[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY OF CORNELL UNIVERSITY]

ISOPHENOLPHTHALEIN AND SOME OF ITS DERIVATIVES[1]

BY W. R. ORNDORFF AND W. R. BARRETT

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Phenolphthalein was first prepared by Baeyer[2] in 1871, but it was not until 1880[3] that he proved it to be di-*p*-dihydroxy-diphenylphthalide. Baeyer also isolated fluoran,[4] a by-product in the preparation of phenolphthalein and explained its formation as due to the phthalic acid residue entering the two phenol molecules in the *ortho* positions to the two hydroxyl groups instead of in the *para* positions. Under the influence of the condensing agent these two *ortho* hydroxyl groups split off water to form fluoran. It will be seen from the above that it should be possible to prepare a phenolphthalein in which one of the hydroxyl groups is *ortho* and the other *para* to the methane carbon atom. This product has now been made, as will be shown later in this article, and in order to distinguish it from the ordinary phenolphthalein it will be called *iso*-phenolphthalein (*o,p*-dihydroxy-diphenylphthalide). Pawlewski[5] has prepared a compound isomeric with phenolphthalein and which he called isophenolphthalein, by the action of phthalyl chloride on phenol. This substance is the diphenyl ester of phthalic acid[6] and, as it gave no color with alkalies and had none of the other properties of a phthalein, it is not a phthalein and should not be called isophenolphthalein. Recent investigations[7] in this Laboratory have shown that the formation of the phthalein takes place in two stages; first the phenol combines with the phthalic anhydride to form *p*-hydroxybenzoyl-*o*-benzoic acid, and this then unites with another molecule of phenol under the influence of the condensing agent to form phenolphthalein and water. It seemed quite likely, therefore, that *o*-hydroxybenzoyl-*o*-benzoic acid would combine with phenol to form isophenolphthalein. This supposition proved to be correct.

Experimental Part

The melting and decomposition points given in the following pages are uncorrected and were made in an electrically heated Dennis melting-point

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[1] From a dissertation presented by W. R. Barrett in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Baeyer, *Ber.*, **4**, 658 (1871); **9**, 1230 (1876).

[3] Baeyer, *Ann.*, **202**, 68 (1880).

[4] Baeyer, *Ann.*, **212**, 347 (1882).

[5] Pawlewski, *Ber.*, **28**, 108 (1895).

[6] Schreder, *Ber.*, **7**, 705 (1874). von Gerichten, *Ber.*, **13**, 419 (1880). Bischoff and Henderstrom, *Ber.*, **35**, 4091 (1902). R. Meyer, *Ber.*, **31**, 512 (1898).

[7] Orndorff and Murray, THIS JOURNAL, **39**, 680 (1917).

apparatus,[8] the heat being so regulated as to give a rise in temperature of 1° in seven seconds and much slower through the last[9] 10°. The thermometer used was calibrated by the Bureau of Standards. An electrically heated tube[10] was used to determine the loss in weight of the substance on heating at a constant temperature. A narrow strip of asbestos board was placed in the bottom of the tube to prevent the superheating of the bottom of the boat. In stating the approximate solubility in various solvents of the substances obtained, the classification of Mulliken[11] was used. The values used for the atomic weights are those given in the 1922 International Table of Atomic Weights.[12]

Isophenolphthalein.—Most of the isophenolphthalein used in the following work was obtained from a tar furnished by the Monsanto Chemical Company of Saint Louis, Missouri. This tar appeared in the form of a hard, black pitch with a low softening point and represented a by-product which they obtained in their former method of manufacture of phenolphthalein.

The tar was boiled with 10% sodium hydroxide solution and the dark red solution filtered to remove fluoran. The filtrate was cooled to 10°, acidified with hydrochloric acid, the precipitate filtered off, washed with water and dried. It was then extracted with boiling xylene until about half the material had been removed. The material that had dissolved in the xylene separated on cooling and was dissolved in boiling sodium hydroxide solution, acidified and filtered. This product when dried in the air was a brownish-yellow powder and contained a large quantity of isophenolphthalein, which was separated in two ways. In the first method the powder was dissolved in glacial acetic acid, the solution boiled with bone black, filtered and diluted with water until turbid. After standing some time the clear cold solution was decanted from the oil that separated, and more water added, a few drops at a time, over a period of several weeks when practically pure crystals of isophenolphthalein were obtained. The second method was the better, but a little longer. The brown powder was acetylated by boiling with five times its weight of acetic anhydride for two hours, an equal volume of glacial acetic acid added, and the mixture poured into water. After filtering off and drying the crude diacetate it was dissolved in 95% ethyl alcohol, the solution boiled with bone black, filtered, diluted with water until turbid and allowed to stand. The clear solution was decanted from the oil that separated, more water added, and the mixture then allowed to stand at room temperature for some time. Crystals of almost pure isophenolphthalein diacetate separated. After one crystallization from acetone this material was boiled with 10% sodium hydroxide solution until all of it dissolved. The solution was then cooled to 10° and acidified with hydrochloric acid. The isophenolphthalein was filtered off, washed, dried and crystallized from dil. ethyl alcohol. Colorless needles were obtained which, after drying in the air, lost one molecule of water when heated to constant weight at 120°.

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[8] Dennis, *J. Ind. Eng. Chem.*, **12**, 366 (1920).

[9] Wegscheider, *Chem.-Ztg.*, **29**, 1224 (1905).

[10] Orndorff and Nichols, *Am. Chem. J.*, **48**, 477 (1912).

[11] Mulliken, "Identification of Pure Organic Compounds," Wiley and Sons, **1904**, vol. I, p. 38.

[12] THIS JOURNAL, **44**, 427 (1922).

Anal. Subs., 0.3716, 0.1550: loss, 0.0201, 0.0088. Calc. for $C_{20}H_{14}O_4.H_2O$: H_2O, 5.36. Found: 5.41, 5.68.

The material dried to constant weight at 120° was analyzed with the following results.

Anal. Subs., 0.1462, 0.2486: CO_2, 0.4051, 0.6870; H_2O, 0.0598, 0.0993. Calc. for $C_{20}H_{14}O_4$: C, 75.45; H, 4.44. Found: C, 75.59, 75.39; H, 4.58, 4.47.

When crystallized from glacial acetic acid the crystals contain no water. Isophenolphthalein containing one molecule of water of crystallization melts at about 120°. On further heating it loses this water of crystallization and becomes solid. The anhydrous isophenolphthalein melts sharply at 200°.

Crystallization of Phenolphthalein and Isophenolphthalein

Baeyer[13] states that phenolphthalein is precipitated from alkaline solution by acids in the form of colorless, resinous drops, which cause the fluid to appear milky and which change, after a time, to a granular, colorless or yellow, crystal powder. From the mother liquor after long standing larger crystals separate, which may also be obtained by heating with water or dil. hydrochloric acid to 150–200°. These crystals were those examined by Professor Groth and measured by Lehmann. According to them the crystals are apparently monoclinic, but their optical properties prove them to be triclinic. It is quite apparent from the above description that Baeyer had a mixture of phenolphthalein and isophenolphthalein, and it is quite probable that the crystals measured by Lehmann were isophenolphthalein and not phenolphthalein. Unfortunately, Baeyer gives no melting point of these crystals.

Crystals of *pure phenolphthalein* from dil. methyl alcohol have been measured by Professor H. F. Vieweg of the Department of Mineralogy and Crystallography of this University and shown to be *orthorhombic* with pyramidal symmetry, as evidenced by hemimorphic shape and pyroelectric behavior. The axial ratio is $a:b:c = 0.7685:1:1.18$. The cleavage is brachy-pinacoidal, according to this setting, and cleavage pieces show the acute bisectrix of a negative crystal with rather large optical angle and strong double refraction.

Crystals of *pure isophenolphthalein* from dil. alcohol containing a molecule of water have been examined by Professor Gill, who reports as follows.

"Many of the crystals are cloudy and opaque in patches, or in some cases wholly so, as though a secondary change had taken place since the original crystallization. The clear portions show parallel extinction, biaxial interference figure and positive optical character. The principal faces make an angle of 73° 15′ to 73° 25′ with each other as determined by rather poor reflections on the goniometer. The double refraction is between 0.040 and 0.050, plane of the optical axes parallel to the elongation. The crystals are probably monoclinic with elongation parallel to the ortho axis. Lehmann reports an angle of 73° 26′ on what Baeyer gave him as phenolphthalein, but his determinations are not given in enough detail to decide whether, as seems very possible, he really had isophenolphthalein or not."

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[13] Ref. 3, p. 71.

When crystallized from strong acetic acid the crystals do not contain any water. Professor Gill gives the following description of them.

> "The crystals are not perfect enough to give good reflections on the goniometer, but sufficiently concordant data were obtainable to establish their triclinic character. They are pale brownish to straw colored, rather highly doubly refracting, biaxial, with an extinction angle of 33° to 37° with elongation in the acute angle of the principal face. In this zone the angles are approximately 51°, 60° and 69°, thus proving the triclinic crystallization."

Isophenolphthalein is very soluble in hot acetone; easily soluble in hot 95% ethyl alcohol, absolute ethyl alcohol, methyl alcohol and glacial acetic acid; slightly soluble in hot benzene, xylene, ether, ethyl acetate and carbon tetrachloride and difficultly soluble in petroleum ether. It is soluble only in traces in water at room temperature, and at 100° one part of anhydrous isophenolphthalein dissolves in approximately 3000 parts of water. The exact solubility of the crystallized isophenolphthalein containing a molecule of water in 95% ethyl alcohol, methyl alcohol, acetone, benzene and acetic acid at 21° was determined.

TABLE I

SOLUBILITY OF ISOPHENOLPHTHALEIN

Solvent	Pts. of solvent which dissolve 1 part of phthalein	G. of phthalein soluble in 100 cc. of solvent
95% ethyl alcohol	4.10	20.02
Methyl alcohol	3.91	20.26
Acetone	1.68	47.26
Benzene	113.9	0.77
Glacial acetic acid	92.8	1.13

Isophenolphthalein dissolves in *very* dilute alkalies in the cold giving a pale yellow solution. The addition of a stronger solution of the alkali changes the color to purple, much bluer than the corresponding color obtained with phenolphthalein. This color fades rapidly on standing, but returns when the solution is warmed. Concentrated alkalies cause the color to fade almost immediately, giving a perfectly colorless solution, but the color returns when the solution is warmed or when it is diluted with water.

The hydrogen-ion concentration at which isophenolphthalein changes from colorless to yellow and from yellow to purple in the presence of an alkali has been determined by Dr. J. E. McCorvie of the Mayo Clinic, Rochester, Minnesota, who reports as follows.

> "The indicator is colorless in acid solution, but develops a yellowish tint at P_H 8.4. The useful range is between P_H 8.4 and P_H 12.0 with a color change from yellow to purple. The apparent dissociation constant is P_{Ka} 10.2. The color is brilliant, although less so than that of phenolphthalein, and when freshly prepared it is a very useful indicator. Unfortunately the color fades rapidly and in standard buffer mixtures is not reliable for more than 24 hours. Because of this, no attempt was made to determine the magnitude of possible protein or salt effects."

The use of isophenolphthalein as compared with phenolphthalein as an indicator for titrating a strong base against both strong and weak acids was investigated and it was found that identical results were obtained in all cases when the two indicators were interchanged. The end-point using isophenolphthalein as indicator was taken as the first appearance of yellow, while with phenolphthalein it was, of course, the first appearance of a permanent pink. The color change of isophenolphthalein from yellow to purple was not investigated as it is too indefinite to warrant its application in alkalimetry-acidimetry titrations.

Dr. R. A. Hatcher of the Cornell University Medical College, New York City, has studied the effect of isophenolphthalein on the human system. He states that, at least in his preliminary experiments, isophenolphthalein does not appear to have a laxative effect. This is in remarkable contrast with phenolphthalein which is, of course, an excellent purgative.

Synthetic Preparation of Isophenolphthalein.—A large number of condensations of phenol with phthalic anhydride, of phenol with *p*-hydroxybenzoyl-*o*-benzoic acid, and of phenol with *o*-hydroxybenzoyl-*o*-benzoic acid were made in order to determine whether any isophenolphthalein is formed and, if so, the best conditions for its preparation.

CONDENSATION OF PHENOL WITH *p*-HYDROXYBENZOYL-*o*-BENZOIC ACID.—The acid was prepared by the method of Orndorff and Kelley.[14] A large excess of the condensing agent was added to a mixture of one molecule of the acid with one molecule of phenol and the mass heated in an electrically controlled oven. When the reaction was complete, water was added, any excess of phenol removed with steam, and the solution filtered hot. The material insoluble in hot water was dissolved in dil. sodium hydroxide solution and precipitated with hydrochloric acid. It was then subjected to fractional crystallization from dil. ethyl alcohol, by means of which phenolphthalein can be separated from isophenolphthalein. The results are given in Table II.

TABLE II

CONDENSATION OF *p*-HYDROXYBENZOYL-BENZOIC ACID WITH PHENOL

Temperature, 110–120°

Time	Until solid	Until solid	5 hrs.	5 hrs.	5 hrs.
Cond. agent	none	$ZnCl_2$	$SnCl_4$	H_2SO_4	$AlCl_3$
Isophthalein	neg.	trace	none	trace	trace

Even though some isophenolphthalein was actually isolated, the amount in each case was very small.

TABLE III

CONDENSATION OF PHENOL WITH PHTHALIC ANHYDRIDE

	At 120–130°			At 150–160°		
Cond. agent	Time Hours	Phenolphthalein %	Isophthalein	Time Hours	Phenolphthalein %	Isophthalein
$ZnCl_2$......	72	54	none	24	40	trace
H_2SO_4......	18	43	trace	14	37	trace
$SnCl_4$......	18	45	none	24	32	none
P_2O_5.......	30	23	none	30	22	none
$AlCl_3$......	10	7	trace	..	..	..

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[14] Orndorff and Kelley, THIS JOURNAL, **44,** 1518 (1922).

CONDENSATION OF PHENOL WITH PHTHALIC ANHYDRIDE.—In these condensations the condensing agent was added to a mixture of two molecules of phenol with one of the anhydride. The procedure was the same as when the *p*-hydroxy acid was used.

It thus appears that under certain conditions isophenolphthalein is formed in these condensations, but the quantity is very small. Some fluoran was formed in each condensation.

CONDENSATION OF PHENOL WITH *o*-HYDROXYBENZOYL-*o*-BENZOIC ACID.—Pure *o*-hydroxybenzoyl-*o*-benzoic acid was prepared by the method of Ullmann and Schmidt.[15] To a mixture of one molecule of this acid with a slight excess of phenol was added a large excess of the condensing agent and the mass heated at the desired temperature. When the reaction was complete, water was added, the excess of phenol removed with steam and the solution filtered hot. Any unchanged acid was recovered from the filtrate. The material insoluble in water was treated with 10% sodium hydroxide solution and the solution filtered in order to separate any fluoran. The filtrate was acidified with dil. hydrochloric acid and the precipitate crystallized from dil. ethyl alcohol. It was pure isophenolphthalein.

TABLE IV

CONDENSATION OF PHENOL WITH *o*-HYDROXYBENZOYL-*o*-BENZOIC ACID

Time, six hours

Temp. °C.	Cond. agent	Fluoran %	Isophenolphthalein %
120–130	$ZnCl_2$	15	55
120–130	$ZnCl_2$	21	38
120–130	H_2SO_4	10	50
110–120	H_2SO_4	<5	65
100–110	$SnCl_4$	<5	87
120–130	$SnCl_4$	<5	78

We thus have a method for preparing isophenolphthalein in any quantity desired.

Action of Fused Potassium Hydroxide on Isophenolphthalein.—If, in isophenolphthalein, one of the hydroxyl groups is *ortho* and the other *para* with respect to the methane carbon atom, then it should give *o,p*-dihydroxy-benzophenone and benzoic acid when fused with potassium hydroxide under the proper conditions. Such was found to be the case. The pure isophenolphthalein was made into a thick paste with aqueous potassium hydroxide and the mass heated in a nickel crucible immersed in an oil-bath at 180–190°. The mixture was stirred continuously until a small portion gave no test for isophenolphthalein. It was then dissolved in water, acidified with hydrochloric acid and distilled with steam. When the distillate gave no further test for benzoic acid, the distillation was stopped and the solution filtered hot. On cooling, the filtrate deposited yellow needles, or flat plates, depending upon the rate of cooling, of practically pure *o,p*-dihydroxy-benzophenone. They were recrystallized from benzene. Fine, yellow needles were obtained which melted at 143–144°.

Anal. Subs., 0.1901, 0.2353: CO_2, 0.5093, 0.6288; H_2O, 0.0807, 0.0972. Calc. for $C_{13}H_{10}O_3$: C, 72.88; H, 4.71. Found: C, 73.09, 72.90; H, 4.75, 4.62.

The melting point and analyses prove that the substance is *o,p*-dihydroxy-benzophenone.[16]

Diacetate of *o,p*-Dihydroxybenzophenone.—This was prepared by acetylating the

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[15] Ullmann and Schmidt, *Ber.*, **52**, 2106 (1919).

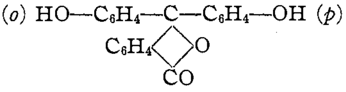
[16] Michael, (a) *Ber.*, **14**, 656 (1881); (b) *Am. Chem. J.*, **5**, 85 (1893). (c) Staedel, *Ann.*, **283**, 177 (1894).

pure *o,p*-dihydroxybenzophenone with acetic anhydride and fused sodium acetate. It crystallized from dil. ethyl alcohol in fine needles which melted at 88°.

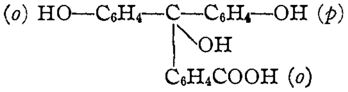
Anal. Subs., 0.1141: CO_2, 0.2855; H_2O, 0.0510. Calc. for $C_{13}H_8O_3(COCH_3)_2$: C, 68.44; H, 4.73. Found: C, 68.26; H, 5.00.

The melting point and analysis show that the substance is the diacetate of *o,p*-dihydroxybenzophenone.[16b]

The synthetic preparation of isophenolphthalein from *o*-hydroxybenzoyl-*o*-benzoic acid and phenol, together with its decomposition into *o,p*-dihydroxy-benzophenone and benzoic acid when fused with potassium hydroxide, proves that it is unquestionably *o,p*-dihydroxy-diphenylphthalide, having the structure I.



I



$$(o)\ HO{-}C_6H_4{-}\underset{\underset{C_6H_4COOH\ (o)}{|}}{\overset{}{C}}(OH){-}C_6H_4{-}OH\ (p)$$

II

The isophenolphthalein crystallized from dil. ethyl alcohol was shown to contain one molecule of water. This water may be water of constitution and in this form the substance may have the carbinol carboxylic acid structure II. A few of the more important derivatives of isophenolphthalein were prepared and in no case was there any evidence in favor of any other structural formula for the phthalein.

Isophenolphthalein Derivatives. Monosodium Salt.—Pure anhydrous isophenolphthalein was added slowly to a warm solution of 0.25 g. of sodium in 20 cc. of absolute ethyl alcohol until the blue color of the solution changed to deep red. A slight excess of phthalein was then added, the solution boiled, cooled and diluted with a large volume of anhydrous ether. The precipitate was filtered off, washed with anhydrous ether and dried in a vacuum desiccator over calcium chloride. It appeared red except when finely pulverized and spread in thin layers, when it was yellow. It dissolved in water and in alcohol giving a red solution, but when the solutions were diluted they also were yellow. It was heated to constant weight at 100° and analyzed for sodium by fuming down with concd. sulfuric acid.

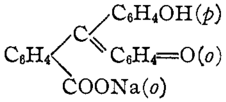
Anal. Subs., 0.5175, 0.6752: Na_2SO_4, 0.1101, 0.1416. Calc. for $C_{20}H_{13}O_4Na$: Na, 6.76. Found: 6.89, 6.79.

Disodium Salt.—To 1.0 g. of sodium dissolved in 100 cc. of absolute ethyl alcohol was added a solution of 6.0 g. of pure anhydrous isophenolphthalein in 100 cc. of absolute alcohol. The blue disodium salt was then precipitated with a large volume of anhydrous ether, filtered off, washed with anhydrous ether and dried in a vacuum desiccator. It was finally heated to constant weight at 120° and analyzed for sodium.

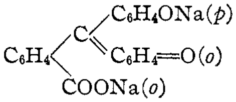
Anal. Subs., 0.3304, 0.2232: Na_2SO_4, 0.1278, 0.0887. Calc. for $C_{20}H_{12}O_4Na_2$: Na, 12.70. Found: 12.53, 12.87.

The disodium salt dissolves in water with the formation of a red solution of the monosodium salt due to hydrolysis.

These salts probably have the *ortho* quinoid structure and may be represented by the following formulas.



Monosodium salt
(yellow)



Disodium salt
(blue)

Diacetate.—Five g. of pure isophenolphthalein was boiled with 20 g. of acetic anhydride for a half hour and the solution was then poured into cold water. After the mixture had been stirred for two hours the colorless precipitate was filtered off, washed with water and dried. It crystallized from dil. ethyl alcohol in colorless needles melting at 166–167°. It lost no weight when heated at 120°.

Anal. Subs., 0.1123, 0.1468: CO_2, 0.2943, 0.3851; H_2O, 0.0460, 0.0584. Calc. for $C_{20}H_{12}O_4(COCH_3)_2$: C, 71.62; H, 4.51. Found: C, 71.50, 71.57; H, 4.58, 4.45.

The diacetate is easily soluble in alcohol, acetone, benzene, ethyl acetate and acetic acid, and insoluble in water and ligroin.

DIBENZOATE.—This substance was prepared by the Schotten-Baumann reaction. When the reaction was complete the colorless precipitate was filtered off and dried. It crystallized from ethyl alcohol, methyl alcohol and acetone in fine, colorless needles; m. p., 208–209°. It lost no weight when heated at 120°.

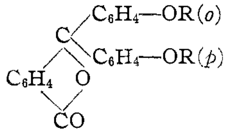
Anal. Subs., 0.2061, 0.1797: CO_2, 0.5866, 0.5120; H_2O, 0.0809, 0.0696. Calc. for $C_{20}H_{12}O_4(COC_6H_5)_2$: C, 77.55; H, 4.21. Found: C, 77.65, 77.73; H, 4.39, 4.34.

DIMETHYL ETHER.—Five g. of pure isophenolphthalein was dissolved in 100 cc. of 10% potassium hydroxide solution and to this was added slowly and with constant shaking, 4 g. of dimethyl sulfate. After the mixture had been shaken for two hours, the yellow precipitate was filtered off and dried. After several crystallizations from dilute ethyl alcohol, a colorless substance was obtained which melted at 122°. It lost no weight when heated at 80°.

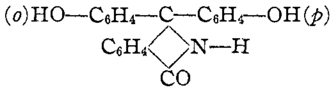
Anal. Subs., 0.2048, 0.1019: CO_2, 0.5737, 0.2855; H_2O, 0.0987, 0.0495. Calc. for $C_{20}H_{12}O_2(OCH_3)_2$: C, 76.27, H, 5.24. Found: C, 76.42, 76.44; H, 5.39, 5.44.

The dimethyl ether is easily soluble in hot ethyl alcohol, methyl alcohol, acetone, ether, chloroform, benzene and ethyl acetate, and insoluble in water and ligroin. It does not dissolve when boiled with solutions of the dilute alkalies.

Since the diacetate, dibenzoate and dimethyl ether of isophenolphthalein are colorless, their structures must be represented by the lactoid formula, III,



III



IV

in which R = CH_3CO, C_6H_5CO or CH_3.

Action of Ammonia on Isophenolphthalein. Isophenolphthalein Imide.—Dry ammonia gas has no action on isophenolphthalein. Concd. aqueous ammonia dissolves isophenolphthalein giving a deep bluish-red solution, but on standing, this color gradually fades until after 10–14 days it is green. At this point practically all of the isophenolphthalein has been converted into the imide. The imide can be separated from the solution either by evaporating the excess of ammonia, or by neutralizing it with dil. hydrochloric acid. In either case the product was colored—from a light pink to a dark brown. A colorless product was only obtained by acetylating the colored material with acetic anhydride, purifying the diacetate and saponifying it with alkali. This crude diacetate was yellow but several crystallizations from dil. ethyl alcohol, with the aid of boneblack, gave a colorless product. It was then boiled with 10% sodium hydroxide solution, in which it dissolved, coloring the liquid a pale green. The imide was obtained crystalline from this solution by neutralizing with dil. hydrochloric acid. After one crystallization from dil. ethyl alcohol, colorless needles melting at 269–270° were obtained. They lost no weight when heated at 120° and were analyzed for nitrogen by the Kjeldahl method.

Anal. Subs., 0.5948, 0.5739: cc. of 0.1 *N* H_2SO_4, 18.82, 18.31. Calc. for $C_{20}H_{15}O_3N$: N, 4.42. Found: 4.43, 4.47.

The imide is easily soluble in alcohol, acetone and ethyl acetate, slightly soluble in ether and practically insoluble in benzene, xylene, carbon tetrachloride and ligroin. When pure it dissolves in solutions of the alkalies without development of color. The structure of the imide is shown in IV.

DIACETATE.—This was prepared by acetylating the pure imide with acetic anhydride and pouring the product into water. It was crystallized several times from dil. ethyl alcohol. Fine colorless needles were obtained, melting at 210°. They lost no appreciable weight at 120° and were analyzed for nitrogen.

Anal. Subs., 0.4878, 0.6119: cc. of 0.1 *N* H_2SO_4, 12.11, 14.97. Calc. for $C_{20}H_{13}O_3N(COCH_3)_2$: N, 3.49. Found: 3.48, 3.43.

Further evidence that the substance was the diacetate of the imide was obtained from the determination of the number of acetyl groups, using the modified Wenzel method.[17]

Anal. Subs., 0.6202, 0.6300: cc. of 0.1 *N* NaOH, 30.90, 31.34. Calc. for $C_{20}H_{13}O_3N(COCH_3)_2$: CH_3CO, 21.45. Found: 21.44, 21.40.

The diacetate is easily soluble in hot ethyl alcohol, methyl alcohol, acetone, ethyl acetate, chloroform and benzene, slightly soluble in ether and very difficultly soluble in ligroin.

TRIACETATE.—When acetylated with acetic anhydride and fused sodium acetate, a triacetate of the imide is formed. It was crystallized from dil. ethyl alcohol and then from dil. acetone. This gave a colorless product which melted at 178°, and which lost no weight when heated at 120°.

Anal. Subs., 0.3145, 0.3140: cc. of 0.1 *N* H_2SO_4, 7.26, 7.14. Subs., 0.2000, 0.2000: cc. of 0.1 *N* NaOH, 13.57, 13.58. Calc. for $C_{20}H_{12}O_3N(COCH_3)_3$: N, 3.16; CH_3CO, 29.12. Found: N, 3.23, 3.19; CH_3CO, 29.20, 29.22.

The triacetate is easily soluble in hot ethyl alcohol, acetone, glacial acetic acid, ethyl acetate and chloroform, soluble in benzene and ether and insoluble in ligroin. It also gives the imide when boiled with a solution of a dil. alkali.

DIBENZOATE.—This substance was prepared by the Schotten-Baumann reaction. It was crystallized from dilute acetone. A colorless product was obtained which gave no loss in weight when heated at 120°.

Anal. Subs., 0.4038, 0.3381: cc. of 0.1 *N* H_2SO_4, 7.84, 6.30. Subs., 0.3538, 0.2245: CO_2, 1.0060, 0.6385; H_2O, 0.1428, 0.0945. Calc. for $C_{20}H_{13}O_3N(COC_6H_5)_2$: C, 77.70; H, 4.40; N, 2.68. Found: C, 77.57, 77.59; H, 4.52, 4.71; N, 2.72, 2.61.

The dibenzoate is easily soluble in hot alcohol, acetone, chloroform and glacial acetic acid; soluble in benzene; slightly soluble in ethyl acetate; difficultly soluble in ether and practically insoluble in ligroin. It crystallizes in fine, white needles which melt at 255°. It is not attacked by solutions of cold dilute alkalies.

TRIBENZOATE.—When benzoylated by heating with benzoyl chloride, a tribenzoate of the imide results. A colorless product was obtained by crystallizing from dilute acetone. It lost no weight when heated at 100°.

Anal. Subs., 0.4000, 0.4000: cc. of 0.1 *N* H_2SO_4, 6.02, 6.01. Subs., 0.1776, 0.1685: CO_2, 0.5101, 0.4832; H_2O, 0.0720, 0.0672. Calc. for $C_{20}H_{12}O_3N(COC_6H_5)_3$: C, 78.20; H, 4.32; N, 2.23. Found: C, 78.36, 78.23; H, 4.54, 4.46; N, 2.11, 2.10.

The tribenzoate is easily soluble in hot glacial acetic acid, acetone, benzene and ethyl acetate; soluble in hot methyl alcohol and ethyl alcohol; difficultly soluble in ether and almost insoluble in ligroin. It melts at 220°. It is not attacked by solutions of cold dilute alkalies.

The structures of the acetates and benzoates of the imide are shown in V and VI, where R stands for either the acetyl or benzoyl group.

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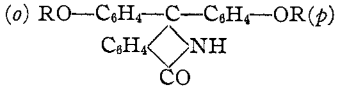
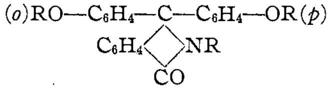
[17] *Am. Chem. J.*, **26**, 121 (1901); **42**, 227 (1909).



$(o)\,RO{-}C_6H_4{-}C{-}C_6H_4{-}OR(p)$; $C_6H_4\langle\rangle NH$; CO

V. Diacetate and dibenzoate



$(o)RO{-}C_6H_4{-}C{-}C_6H_4{-}OR(p)$; $C_6H_4\langle\rangle NR$; CO

VI. Triacetate and tribenzoate

Isophenolphthalein Oxime.—This substance was prepared by a method similar to that given for the preparation of phenolphthalein oxime.[18] It is much more soluble, however, and hence cannot be separated from the solution in quite the same manner as can the phenolphthalein oxime. No alcohol can be added and the solution must be cooled with ice water before neutralizing with dil. acetic acid. The yellow oxime was dried over sulfuric acid. It is easily soluble in ethyl alcohol, acetic acid, acetone and ether, and practically insoluble in benzene. It dissolves in alkalies and in sulfuric acid forming a yellow solution. It darkens when heated above 160°, begins to melt at about 180°, turns very dark above 180° and melts completely to a black liquid at 198°. The structure of the oxime is similar to that of phenolphthalein oxime.[19]

Anal. Subs., 0.2102, 0.1946: cc. of 0.1 N H_2SO_4, 6.30, 5.74. Calc. for $C_{20}H_{15}O_4N$: N, 4.20. Found: 4.20, 4.13.

Isophenolphthalein Hydrazide.—Hot concd. solutions of hydrazine hydrate dissolve isophenolphthalein forming blue liquids. This color changes very rapidly to green and then to light yellow. When this yellow solution was diluted with water and allowed to cool, colorless crystals of isophenolphthalein hydrazide separated. They were recrystallized from dil. ethyl alcohol.

Anal. Subs., 0.2413, 0.2642: CO_2, 0.6390, 0.7001; H_2O, 0.1104, 0.1164. Calc. for $C_{20}H_{16}O_3N_2$: C, 72.27; H, 4.85. Found: C, 72.25, 72.29; H, 5.12, 4.93.

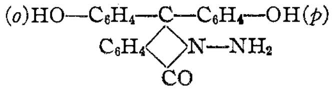
The hydrazide turns red when heated to about 210°, and then darkens rapidly, melting indefinitely at 225–235°. It dissolves in solutions of cold alkalies without development of color. It is easily soluble in hot ethyl alcohol, absolute alcohol and glacial acetic acid; soluble in hot acetone; slightly soluble in ethyl acetate and benzene and very difficultly soluble in ether, chloroform and ligroin.

TRIBENZOATE.—This was prepared by the Schotten-Baumann reaction. It crystallized from 90% ethyl alcohol in colorless needles which melted at 121–123°.

Anal. Subs., 0.1428, 0.1328; CO_2, 0.3987, 0.3719; H_2O, 0.0586, 0.0557. Calc. for $C_{20}H_{13}O_3N_2(COC_6H_5)_3$: C, 76.38; H, 4.38. Found: C, 76.17, 76.40; H, 4.59, 4.69.

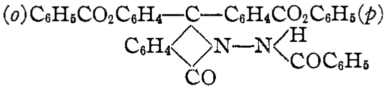
The tribenzoate is extremely soluble in acetone and easily soluble in hot ethyl alcohol, methyl alcohol, ethyl acetate, chloroform and benzene. It is almost insoluble in ligroin and does not dissolve in dilute solutions of the alkalies.

The structures of the hydrazide and its tribenzoate are shown in VII and VIII.



$(o)HO{-}C_6H_4{-}C{-}C_6H_4{-}OH(p)$; $C_6H_4\langle\rangle N{-}NH_2$; CO

VII. Hydrazide



$(o)C_6H_5CO_2C_6H_4{-}C{-}C_6H_4CO_2C_6H_5(p)$; $C_6H_4\langle\rangle N{-}N\langle^{H}_{COC_6H_5}$; CO

VIII. Tribenzoate

Phenolphthalein Hydrazide.—Phenolphthalein dissolves in a hot concentrated solution of hydrazine hydrate giving a blood-red liquid. In a very short time a heavy, colorless, crystalline precipitate of phenolphthalein hydrazide separates with decoloration of the solution. It was crystallized from dilute acetone.

Anal. Subs., 0.1946, 0.2029: CO_2, 0.5147, 0.5385; H_2O, 0.0946, 0.0921. Calc. for $C_{20}H_{16}O_3N_2$: C, 72.27; H, 4.85. Found: C, 72.16, 72.40; H, 5.44, 5.08.

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[18] Ref. 7, p. 679.

[19] Orndorff and Yang, THIS JOURNAL, **45**, 1926 (1923).

The hydrazide is difficultly soluble in benzene and ethyl acetate; slightly soluble in ether; soluble in methyl alcohol and ethyl alcohol and very soluble in acetone. It dissolves in cold dilute solutions of the alkalies without development of color. When heated above 120° it turns pink and then dark red and melts indefinitely at 255–265°.

TRIBENZOATE.—This was prepared by the Schotten-Baumann reaction. The product was crystallized from absolute methyl alcohol.

Anal. Subs., 0.1053, 0.1226: CO_2, 0.2944, 0.3440; H_2O, 0.0486, 0.0539. Calc. for $C_{20}H_{13}O_3N_2(COC_6H_5)_3$: C, 76.38; H, 4.38. Found: C, 76.27, 76.55; H, 5.16, 4.92.

The tribenzoate is easily soluble in acetone, benzene, ethyl acetate and chloroform and less soluble in methyl alcohol, ethyl alcohol, ether and glacial acetic acid. It is practically insoluble in petroleum ether and is not attacked by cold dilute solutions of the alkalies; m. p., 181–183°.

TRIACETATE.—This was prepared by acetylating the hydrazide with acetic anhydride and fused sodium acetate. It crystallized from dil. acetone in fine colorless needles; m. p., 199–202°.

Anal. Subs., 0.2653, 0.2023: CO_2, 0.6642, 0.5043; H_2O, 0.1213, 0.0927. Subs., 0.2000, 0.2000: cc. of 0.1 N NaOH, 13.16, 13.27. Calc. for $C_{20}H_{13}O_3N_2(COCH_3)_3$: C, 68.10; H, 4.84; CH_3CO, 28.17. Found: C, 68.30, 68.01; H, 5.12, 5.13; CH_3CO, 28.32, 28.55.

The triacetate is easily soluble in hot ethyl alcohol, methyl alcohol, acetone, ethyl acetate and benzene.

The structures of phenolphthalein hydrazide and its derivatives are similar to the corresponding derivatives of isophenolphthalein.

Tetrabromo-isophenolphthalein was made by brominating pure isophenolphthalein in glacial acetic acid with an excess of bromine dissolved in glacial acetic acid and then heating the mixture on the water-bath for an hour. On cooling, crystals of almost pure tetrabromo-isophenolphthalein separated. They crystallized from alcohol and ether in colorless needles melting with decomposition at 277–279°. They lost no weight when heated at 120° and were analyzed for bromine by the Parr bomb method.

Anal. Subs., 0.1068, 0.1009: AgBr, 0.1262, 0.1192. Calc. for $C_{20}H_{10}Br_4O_4$: Br, 50.43. Found: 50.29, 50.28.

It is easily soluble in acetone and ethyl acetate; soluble in chloroform; slightly soluble in ethyl alcohol, ether and acetic acid and difficultly soluble in benzene. Its solution in 0.01 N alkalies has a very faint yellow color, difficult to detect. With 0.1 N alkalies it gives a faint green solution. This green color, however, disappears very rapidly. In a stronger alkaline solution (10%), it dissolves without the development of any apparent color. Because these color changes are not sharp, it is not possible to determine at what Sörensen (P_H) value they occur.

DIACETATE.—Pure tetrabromo-isophenolphthalein was acetylated by boiling with acetic anhydride. The diacetate crystallized from ethyl acetate in needle-like clusters; m. p., 235°.

Anal. Subs., 0.1357, 0.1469: AgBr, 0.1426, 0.1538. Calc. for $C_{20}H_8Br_4O_4(COCH_3)_2$: Br, 44.53. Found: 44.72, 44.56.

It is easily soluble in ethyl acetate, alcohol and acetic acid; soluble in chloroform; difficultly soluble in ether and benzene and insoluble in ligroin.

The structures of the tetrabromo-isophenolphthalein and its diacetate are similar to those of the corresponding derivatives of phenolphthalein.[20]

MONOSODIUM SALT.—The formation of the colorless trisodium salt of the carbinol

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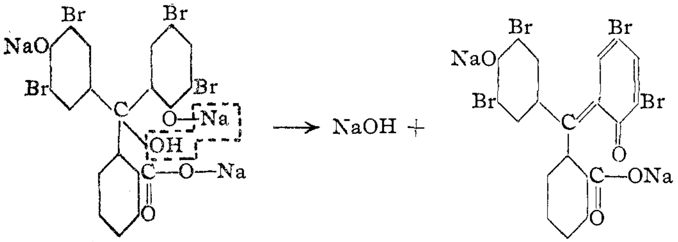
[20] *Ann.*, **202**, 136 (1880).

acid takes place so readily that it was not possible to isolate the monosodium salt in pure condition, although it does exist in solution as a yellow substance.

Disodium Salt.—To a boiling solution containing 2 g. of pure tetrabromo-isophenolphthalein in 100 cc. of absolute alcohol, was added a 1% solution of sodium ethylate (made by dissolving sodium in absolute alcohol), until there was a slight excess present. The green solution on cooling became colorless and deposited a heavy, white, crystalline precipitate. It was filtered off, washed with absolute alcohol and anhydrous ether and placed in a vacuum desiccator over sulfuric acid. The mass dried down to a hard white cake containing an indefinite amount of ether. On standing in the desiccator until free from ether it became dark green. This material was heated at 100° with only a slight loss and analyzed.

Anal. Subs., 0.5322, 0.6804: Na_2SO_4, 0.1554, 0.1992. Subs., 0.1310, 0.0945: AgBr, 0.1369, 0.0985. Calc. for $C_{20}H_9Br_4O_5Na_3$: Na, 9.61; Br, 44.53. Found: Na, 9.46, 9.48; Br, 44.47, 44.36.

The results would seem to indicate that the substance is the trisodium salt of the carbinol acid, notwithstanding its color. This can be accounted for by assuming that the white compound first formed was the salt of the carbinol acid and that on drying, a molecule of sodium hydroxide splits off.



Trisodium salt of carbinol acid (colorless) Disodium salt (green)

The *ortho* quinoid structure will account for the color and the presence of the sodium hydroxide would make the analyses agree with those for the trisodium salt of the carbinol acid. When allowed to stand exposed to moisture the green salt took up water very rapidly. After two days it had almost doubled its weight and changed to a red-brown paste.

Tetra-iodo-isophenolphthalein.—To a well-stirred solution of 10 g. of pure isophenolphthalein in 500 cc. of 2 *N* sodium hydroxide solution was added slowly a solution of 35 g. of iodine and 40 g. of potassium iodide in 500 cc. of water. The mixture had a yellow-brown color which did not change after six hours' stirring. It was then neutralized with acetic acid. The precipitate was dissolved in 2 *N* sodium hydroxide solution and reprecipitated with acetic acid. It was again dissolved in sodium hydroxide solution and a slight excess of hydrochloric acid added. The iodophthalein had a pink color which was removed by washing with acetone. It crystallized from acetone in colorless needles.

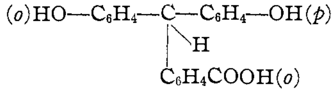
Anal. Subs., 0.1122, 0.1131: AgI, 0.1286, 0.1298. Calc. for $C_{20}H_{10}I_4O_4$: I, 61.77. Found: 61.95, 62.03.

It is very difficultly soluble in acetone, methyl alcohol, ethyl alcohol, ether, chloroform, benzene, ethyl acetate and acetic acid. The acetone solution turns brown on standing due to the liberation of iodine. When moistened with a dilute solution of sodium hydroxide, the tetra-iodophthalein turns green. The addition of water or more of the alkali causes the color to fade almost instantly. Hence, like the tetrabromophthalein, it cannot be used as an indicator. The pure compound begins to darken when heated to 260° and melts to a brown liquid at 277–279°, with evolution of iodine.

Diacetate was made by boiling tetra-iodo-isophenolphthalein with acetic anhydride and fused sodium acetate. It crystallized from glacial acetic acid in colorless needles; m. p., 224°. It is easily soluble in acetone and less soluble in ethyl alcohol, acetic acid, ether and methyl alcohol.

Anal. Subs., 0.1077, 0.1069: AgI, 0.1113, 0.1107. Calc. for $C_{20}H_8I_4O_4(COCH_3)_2$: I, 56.04. Found: 55.85, 55.97.

The Reduction Products of Isophenolphthalein.—When isophenolphthalein is gently reduced, the lactone ring is broken and two hydrogen atoms are taken up, with the formation of isophenolphthalin.



$$\begin{array}{l} (o)\mathrm{HO{-}C_6H_4{-}C{-}C_6H_4{-}OH}(p) \\ \qquad\qquad\quad\;\; |\diagdown \mathrm{H} \\ \qquad\qquad\quad\;\; \mathrm{C_6H_4COOH}(o) \end{array}$$

Isophenolphthalin

This substance still retains the two hydroxyl groups, as was shown by the formation of a diacetate. Using a more vigorous reducing agent, the *ortho* hydroxyl group is replaced by hydrogen, thus forming *p*-hydroxy-triphenylmethane carboxylic acid. That this has but one hydroxyl group was shown by the formation of a mono-acetate.

Isophenolphthalin.—This was prepared by boiling a dilute acetic acid solution of pure isophenolphthalein with zinc dust until a small test portion gave no color with dil. alkalies. The excess of zinc was then removed and the solution diluted with water until it began to appear turbid. On cooling, a small amount of an oil separated. This was removed and more water added. On standing, fine colorless crystals separated. They were recrystallized from dil. acetic acid and dried in an atmosphere of carbon dioxide; m. p., 189–190°.

Anal. Subs., 0.1709, 0.1470: CO_2, 0.4687, 0.4035; H_2O, 0.0822, 0.0694. Calc. for $C_{20}H_{16}O_4$: C, 74.98; H, 5.04. Found: C, 74.82, 74.88; H, 5.38, 5.28.

Isophenolphthalin dissolves in solutions of the alkalies without development of color, but the solution becomes red when boiled or allowed to stand. It is readily soluble in hot ethyl alcohol, methyl alcohol, acetic acid and acetone.

Diacetate.—This was prepared by acetylating the pure phthalin with acetic anhydride and fused sodium acetate. It was crystallized from dil. acetic acid and dried at 100° in an atmosphere of carbon dioxide; m. p., 143–144°. It is easily soluble in acetone ethyl alcohol, methyl alcohol, acetic acid and benzene. It is insoluble in dilute solutions of the alkalies.

Anal. Subs., 0.2033, 0.2115: CO_2, 0.5300, 0.5505; H_2O, 0.0859, 0.0845. Calc. for $C_{20}H_{14}O_4(COCH_3)_2$: C, 71.27; H, 4.99. Found: C, 71.12, 71.01; H, 4.73, 4.47.

***p*-Hydroxy-triphenylmethane Carboxylic Acid.**—This was obtained together with a small amount of isophenolphthalin by the reduction of isophenolphthalein with zinc and hydrochloric acid in a glacial acetic acid solution. When the reaction was complete, the excess of zinc was filtered off and the filtrate diluted with water. Colorless crystals of *p*-hydroxy-triphenylmethane carboxylic acid separated on cooling. Any isophenolphthalin formed remained in the mother liquor. The acid crystallized from dil. ethyl alcohol in long needles; m. p., 210–211°.

Anal. Subs., 0.1645, 0.1819: CO_2, 0.4756, 0.5266; H_2O, 0.0690, 0.0757. Calc. for $C_{20}H_{16}O_3$: C, 78.92; H, 5.30. Found: C, 78.87, 78.98; H, 4.69, 4.66.

The acid is very soluble in acetone and soluble in acetic acid, ethyl alcohol and benzene. The melting point, properties and analyses of the substance show that it is unquestionably *p*-hydroxy-triphenylmethane carboxylic acid.[21]

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[21] *Ber.*, **13**, 1616 (1880).

ACETATE.—This was prepared by acetylating pure *p*-hydroxy-triphenylmethane carboxylic acid with acetic anhydride and fused sodium acetate. It crystallized from dil. acetic acid in colorless needles; m. p., 148°.

Anal. Subs., 0.2058, 0.1742: CO_2, 0.5758, 0.4863; H_2O, 0.0835, 0.0727. Calc. for $C_{20}H_{15}O_3COCH_3$: C, 76.27; H, 5.24. Found: C, 76.33; 76.16; H, 4.54, 4.67.

The acetate is very soluble in acetone and easily soluble in hot ethyl alcohol, methyl alcohol, acetic acid and benzene.

Absorption Spectra of Phenolphthalein and Isophenolphthalein

Miss S. Alice McNulty, Heckscher Research Assistant in Chemistry and Physics, 1921–1923, working under the direction of Professor R. C. Gibbs of the Department of Physics, has made ultraviolet absorption measurements on phenolphthalein and isophenolphthalein in various solvents. Visible absorption measurements have also been made when the color of the solutions warranted such examination.

In absolute ethyl alcohol solution, phenolphthalein gives two bands of about equal intensity at frequency numbers 35,230 and 36,130. The curve obtained for isophenolphthalein in the same solvent is similar to that of phenolphthalein and shows bands at frequency numbers 35,110 and 36,060. These bands are slightly more intense than those of phenolphthalein.

In concd. sulfuric acid solution phenolphthalein gives five bands. A very intense one occurs at 20,250, another of less intensity at 25,600, a very faint band at about 30,850, while shoulders appear in approximately the positions 35,550 and 38,750. Isophenolphthalein also gives five bands in concd. sulfuric acid solution. The prominent band at the visible end of the spectrum occurs at 22,250 and is only 1/120 as intense as the phenolphthalein band occurring at 20,250. Shoulders of even less intensity occur at about 20,000 and 23,500. The ultraviolet end of the spectrum more closely resembles that of phenolphthalein, with shoulders at approximately the positions 35,000 and 38,500.

Both phenolphthalin and isophenolphthalein give colorless solutions when a large excess of alkali is present. When 33% aqueous potassium hydroxide is used as a solvent, both substances give similar curves with two bands. Phenolphthalein has one band at 33,800 and another five times as intense at 40,650. Isophenolphthalein gives a band at 34,000 which is more intense and another at 41,150 which is less intense, than the corresponding bands in phenolphthalein.

Both substances yield colored solutions when dissolved in weak alcoholic potassium hydroxide. The colored solution of phenolphthalein showed two bands at 17,850 and 27,300 while the characteristic bands of the phthalein itself merged into general absorption. The addition of more alkali intensified the bands at 17,850 and 27,300, while there also appeared as broad shoulders, the beginning of the characteristic bands for the phthalein in colorless alkaline solution in the vicinity of 34,000 and 39,500.

The absorption of the colored alkaline solution of isophenolphthalein was very much weaker at the visible end of the spectrum than that of phenolphthalein. One band developed at 16,950 and a shoulder at about 24,400, while the characteristic bands for the phthalein in alcohol were still present. With the addition of more alkali the bands in the visible part of the spectrum were intensified, the bands for the phthalein in alcohol disappeared and the beginnings of the characteristic bands for the phthalein in colorless alkaline solution appeared as broad shoulders in the vicinity of 34,000 and 40,600.

Summary

The results obtained in this work may be briefly summarized as follows.

1. Isophenolphthalein, which is *o,p*-dihydroxy-diphenylphthalide, has been prepared and its reactions have been studied.
2. The condensation of phenol with phthalic anhydride, of phenol with *p*-hydroxybenzoyl-*o*-benzoic acid and of phenol with *o*-hydroxybenzoyl-*o*-benzoic acid has been studied.
3. The position of the two hydroxyl groups in isophenolphthalein was determined by fusing it with potassium hydroxide.
4. The mono- and disodium salts of isophenolphthalein have been prepared.
5. The diacetate, dibenzoate and dimethyl ether of isophenolphthalein have been prepared.
6. The action of ammonia on isophenolphthalein has been studied. Isophenolphthalein imide and its diacetate, dibenzoate, triacetate and tribenzoate have been prepared.
7. Isophenolphthalein oxime has been prepared.
8. Isophenolphthalein hydrazide and its tribenzoate have been prepared together with phenolphthalein hydrazide and its triacetate and tribenzoate.
9. Tetrabromo-isophenolphthalein and its diacetate have been prepared. The sodium salts were also studied.
10. Tetra-iodo-isophenolphthalein and its diacetate have been prepared.
11. The reduction products of isophenolphthalein have been investigated. Isophenolphthalin, its diacetate and *p*-hydroxytriphenylmethane carboxylic acid and its mono-acetate have been prepared.
12. The absorption spectra of phenolphthalein and of isophenolphthalein have been studied.

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