896); Reformatsky and Pleskonosoff, *Ber.*, **28**, 2838 (1895); Lindenbaum, *ibid.*, **50**, 1272 (1917).

³ Reformatsky, *ibid.*, **28**, 2842-2847 (1895); *J. Chem. Soc.*, **70**, 126 (1896).

⁴ Feyerabend, *Ber.*, **38**, 697 (1905).