between experiments in which the quantities of reactants in one series were usually 120 times as great as in the other.

Summary

1. A study has been made of the following conditions affecting the yield of Grignard reagent formed from *n*-butyl bromide: rate of addition of butyl bromide, reverse process of addition, excess of butyl bromide and excess of magnesium.

2. The yields obtained on the large scale are in close agreement with those obtained by Gilman and co-workers in quantitative work on the small scale.

BALTIMORE, MARYLAND

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

PHENOL-HALO-PHTHALEINS. PRELIMINARY PAPER[1]

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Extensive practical use has been made of the fact that the halogens, chlorine, bromine and iodine, when introduced into certain synthetic organic compounds, greatly increase the hypnotic activity in some cases and in other instances augment the antiseptic power of the parent substance; chlorine and bromine are used especially for the former purpose, iodine for the latter.

It would be of considerable interest to know just what change could be effected by the introduction of fluorine instead of the other halogens. At present very little information is to be found in the literature regarding the physiological activity of any type of organic fluorine compounds;[2] to a large extent our lack of knowledge of these substances may be attributed to the fact that comparatively few organic fluorides have been prepared.

Phenolphthalein and various tetra-halogen substitution products have found extensive use in medicine, the former as a laxative, the latter as diagnostic agents. Fluoro derivatives of phenolphthalein have never been described. Since the effect of fluorine can be determined only by comparison of the fluoro compound with the corresponding chloro, bromo and iodo derivatives, we decided to attempt the preparation of the complete series of substances—phenol-fluoro-, -chloro-, -bromo- and -iodo-phthalein.

We prepared, first, five mono-halogenated phthalic acids, the 4-fluoro-,

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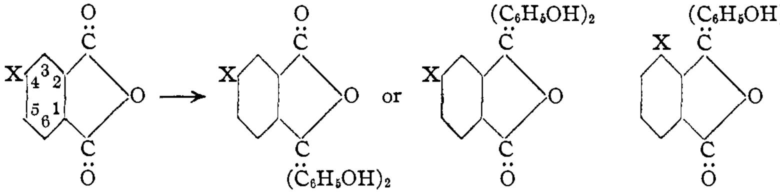
[1] This investigation was made possible by a grant from the American Pharmaceutical Association Research Fund and by the establishment of the Michigan State Pharmaceutical Association Research Fund. We wish to express our appreciation for the aid which has been given us.

[2] Frankel, "Die Arzneimittel-Synthese," J. Springer, Berlin, **1927**, p. 616.

4-chloro-, 4-bromo-, 4-iodo- and the 3-iodophthalic acid. After a considerable number of attempts had been made to obtain these acids from the corresponding aminophthalic acids and from the aminophthalimides by the aid of the Sandmeyer reaction, it was found, finally, that the halogenated phthalic acids could be prepared most satisfactorily from the aminodiethylphthalates. Each acid was then converted into its anhydride and the latter condensed with phenol to form the phenol-halophthalein.

Obviously the condensation of a 4-halophthalic anhydride with phenol may yield two isomeric phenol-halo-phthaleins, I or II, or a mixture of these compounds.



I II III

In the case of the 3-halo derivatives, likewise, two types of isomeric phthaleins are possible. Hitherto, as far as we have been able to discover, no mono-substitution products of phthalic anhydride have been condensed with phenol to form mono-substituted phthaleins. However, Stephens[3] has shown that 4-bromophthalic anhydride condenses with benzene to form a mixture of two isomeric bromobenzoylbenzoic acids; 3-bromophthalic anhydride and benzene yielded only one bromobenzoylbenzoic acid. From the condensation of benzene with 4-nitrophthalic anhydride and also with 3-nitrophthalic anhydride, Lawrance,[4] in each instance, isolated two isomeric nitrobenzoylbenzoic acids. According to Orndorff and Kline[5] benzoylbenzoic acids are intermediate products in the formation of phthaleins.

We found that all of the 4-halo-phthalic anhydrides, when condensed with phenol, formed products which, based on halogen analysis, were pure phenol-halo-phthaleins. The products, however, showed great tendency to separate from solution in the form of oils which were very difficult to convert into a crystalline state. The crystalline material, when it was finally obtained, did not melt sharply but melted over a considerable range. 3-Iodophthalic anhydride, when condensed with phenol, was converted into a product which crystallized readily and melted sharply. These results indicate that 4-substituted phthalic anhydrides condense

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[3] Stephens, THIS JOURNAL, **43**, 1950 (1921).

[4] Lawrance, *ibid.*, **42**, 1871 (1920).

[5] Orndorff and Kline, *ibid.*, **46**, 2276 (1924).

with phenol to form a mixture of isomeric phthaleins, but in the case of the 3-substituted phthalic anhydride only one phthalein is formed.[6]

In order to secure proof that the phthaleins obtained from the 4-halo-phthalic anhydrides were mixtures, and to determine the structure of the phthalein obtained from 3-iodophthalic anhydride, the various phenol-halo-phthaleins were fused with alkali. Baeyer[7] showed that phenolphthalein, when fused with alkali, yields *p,p'*-dihydroxybenzophenone and benzoic acid. A compound of Structure I should yield, accordingly, a *m*-halo-benzoic acid, or a *m*-hydroxybenzoic acid if the halogen were removed during the fusion, and *p,p'*-dihydroxybenzophenone, while from Compound II there should be formed, in addition to the ketone, a *p*-halo- or *p*-hydroxybenzoic acid. We found that the phthaleins obtained from the condensation of a 4-halo-phthalic acid and phenol yielded upon fusion with alkali small amounts of *p,p'*-dihydroxybenzophenone and a mixture of *m*- and *p*-hydroxybenzoic acids; the acids were separated in the form of their *p*-nitrobenzyl ester-ethers.[8] From the alkali fusion of the phthalein prepared from 3-iodophthalic anhydride and phenol there was obtained only *m*-hydroxybenzoic acid. It appears, therefore, that condensations of 4-halo-phthalic anhydrides with phenol yield mixtures of phthaleins of the type I and II, while a 3-halo-phthalic anhydride condenses with phenol to form only one phthalein, a substance of Type III.

Several questions arose in connection with the alkali fusions. Is the decomposition into dihydroxybenzophenone and substituted benzoic acid quantitative and are these fusion products stable under the conditions to which they are subjected during the fusion? The first question should be answered, we believe, in the affirmative. From the fusion of phenolphthalein with potassium hydroxide results were obtained which indicate that the initial fusion is probably quantitative. *p,p'*-Dihydroxybenzophenone, however, as Baeyer has shown,[9] is converted into phenol and carbon dioxide by vigorous fusion with alkali. Since a more prolonged alkali treatment was required to decompose the phenol-halo-phthaleins than was necessary for phenolphthalein, it is not surprising that phenol and only small yields of dihydroxybenzophenone were obtained from the fusion of phenol-halo-phthaleins. It was shown by experiment that under the conditions used in our fusions dihydroxybenzophenone was decomposed to a considerable extent but no *p*-hydroxybenzoic acid resulted

[6] We had hoped to obtain further evidence to support this view by a study of the interaction of 3-fluoro-, 3-chloro- and 3-bromophthalic anhydride with phenol. However, due to certain circumstances, these condensations could not be studied at this time. It is our intention to investigate these reactions and to prepare, also, a series of halo-phenolphthaleins.

[7] Baeyer, *Ann.*, **202**, 127 (1880).

[8] Blicke and Smith, THIS JOURNAL, **51**, 1558 (1929).

[9] Baeyer, *Ann.*, **202**, 129 (1880).

as a decomposition product; *p*-hydroxybenzoic acid, under the same conditions, remained unchanged. *p*-Bromobenzoic acid was converted practically quantitatively into *p*-hydroxybenzoic acid.

Experimental Part

4-Aminodiethylphthalate.—Phthalic anhydride was nitrated,[10] with the formation of 3- and 4-nitrophthalic acids. After nitration had been effected the reaction mixture was poured into 300 cc. of water. Twenty-four hours later the nitro acids, which had precipitated completely, were filtered through a Jena filter and washed with a small amount of concd. hydrochloric acid in order to remove nitric and sulfuric acids. It was found that the nitrophthalic acids which are very soluble in water are only moderately soluble in concd. hydrochloric acid. The nitro acids were dried thoroughly and then suspended in an amount of absolute alcohol equal to one and one-half times the weight of the nitro acids. After the mixture had been partially saturated with hydrogen chloride, it was refluxed for twenty-four hours. The greater part of the alcohol was removed under diminished pressure and the residue was poured into three times its volume of water. The oily ester layer, which consisted of a mixture of the diethyl ester of 4-nitrophthalic acid and the mono-ethyl ester of 3-nitrophthalic acid, was washed thoroughly with small amounts of water and then treated with 10% sodium carbonate solution. The former compound remained undissolved while the latter passed into solution in the form of the sodium salt.[11] After separation of the insoluble diethyl ester of 4-nitrophthalic acid, it was dried over fused sodium sulfate and fractionated under diminished pressure. The portion which boiled at 210–213° under 21-mm. pressure, a light yellow, viscous oil, was dissolved in an equal volume of absolute alcohol and cooled with ice. After some time the ester separated in crystalline form. The material was filtered quickly through a Büchner funnel which had been cooled previously to 0°. Unless the mixture of ester and alcohol is kept cold, the ester redissolves in the solvent. The crystalline ester was suspended in a small amount of absolute alcohol, cooled to 0° for a short time and filtered again. The compound was then obtained in the form of colorless crystals; m. p. 33–34°.[12]

In order to prepare 4-aminodiethylphthalate, 26.7 g. of the 4-nitrophthalic ester was dissolved in 100 cc. of absolute alcohol and reduced with hydrogen in the presence of 0.1 g. of platinum oxide catalyst,[13] under an initial pressure of 4 atmospheres. The reduction was complete in twenty minutes; some heat was evolved during the reaction. The catalyst was used for several reductions without reactivation with air and showed only a slight decrease in activity. The colorless or slightly yellow alcoholic solution was filtered and the filtrate concentrated on a steam-bath. After the oily residue had been cooled the amino ester was obtained in the form of colorless crystals which melted at 97–98° after recrystallization from alcohol. The melting point of this substance recorded in the literature[14] is 95°. The yield was 21.5 g. or 92% of the calculated amount.

4-Fluorodiethylphthalate.—Eleven and eight-tenths g. of 4-aminodiethylphthalate was dissolved in a mixture of 20 cc. of concd. hydrochloric acid and 10 cc. of water, the solution was cooled to 0° and then diazotized with 3.5 g. of sodium nitrite dissolved in 15 cc. of water. To the cold, diazotized solution there was added a solution of hydro-

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[10] Littmann, This Journal, **47,** 1980 (1925).

[11] Miller, *Ann.*, **208,** 227 (1881).

[12] Miller, *ibid.*, **208,** 227, 234 (1881).

[13] "Organic Syntheses," John Wiley and Sons, Inc., New York, **1928,** Vol. VIII, p. 92.

[14] Miller, *Ann.*, **208,** 237 (1881).

borofluoric acid. The latter had been prepared previously by the addition of 9.2 g. of pure boric acid to 21.8 cc. of pure 48% hydrofluoric acid in a bakelite beaker. The mixture was stirred rapidly, whereupon the diazonium borofluoride of diethylphthalate precipitated in crystalline form.[15] The latter was filtered and washed with absolute alcohol and then absolute ether. The diazonium compound was dried in a vacuum desiccator over sulfuric acid for twenty-four hours. The yield was 16.5 g. or 98% of the calculated amount. The compound decomposes at 125° with the evolution of nitrogen and boron fluoride.

Ten g. of the dry diazonium compound was placed in a 500-cc. round-bottomed flask connected to a wash bottle which contained a 10% solution of sodium hydroxide. The flask was heated slowly to 125° in an oil-bath and when the evolution of gases had abated the temperature of the bath was raised to 140° and maintained there for one hour. The oily residue was dissolved in carbon tetrachloride, the solution washed with 10% aqueous sodium hydroxide, separated and dried over fused sodium sulfate. The solvent was removed and the residue distilled. There were obtained 3.5 g. of a product which boiled at 165–170° under 25 mm. pressure and 2.5 g. of material which boiled at 200–250°. The lower-boiling portion was 4-fluorodiethylphthalate; the yield corresponded to 50% of the calculated amount.

4-Fluorophthalic Acid.—Twenty-one g. of the fluoro ester was added to 20 g. of sodium hydroxide dissolved in 50 cc. of 50% alcohol. The mixture was then refluxed for three hours, the alcohol removed and the solution acidified with sulfuric acid; the fluorophthalic acid was extracted with ether, the solvent removed and the oily residue allowed to crystallize. After recrystallization from acetic acid the acid melts at 147–148° in a sealed tube. It is very soluble in water, acetic acid and ether.

4-Chlorodiethylphthalate.—Eleven and eight-tenths g. of 4-aminodiethylphthalate was dissolved in a mixture of 20 cc. of concd. hydrochloric acid and 10 cc. of water and diazotized with 3.5 g. of sodium nitrite dissolved in 15 cc. of water. Cuprous chloride had been prepared previously from 21 g. of copper sulfate, 5.4 g. of sodium chloride, 4.4 g. of sodium bisulfite and 3 g. of sodium hydroxide.[16] The cuprous chloride was suspended in a mixture of 100 cc. of water and 25 cc. of concd. hydrochloric acid. The diazotized solution was introduced slowly and with rapid stirring below the surface of the suspension of cuprous chloride. The mixture was then heated on a steam-bath for some time. The oily layer was extracted with carbon tetrachloride, the solution washed with dilute hydrochloric acid and then dried over fused sodium sulfate. The solvent was removed and the residue distilled. The greater portion of the material boiled at 185–190° under 25 mm. pressure.[17] The yield was 9 g. or 70% of the calculated amount.

4-Chlorophthalic Acid.—Thirty-five g. of 4-chlorodiethylphthalate was hydrolyzed with 30 g. of sodium hydroxide which had been dissolved in 60 cc. of 50% alcohol. The chloro acid, after recrystallization from acetic acid, melted at 150° in a sealed tube.[18] The acid is soluble in water, ether and acetic acid.

4-Bromodiethylphthalate.[19]—Eleven and eight-tenths g. of the 4-amino ester was

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[15] The preparation of nuclear fluorine compounds by means of diazonium borofluorides has been patented by Bart (German Patent 281,055) and has been used by Wilke-Dörfurt and Balz, *Ber.*, **60**, 115 (1927); Balz and Schiemann, *ibid.*, **60**, 1186 (1927), and by Schiemann and Bolstad, *ibid.*, **61**, 1403 (1928).

[16] "Organic Syntheses," John Wiley and Sons, Inc., New York, **1923**, Vol. III, p. 33.

[17] Rée, *Ann.*, **233**, 238 (1886), states that the substance, prepared by esterification of 4-chlorophthalic acid with ethyl alcohol, boils at 300–305° under ordinary pressure.

[18] Egerer and Meyer, *Monatsh.*, **34**, 81 (1913), record the melting point as 150°.

[19] 4-Bromodiethylphthalate has been prepared by Faust, *Ann.*, **160**, 64 (1871), by esterification of the acid.

dissolved in a mixture of 20 cc. of 48% hydrobromic acid and 10 cc. of water and was then diazotized with 3.5 g. of sodium nitrite dissolved in 15 cc. of water. Cuprous bromide was suspended in 100 cc. of water and 15 cc. of 48% hydrobromic acid and the diazotized solution introduced slowly below the surface of the suspension with rapid stirring. The cuprous bromide had been prepared from 10.5 g. of copper sulfate, 5.5 g. of sodium bromide, 2.2 g. of sodium bisulfite and 1.5 g. of sodium hydroxide.[20] The mixture was heated on a steam-bath and the oily layer was extracted with carbon tetrachloride. The carbon tetrachloride solution was washed with dilute hydrochloric acid, dried over fused sodium sulfate and the solvent removed. From the residue there was obtained 11 g. of material which boiled at 225° under 60-mm. pressure. The yield is 70% of the calculated amount.

4-Bromophthalic Acid.—Forty-two g. of the above ester was hydrolyzed with 30 g. of sodium hydroxide and 100 cc. of 50% alcohol. The bromo acid was recrystallized from acetic acid; m. p. 170° in a sealed tube. Stephens[21] found 170.5° as the melting point.[22]

4-Iododiethylphthalate.—Eleven and eight-tenths g. of 4-aminodiethylphthalate was dissolved in a mixture of 20 cc. of concd. hydrochloric acid and 10 cc. of water and diazotized with 3.5 g. of sodium nitrite dissolved in 15 cc. of water. The diazotized solution was treated with 12 g. of potassium iodide in 100 cc. of water. The iodo ester was obtained in the form of a red oil.[23]

4-Iodophthalic Acid.—Thirty-two g. of iodo ester was hydrolyzed with 25 g. of sodium hydroxide in 75 cc. of 50% alcohol. The crude acid was dissolved in water and boiled with charcoal. After filtration the filtrate was concentrated to a small volume. The iodo acid was recrystallized from acetic acid; m. p. 185–186° in a sealed tube. Edinger[23] found 182°. The yield based on the iododiethylphthalate was 59% of the calculated amount. The acid is soluble in water, ether and acetic acid.

3-Aminodiethylphthalate.—The solution of the sodium salt of the mono-ethyl ester of 3-nitrophthalic acid was acidified with hydrochloric acid. Most of the acid ester was precipitated in the form of an oil, which was separated from the aqueous layer and then washed several times with small amounts of water. The acid ester was converted into the ammonium salt and precipitated as the silver salt with silver nitrate.[24] The silver salt was thoroughly dried, suspended in benzene and then refluxed with an excess of ethyl bromide for eight hours.[25] The silver bromide was filtered and the benzene removed on a steam-bath. The oily residue was dissolved in absolute alcohol and the ester reduced with hydrogen and platinum oxide catalyst. The amount of ester obtained from 0.1 mole of silver salt was reduced with hydrogen under an initial pressure of 4 atmospheres in the presence of 0.1 g. of catalyst. After ten minutes no more

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[20] This preparation of cuprous bromide is entirely analogous to the preparation of cuprous chloride given in "Organic Syntheses," except that sodium bromide was used instead of sodium chloride.

[21] Stephens, THIS JOURNAL, **43**, 1952 (1921).

[22] At the time this investigation was finished, Baker published a note, *J. Chem. Soc.*, 2829 (1928), stating that he had prepared *p*-bromophthalic acid from 4-nitrodiethylphthalate. The latter substance was reduced by means of zinc and hydrochloric acid, the amino compound was converted into the bromo derivative by the aid of the Sandmeyer reaction and the bromo ester finally hydrolyzed by barium hydroxide. The melting point of 4-bromophthalic acid was recorded as 173–175°.

[23] Edinger, *J. prakt. Chem.*, [2] **53**, 386 (1896).

[24] Miller, *Ann.*, **208**, 244 (1881).

[25] The diethyl ester of 3-nitrophthalic acid has been prepared by Miller[24] from the di-silver salt of 3-nitrophthalic acid and ethyl iodide.

hydrogen seemed to be absorbed. The alcohol was then removed and the 3-aminodiethylphthalate obtained in the form of an oil.[26] The amount of hydrogen absorbed indicated the presence of 0.07 mole of 3-aminodiethylphthalate.

3-Iododiethylphthalate.—The oily residue obtained from the previous experiment was treated with 20 cc. of concd. hydrochloric acid and 10 cc. of water and then diazotized. The diazotized solution was introduced slowly, with rapid stirring, below the surface of a solution prepared from 12 g. of potassium iodide and 100 cc. of water. The oily layer which formed was decolorized by the addition of sodium bisulfite and then cooled. The crystalline material which formed melted at 70°.[23] The yield, based on the silver salt of the mono-ethyl ester of 3-nitrophthalic acid, was 40% of the calculated amount.

3-Iodophthalic Acid.—3-Iododiethylphthalate was hydrolyzed with alcoholic sodium hydroxide.[23] The alkaline solution was acidified with sulfuric acid, the organic acid extracted with ether, the ether layer separated and the solvent removed. The residue was dissolved in water and the solution boiled with charcoal. After filtration and concentration of the filtrate, the 3-iodophthalic acid separated in crystalline form; m. p. 206°. The compound is soluble in water, ether and acetic acid.

The acid was prepared by a second method. 3-Nitrophthalic acid was reduced with stannous chloride and hydrochloric acid.[27] The hydrochloride of the amino acid which formed was filtered, suspended in dilute hydrochloric acid, diazotized and then treated with potassium iodide.

TABLE I

HALO-PHTHALIC ANHYDRIDES

			Analyses (Volhard)		
Anhydride	B. p., °C.	M. p., °C.	Calcd. for $C_8H_3O_3X$	Found	
4-Fluoro[a]	260 (746 mm.)	76–78	F[b] 11.47	11.08	11.12
4-Chloro[a]	284[c] (750 mm.)	98	Cl 19.45	19.30	19.30
4-Bromo[a]	290–293 (750 mm.)	108–109[d]	Br 35.20	35.10	35.18
4-Iodo[e]	......	125–126	I 46.32	46.32	
3-Iodo[e]	......	159–161	I 46.32	46.28	46.31

[a] Prepared by heating the acid until all of the water formed through the conversion of the acid into the anhydride had been removed. The residue was then distilled. The distillate solidified immediately; it was recrystallized from acetic anhydride.

[b] Starck, *Z. anorg. Chem.*, **70**, 173 (1911).

[c] Egerer and Meyer, *Monatsh.*, **34**, 81 (1913), state that the anhydride boils at 297° and melts at 98°.

[d] Stephens, ref. 3, states that the compound melts at 104–106°.

[e] Prepared by heating the acid for ten minutes with an equal weight of acetic anhydride. The iodo-anhydride separated when the solution was cooled. The material was recrystallized from acetic anhydride and washed with absolute ether.

Phenol-halo-phthaleins

Preparation.—Five-hundredths mole of the halo-phthalic anhydride, 0.10 mole of freshly distilled phenol and 0.10 mole of fused zinc chloride were heated by means of an oil-bath at 115–130° for twenty-four hours. An additional quantity of phenol, 0.10 mole, was added and the mixture heated for twenty-four hours longer.

The reaction mixture was treated with 20 cc. of concentrated hydrochloric acid and 10 cc. of water and steam distilled for one hour. The hot supernatant liquid was de-

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[26] Miller, *Ann.*, **208**, 246 (1881).

[27] Bogert and Jouard, THIS JOURNAL, **31**, 484 (1909).

canted from the oily residue and the latter again steam distilled for one hour. The combined supernatant liquors were cooled and extracted with ether. The ether layer was washed with dilute hydrochloric acid, the solvent removed and the residue dissolved in water, filtered and the filtrate evaporated to dryness. The residue was unchanged halo-phthalic acid. The oily water-insoluble residue from the steam distillation solidified to a resinous mass when cooled. The latter was pulverized, extracted with 10% sodium hydroxide, filtered and the filtrate acidified with dilute hydrochloric acid, whereupon the phenol-halo-phthalein was precipitated. There was obtained a small amount of alkali-insoluble material, which was probably a halo-fluoran.

The crude phthalein was filtered, washed with water and dissolved in 100 cc. of methyl alcohol; then 40 cc. of water and 2 g. of charcoal were added and the mixture refluxed for three hours. The hot solution was filtered and the solvent allowed to evaporate slowly. A gum was obtained, which was dissolved in 10% sodium hydroxide, filtered, the filtrate diluted to 500 cc. and the phthalein precipitated with dilute hydrochloric acid. The precipitate was filtered, washed well and air dried. The substance obtained was electrostatic and was very soluble in practically all organic solvents; it had no definite melting point. The resinous material was dissolved in acetic acid. After several days the crystalline material which had deposited was recrystallized from acetic acid. The amount of alkali-insoluble material from the several halo-phthalic anhydrides varied from 0.05–1.3 g. The amorphous phthaleins were very soluble in all organic solvents but after conversion into the crystalline state they were found to be very insoluble except in hot acetic acid. In the case of 3-iodophthalic anhydride the reaction product became granular during the steam distillation. The granular material was recrystallized from dilute methyl alcohol and then from acetic acid.

TABLE II

3- AND 4-HALO-PHTHALIC ANHYDRIDES AND PHENOL

Anhydride	Yield of alkali-soluble material[a] (halo-phenol phthalein), %	M. p. of crystalline material, °C.	Analyses (Volhard), % Calcd. for $C_{20}H_{13}O_4X$		Found	
4-Fluoro	54	230–240	F[b]	5.65	5.34	5.42
4-Chloro	76	214–233	Cl	10.05	9.86	9.93
4-Bromo	73	226–236	Br	20.15	20.20	20.00
4-Iodo	63	240–255	I	28.58	28.68	28.30
3-Iodo	45	252–254	I	28.58	28.70	28.80

[a] Based on the halo-phthalic anhydride.

[b] Starck, *Z. anorg. Chem.*, **70**, 173 (1911).

Alkali Fusions

Two g. of phenolphthalein was fused with 10 g. of potassium hydroxide[28] and 1-2 cc. of water in a nickel crucible until the color of the reaction mixture had changed to a light yellow. It was not necessary to fuse the material longer than three to four minutes to effect this change. The fusion mixture was dissolved in 75 cc. of water and acidified with dilute sulfuric acid, whereupon *p,p'*-dihydroxybenzophenone and benzoic acid precipitated. After the mixture had cooled the crystalline material was filtered and the latter treated with dilute ammonium hydroxide until the solution was alkaline to phenolphthalein. The ammoniacal solution was extracted twice with 25-cc. portions of ether. Upon evaporation of the solvent there was obtained almost pure *p,p'*-dihydroxybenzophenone; after recrystallization from water the material melted at 212–213°.[29]

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[28] Baeyer, *Ann.*, **202**, 127 (1880).

[29] Montagne, *Rec. trav. chim.*, **39**, 348 (1920).

The yield was 1.15 g. which is 80% of the calculated amount. The aqueous alkaline layer from the ether extraction was acidified and the precipitated benzoic acid filtered. The latter weighed 0.59 g. or 73% of the calculated amount; m. p. 121°. More benzoic acid remained dissolved in the filtrate but through an oversight this was not isolated.

One g. of *p,p'*-dihydroxybenzophenone was fused with 10 g. of potassium hydroxide for ten minutes at 200–250°. Sixty per cent. of the material was recovered unchanged, the remainder having been converted into phenol and carbon dioxide.[30] No *p*-hydroxybenzoic acid was obtained.

One g. of *p*-bromobenzoic acid was fused with 10 g. of potassium hydroxide for ten minutes at 200–250°. The fusion mixture was dissolved in water, acidified and extracted with ether. From the ether layer there was obtained *p*-hydroxybenzoic acid; m. p. 208–210°.[31]

One g. of *p*-hydroxybenzoic acid was fused with 10 g. of potassium hydroxide for ten minutes at 200–250°. Ninety-five per cent. of the acid was recovered; m. p. 210–211°.

Phthalein from 4-Fluorophthalic Anhydride.—Two g. of the phthalein was fused with 8 g. of potassium hydroxide and 1–2 cc. of water at 200–250°. The fusion mixture was dissolved in 50 cc. of water, acidified with dilute sulfuric acid, cooled and the *p,p'*-dihydroxybenzophenone which had precipitated was filtered off. It weighed 0.5 g. or 39% of the calculated amount; m. p. 208–210°. The aqueous, acidic filtrate was extracted with ether. After removal of the solvent the residue was dissolved in water, boiled with charcoal, filtered and the filtrate evaporated to dryness. There was obtained 0.8 g. of a mixture of *m*- and *p*-hydroxybenzoic acids; the yield corresponds to 97% of the calculated amount.

The general procedure used to separate the mixture of hydroxybenzoic acids obtained from the alkali fusions was as follows. The mixture of acids and one molecular equivalent of potassium carbonate were dissolved in 5 cc. of water. This solution was added to 2.1 molecular equivalents of *p*-nitrobenzyl bromide dissolved in 15 cc. of pure acetone. The mixture was refluxed for two hours, cooled and the crystalline material filtered. The latter was treated with cold, dilute sodium hydroxide and the undissolved portion recrystallized from acetone. The dinitrobenzyl derivative of the para acid[8] is practically insoluble in hot acetone while the meta derivative is much more soluble in this solvent; a practically complete separation of the two derivatives can be effected by two recrystallizations from acetone. The yield of the di-nitrobenzyl derivative of the *p*-hydroxy acid was about twice that of the meta compound. The melting point of the former substance was 196–198°, mixed melting point, unchanged. The melting point of the meta derivative was 140–143°, mixed melting point, 138–141°.

Phthalein from 4-Chlorophthalic Anhydride.—From the fusion of 2.0 g. of the phthalein there were obtained 0.7 g. of a mixture of *m*- and *p*-hydroxybenzoic acids and 0.6 g. of *p,p'*-dihydroxybenzophenone; the mixture of acids melted from 160–190°. The yield of the ketone was 50% and that of the acids 91% of the calculated amount. The mixture of acids was treated as outlined previously and the same relative amounts of each derivative were obtained as in the case of the phthalein from 4-fluorophthalic anhydride. The melting point of the di-nitrobenzyl derivative of the para acid was 195–197°; that of the meta isomer, 138–141°.

Phthalein from 4-Bromophthalic Anhydride.—From the alkali fusion there were obtained a 63% yield of *p,p'*-dihydroxybenzophenone and a 92% yield of a mixture of *m*- and *p*-hydroxybenzoic acids; the mixture of acids melted from 165–195°. The acids were separated and identified after they had been converted into their *p*-nitrobenzyl derivatives.

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[30] Baeyer, *Ann.*, **202,** 127 (1880).

[31] Fischer, *ibid.*, **127,** 145 (1863).

Phthalein from 4-Iodophthalic Anhydride.—In this instance there were obtained from the alkali fusion only a small amount of *p,p'*-dihydroxybenzophenone and an 86% yield of a mixture of *m*- and *p*-hydroxybenzoic acids; the mixture melted from 165–190°.

Phthalein from 3-Iodophthalic Anhydride.—From the alkali fusion there was isolated a small amount of *p,p'*-dihydroxybenzophenone; however, *m*-hydroxybenzoic acid, which melted from 190–195° was obtained in a 89% yield. The hydroxy acid was further identified by conversion into the *p*-nitrobenzyl ester ether; the latter melted from 135–140° and a mixed melting point with the pure ether ester was unchanged.

The following crystallographic data have been determined by Dr. C. B. Slawson. These measurements were made upon crystals formed by the slow evaporation at room temperature of acetic anhydride solutions.

4-Fluorophthalic Anhydride.—Crystals of this compound consist almost invariably of pseudo-hexagonal twins. The twins consist of interpenetrating triclinic needles, at an angle of 8°, resembling at the terminations twinned augite crystals, though the front pinacoid is not present. The prism angle is 51°55'. The reëntrant terminal angle is about 60° and the terminal faces are very poorly developed. The reëntrant angle in the prism zone is about 8°; $\alpha = 1.400$; $\beta\gamma = 1.74$; 2V = 3–5°; optically negative with very pronounced $r > v$ dispersion. Extinction (following the augite analogy) is nearly parallel on 100 and −38° on 010. *Bxa* is very commonly observed on crushed fragments.

4-Chlorophthalic Anhydride.—This compound forms elongated triclinic needles with three pairs of faces parallel to the elongation. The measured values between these faces are 23°4', 47°46' and 109°8'. The terminations of the needles are poorly developed. $\alpha = 1.500$; $\beta = 1.700$; $\gamma = 1.775$; 2V = 55–60°; optically negative; crystals lying so that the extinction is nearly parallel to the elongation give a value close to α-perpendicular to the elongation. The extinction angles on the three faces are 3, 9 and 14°.

4-Bromophthalic Anhydride.—These crystals resemble very closely in appearance the 4-iodo crystals described below except that the prisms are 210, the clino domes are 041 and the negative orthodome is absent. The axial ratio is 1.095:1:1.091; $\beta = 59°35'$. The measured interfacial values are $210–2\bar{1}0 = 50°32'$, $\bar{1}00–\bar{1}01 = 60°9'$ and $014–0\bar{1}4 = 26°32'$. It was impossible to measure γ but $\alpha = 1.545$ and $\beta = 1.700$; 2V = 90° ±; optical character indeterminate; $X \wedge c + 15–16°$, and $Z = b$.

4-Iodophthalic Anhydride.—The crystals of this substance are monoclinic with an axial ratio of 1.123:1:1.139, $\beta = 73°29'$. They are elongated parallel to the *c* axis with a pronounced development of the clino-pinacoid. Other faces present are 110, 101, $\bar{1}01$ and 012. The measured interfacial angles are $110–1\bar{1}0 = 94°12'$, $101–\bar{1}01 = 89°37'$, $012–0\bar{1}2 = 57°20'$. Because of its high index of refraction it was impossible to determine γ, but $\alpha = 1.555$ and $\beta = 1.77$, 2V = 60–70°; optically negative; *X* very nearly *c;* and $Z = b$.

The iodo and bromo compounds are probably isomorphous. The chloro and fluoro compounds, being triclinic, may be considered either dimorphous with forms which fall in the iodo–bromo series or distinctly different. In the case of the chloro compound we have many similarities to the bromo especially in the optical properties, so the first supposition is probably correct. With the fluoro compound there is no evidence which shows such a similarity; in fact, what evidence there is seems to support the second supposition, although that cannot be definitely established from the crystallographic data.

Summary

4-Fluoro-, 4-chloro-, 4-bromo-, 4-iodo- and 3-iodophthalic anhydrides have been condensed with phenol to form phenol-halo-phthaleins. From the 4-halophthalic anhydrides, mixtures of isomeric phthaleins were obtained but in the case of 3-iodophthalic anhydride only one phthalein was found.

Data obtained by Dr. Slawson have shown that 4-fluorophthalic anhydride does not fit into the same crystallographic scheme with the three other 4-halophthalic anhydrides.

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[CONTRIBUTION FROM THE LABORATORY OF THE ETHYL GASOLINE CORPORATION]

THE MECHANISM OF THE VAPOR PHASE OXIDATION OF ISOMERIC OCTANES. I. NORMAL OCTANE[1]

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I. Introduction

The oxidation of hydrocarbons represents a subject which has attracted the attention of many investigators, yet it cannot be said that the fundamental mechanism of such reactions has been made perfectly clear. Perhaps this has been partially due, on the one hand, to a natural tendency to generalize from results obtained on the simpler hydrocarbons and, on the other, to failure to differentiate between liquid phase reactions and vapor phase reactions.

The results of the present investigation on octanes may perhaps contribute to the interpretation of the behavior on oxidation of hydrocarbons intermediate in complexity.

No attempt will be made to give an elaborate survey of the literature on the general subject of oxidation, but a few references to vapor phase oxidation of normal paraffins may be cited. Bone[2] and his associates demon-

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[1] Presented in part at the Fall Meeting of the American Chemical Society at Swampscott, Massachusetts, September, 1928.

[2] Bone and co-workers, *J. Chem. Soc.*, **81**, 535 (1902); **83**, 1074 (1903); **85**, 693 (1904); **89**, 660, 1614 (1906).