(IV) A study of the spectroscopic relations of the dichlorophthalic acids will be made in the near future.

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PHTHALIC ACID DERIVATIVES; CONSTITUTION AND COLOR, VII. DIIODO-, TRIIODO-, AND DICHLORODIIODOPHTHALIC ACIDS.

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The replacement of chlorine in halogenated phthalanils[1] by the anilino group results in a new and interesting type of phthalic acid derivatives, but the reaction is slow and the yields not always good. One of the reasons for preparing the diiodophthalic acids was to experiment on the corresponding replacement of iodine by anilino groups. It was expected that iodine would act more smoothly than chlorine in such a replacement. It was found to act readily enough, but unfortunately tarry products were formed from which no pure substances could be isolated.

The value of the iodophthalic acids as intermediate steps in the preparation of hydroxyphthalic acids will be taken up in connection with establishing their structures, and the spectroscopic relations of these acids to other phthalic derivatives will be discussed in a later paper.

Practically no information could be found in the literature concerning the diiodo, and nothing at all concerning triiodo and dichlorodiiodophthalic acids. Edinger and Goldberg[2] prepared a diiodophthalic acid from 4, iodo-*o*-xylene, and recorded a melting point of 195°, which is about ten degrees lower than what we find for 3,4-diiodophthalic acid, but this is probably the isomer they had.

The partial iodination of phthalic acid was carried out in 50% fuming sulfuric acid, the two methods of treatment employed being long heating at 75°, and rapid heating to 200°. The first gave nearly equal amounts of 3,4- and 3,6-acids, and much smaller amounts of 4,5- and triiodo anhydride. Rapid heating gave the same amount of 4,5- with a larger amount of 3,4- and triiodo anhydride at the expense of the 3,6-. Compared with the action of chlorine on phthalic anhydride,[3] the difference indicated a greater tendency toward the 3,4-positions. The formation of a tri-substitution product was not observed in using chlorine. Although the yield of the 4,5-derivative is small in both chlorination and iodination, it is interesting to note that the only product so far isolated from the mixture obtained by partial bromination is 4,5-dibromophthalic anhydride.[4]

[1] Cf. two preceding papers.
[2] *Ber.*, **33**, 2880 (1900).
[3] V. Villiger, *Ber.*, **42**, 3530 (1909).
[4] Lesser and Weiss, *Ber.*, **46**, 3937 (1913). But cf. *Ibid.*, p. 3944.

Separation.

The separation of the diiodophthalic acids by the method Villiger used for the dichlorophthalic acids was not found feasible because the zinc salts of all the former acids proved to be insoluble. A partial separation was accomplished by esterification, since only the 4,5- and a part of the 3,4-acid formed neutral esters.

The esterification was effected at room temperature by alcohol saturated with hydrochloric acid. After two days the mixture was treated with a slight excess of dilute sodium hydroxide and the neutral esters extracted with ether. From the ether extract, after saponification by a mixture of sulfuric and acetic acids, a small amount of 4,5-diiodophthalic acid was isolated. The alkaline solution remaining after extraction with ether slowly deposited crystals of nearly pure sodium ethyl 3,4,6-triiodophthalate. Treatment of this salt with hydrochloric acid gave the acid ester, from which pure 3,4,6-triiodophthalic anhydride was obtained by boiling with acetic acid. A complete separation on these principles was not attempted since much better methods were soon available.

It was found that the 3,4- and 4,5-acids crystallize from 95% acetic acid without losing water while the 3,6- and triiodo acids are converted into anhydrides that can then be separated from the above acids by their much greater solubility in benzene. The 3,4- and 4,5- pair were then separated by repeated crystallization from acetic acid. The latter acid goes into solution in boiling acetic acid much more quickly and crystallizes out more readily than the 3,4-isomer.

It was finally found that an easy separation of all four acids can be effected by combining the two principles:

(1) When fractionally precipitated from a solution of their di-sodium salts by acetic acid the order of deposition of the mono-sodium salts is as follows: 4,5-salt, triiodo salt, and 3,4-salt; the 3,6-salt remaining in solution.

(2) The 3,6- and triiodo acids readily lose water giving anhydrides which can then be extracted by benzene.

Structure.

The positions of iodine atoms in the products obtained by iodination of phthalic anhydride were determined by hydrolysis. This was effected by boiling in strong sodium hydroxide solution, but the yields were not good, due to various side reactions. Curiously enough, the most troublesome of these side reactions was *reduction*, which occurred in the case of 3,6-diiodophthalic acid, the final result being 3-hydroxyphthalic acid. Apparently the cause of reduction was the simultaneous oxidation of a part of the product in the presence of strong alkali. Not only was 3-hydroxyphthalic acid an unexpected product, but its identification was attended with some difficulty at first due to incorrect melting points recorded in the

literature for its anhydride. The uncertainty was removed, however, by titration of a number of its derivatives and by a mixed melting point with some known 3-hydroxyphthalic anhydride prepared from 3-nitrophthalic acid.

Since 3,6-diiodophthalic acid could not be directly hydrolyzed to 3,6-dihydroxyphthalic acid, it was hydrolyzed in two steps. Replacement of one iodine atom by hydroxyl was readily affected by silver sulfate in aqueous pyridine solution, of the second by 1:1 sodium hydroxide. Since the final result was 3,6-dihydroxyphthalic acid the acid in question is 3,6-diiodophthalic acid.

Another of our diiodophthalic acids yielded, on treatment with sodium hydroxide, 4,5-dihydroxyphthalic acid and a second substance probably 3,4,5-trihydroxyphthalic acid. It is therefore 4,5-diiodophthalic acid.

Another diiodophthalic acid yielded 3,4-dihydroxybenzoic acid, thus showing that the iodine atoms in it also are *ortho* to each other. It is therefore 3,4-diiodophthalic acid.

The triiodophthalic acid yielded 3,6-dihydroxyphthalic and probably some 3,5-dihydroxybenzoic. It is therefore 3,4,6-triiodophthalic acid.

Iodination of the Dichlorophthalic Anhydrides.

The introduction of iodine into the dichlorophthalic anhydrides took place smoothly except in the case of the 3,6-isomers. Even at a comparatively low temperature this anhydride yielded considerable tetraiodophthalic anhydride. This contamination was easily removed by hydrating the chlorinated product and extracting the unchanged tetraiodophthalic anhydride with benzene.

One of the reasons for preparing the dichlorodiiodophthalic acids was to prepare if possible from them dianilinodichlorophthalanils of known structure. It was hoped that the structure of the dianilino product from tetrachlorophthalanil could then be established by identifying it with one of these. The replacement of iodine by the anilino group, however, was found to be difficult (cf. diiodophthalic acids above) and we succeeded only in obtaining a small amount of impure 3,6-dianilino-4,5-dichlorophthalanil. This was found to be different from the previously obtained isomer, but further investigation will be necessary to decide the structure of the latter.

Experimental.

Iodination of Phthalic Anhydride.—A mixture of 74 g. of phthalic anhydride, 127 g. (two atomic equivalents), of iodine, and 250 g. of 50% fuming sulfuric acid, was placed in an oil bath heated to approximately the following temperatures: 110–120° for 1.5 hrs.; 140–160° for 1 hr.; 160–200° for 15 minutes; and 200° for 5 minutes. A brisk evolution of sulfur dioxide took place during most of this time. The hot mixture was poured into a porcelain dish and exposed to the air several hours. Two

hundred and fifty grams of ice were then added with thorough stirring. The precipitate was filtered off, washed with 100 cc. of cold water, and dissolved in 250 cc. of warm 20% sodium hydroxide solution, avoiding unnecessary heating. The solution after filtering off a slight precipitate of ferric oxide and neutralizing with acetic acid, measured about 450 cc.

The neutral solution of sodium salts was then fractionally precipitated by successive additions of acid, warming after each addition and stirring for 2 hours as it cooled. 10 cc. of acetic acid gave a precipitate of 16 g. 5 cc. of acetic acid then gave a precipitate of 1 g. Both of these precipitates were found to be nearly pure mono-sodium 4,5-diiodophthalate. 10 cc. of acetic acid then gave 31 g., chiefly mono-sodium 3,4,6-triiodophthalate. Twenty cc. of hydrochloric acid then gave 91.5 g., chiefly mono-sodium 3,4-diiodophthalate. The solution was then treated with a large excess of hydrochloric acid and heated several hours in a water oven. The precipitate of 47 g. was chiefly 3,6-diiodophthalic anhydride.

The first two precipitates were treated according to the following general method: Five parts of the impure mono-sodium 4,5-diiodophthalate were dissolved in 50 parts of a hot 10% sodium acetate solution with the aid of a very slight excess of sodium hydroxide. The solution was made neutral to litmus with acetic acid and then one part of the acid added in excess. The solution was allowed to stand several hours before the crystals which formed were filtered off. In this case the mother liquor was added to the triiodo fraction, since it contained some of the triiodo and 3,4-acid. When much triiodo or 3,4-acid was present both the amount of acetic acid and the time allowed for crystallization were reduced. The pure crystals were converted into acid by dissolving in hot dilute sodium hydroxide and precipitating with excess hydrochloric acid.

The third and fourth fractions were separately dissolved in dilute sodium hydroxide and precipitated by a large excess of hydrochloric acid. Heating for several hours seems to be necessary for complete precipitation, especially of the 3,6-acid, which is thereby converted into its anhydride.

The next step was to extract each of the fractions with boiling benzene. The extracts from the third and fifth contained nearly pure triiodo- and 3,6-diiodophthalic anhydrides respectively, and the residue from the fourth contained nearly pure 3,4-diiodophthalic acid.

Although at this point a large part of the iodination product had been separated into its constituents, further quantities were recovered as follows. The residue from the benzene extraction of the third fraction was separated into 3,4- and 4,5-acids by recrystallizing the sodium salts as above described. The benzene extract from the fourth fraction was separated by the same method into mono-sodium triiodophthalate (crystals) and the 3,6-salt (filtrate). Here much more acetic acid may be used, and sodium acetate is unnecessary.

Effect of Temperature.

Phthalic anhydride was again iodinated, using the same quantities as before, but changing the manner of heating. The mixture was kept at about 75° for six days. The anhydrides were precipitated as before but it was found necessary to wash them with sodium sulfite solution to remove a little free iodine still remaining. The separation was carried out practically as before, but different yields of the various anhydrides were obtained. The results of the two methods of heating are compared in the following table. The first two columns show the amounts of fairly pure acids or anhydrides obtained by the process of separation described. The last two columns are calculated from the first two and show what fraction of the original phthalic anhydride each weight represents.

	Low temperature. G.	High temperature. G.	Low temperature. Per cent.	High temperature. Per cent.
3,6-Anhydride................	56.5	34.5	28.3	17.3
3,4-Acid.....................	52.5	62.5	25.1	29.9
4,5-Acid.....................	16.0	16.5	7.6	7.9
3,4,6-Anhydride..............	20.0	34.0	7.6	12.9
Total.................................			68.6	68.0

Only traces of tetraiodophthalic anhydride were formed in the above-mentioned iodinations and several others similarly carried out. The insolubility of its mono-sodium salt sometimes caused it to precipitate with the triiodophthalic fraction, but it generally remained in supersaturated solution until the precipitation of the 3,6-diiodophthalic anhydride. Traces of 4-iodophthalic acid were also found. This substance was isolated from the filtrates resulting in the course of the above-described separation from the precipitation of the diiodophthalic acids with hydrochloric acid. The combined filtrates from a mixture prepared just as stated in the first paragraph, i. e., an iodination at the higher temperatures, were extracted with ether.

The extract, weighing fifteen grams, was dissolved in dilute sodium hydroxide and subjected to fractional precipitation by acetic acid. The first fraction contained mono-sodium 4,5-diiodophthalate, and the last fraction mono-sodium 4-iodophthalate. The acid was freed by strong hydrochloric acid, and converted into anhydride by warming with a small amount of acetic anhydride. The mixture was dissolved in boiling ligroin from which about 0.5 g. of nearly colorless leaflets were deposited on cooling, melting at 124° (corr.). This substance was evidently 4-iodophthalic anhydride, for which a melting point of 123° is recorded.[1]

3,4-Diiodophthalic Acid.—The pure acid was obtained by dissolving the anhydride in warm sodium hydroxide solution, diluting with boiling water,

[1] Edinger, *J. prakt. Chem.*, [2] **53**, 387 (1896).

and acidifying with excess of hydrochloric acid. Colorless leaflets were formed which melted at 212–213° corr. (giving off water), on rapid heating. They were air dried and titrated with standard sodium hydroxide using phenolphthalein and boiling to remove CO_2.

Subst. (I) 0.2154, (II) 0.2252; cc. 0.1 N NaOH, (I) 10.34, (II) 10.80.
Calc. for $C_8H_4O_4I_2$: Molecular weight, 417.9. Found: (I) 416.7, (II) 417.0.

3,4-Diiodophthalic acid is slightly soluble in water. When in the crystalline condition it is only slightly soluble in ether, very soluble when amorphous. One gram dissolves in about 8 cc. of acetic acid on long boiling and crystallizes very slowly after cooling, in warty aggregates. It is partly converted into anhydride by the concentration of its solution in glacial acetic acid.

Mono-sodium 3,4-diiodophthalate is much more soluble than the corresponding salt of the 4,5-isomer or of 3,4,6-triiodophthalic acid. The addition of sufficient sodium acetate to a solution of the disodium salt of the 3,4-acid entirely prevents precipitation by any amount of acetic acid.

3,4-Diiodophthalic Anhydride.—The "nearly pure" 3,4-acid separated from its isomers as above described, was heated with benzene containing acetic anhydride. The product was then recrystallized several times, using boneblack, from benzene containing a slight addition of acetic anhydride. It crystallizes in almost colorless prisms with a fibrous fracture, melting at 198–198.5° (corr.).

Subst. (I) 0.3558, (II) 0.4171; cc. 0.1 N AgNO₃, (I) 17.86, (II) 20.89.
Calc. for $C_8H_2O_3I_2$: I, 63.48. Found: (I) 63.71, (II) 63.57.[1]

Hydrolysis of 3,4-Diiodophthalic Acid.—Fifty grams of 3,4-diiodophthalic acid and 50 g. of sodium hydroxide were added to 350 cc. of water and the solution boiled for 8 hrs. in an atmosphere of natural gas. During this time gradual concentration to 100 cc. was effected. The solution was then strongly acidified with hydrochloric acid and extracted with ether. The ether extract was recrystallized from hydrochloric acid giving 3 g. of product. This was recrystallized from water, melting then at 198–200° (corr.) with evolution of gas. Since its aqueous solution gave a bluish green with ferric chloride that was changed to violet and then red by dilute sodium carbonate the substance was evidently 3,4-dihydroxybenzoic acid, the melting point of which is recorded as 199° with decomposition.[2]

As an additional proof of its identity, the 3,4-dihydroxybenzoic acid

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[1] In this and subsequent iodine determinations the lime combustion method was used, but a slight excess of the standard silver nitrate solution was added before acidification. This prevented the loss of iodine, which otherwise occurred so easily when the nitric acid was added, and the heat of neutralization effected a rapid solution of both lime and silver oxide. Sodium sulfite was added after filtration, to reduce any silver iodate formed and precipitate it as iodide.

[2] Mulliken, "The Identification of Pure Organic Compounds," 1, 50.

was esterified with ethyl alcohol containing hydrochloric acid. The ester melted at 132–135° (corr.) Fittig and Macalpine record 133–134°.[1]

3,4-Diiodophthalanil.—Five parts of 3,4-diiodophthalic anhydride were dissolved in about 65 parts of boiling acetic acid, and 2 parts of aniline added. The yield on cooling was the same as the original weight of anhydride, *i. e.*, 84% theoretical. It was recrystallized twice from xylene, having then a melting point of 270–271° (corr.) unchanged by another crystallization. One gram dissolves in 15 cc. of boiling xylene from which it crystallizes in very pale yellow prisms.

Subst. (I) 0.4448, (II) 0.3555; cc. 0.1 N AgNO$_3$, (I) 18.75, (II) 15.07.

Calc. for C$_{14}$H$_7$O$_2$NI$_2$: I, 53.44. Found: (I) 53.50, (II) 53.80.

3,6-Diiodophthalic Acid.—3,6-Diiodophthalic anhydride (see below) was dissolved in dilute sodium hydroxide and hydrochloric acid added to the cooled solution. Colorless leaflets of the corresponding acid were obtained. This substance loses water slowly at 100°, and is converted to the anhydride below its melting point when rapidly heated in a capillary tube.

Titration of the acid is rendered difficult by the action of boiling water upon it. The iodine is apparently attacked in neutral, slightly acid, or alkaline solution, with the result that too much alkali is taken up unless the period of boiling to effect solution and remove carbon dioxide is very brief. An air-dried sample was titrated as rapidly as possible with standard hydroxide.

Subst. (I) 0.1374, (II) 0.0847; cc. 0.1 N NaOH, (I) 6.56, (II) 4.06.

Calc. for C$_8$H$_4$O$_4$I$_2$: Molecular weight, 417.9. Found: (I) 418.9, (II) 416.9.

3,6-Diiodophthalic acid forms a very soluble mono-sodium salt. A saturated solution of the di-sodium salt gives no precipitate on addition of acetic acid. This behavior affords a nearly complete separation from the products which accompany it in its preparation from phthalic acid.

3,6-Diiodophthalic Anhydride.—The benzene extract containing this substance (see page 222), was treated with a little acetic anhydride, to dehydrate the traces of 3,4- and 4,5- acids present, and then concentrated. The yellow prisms obtained were crystallized several times from benzene, using boneblack, giving a nearly colorless product melting at 234.5–235.5° (corr.).

Subst. (I) 0.3768, (II) 0.4189; cc. 0.1 N AgNO$_3$, (I) 18.92, (II) 20.89.

Calc. for C$_8$H$_2$O$_3$NI$_2$: I, 63.48. Found: (I) 63.73, (II) 63.29.

Hydrolysis of 3,6-Diiodophthalic Acid.—The iodine in 3,6-diiodophthalic acid is readily attacked by hydrolyzing agents but in most cases the isolation of pure products is difficult. A nearly neutral solution of the di-sodium salt or a solution of the acid sodium salt slowly becomes more acidic on boiling, showing that hydrolysis of the iodine takes place even

[1] *Ann.*, **168**, 114 (1873).

in neutral or acid solution. At the same time a reddish brown color developes. Boiling in alkaline solution effects a somewhat more rapid hydrolysis, and less color is developed. Many hours, however, were found to be required for complete hydrolysis using 10% sodium hydroxide and the only product isolated was 3-hydroxyphthalic acid, (see below). This was contaminated with large amounts of tarry matter, which was perhaps produced by the oxidation of some of the 3,6-dihydroxyphthalic acid first formed while the remainder of the dihydroxy acid was reduced. The result of shortening the time of boiling to about 3 hours was that the yield of 3-hydroxyphthalic acid was less, but no 3,6-dihydroxy acid could be isolated.

Attempts to use much stronger alkali failed, due to the insolubility of the salts of 3,6-diiodophthalic acid in strong alkalies. Fusion with potassium or sodium hydroxides resulted in charring. In contrast to this behavior, it was found that 3-hydroxy-6-iodophthalic acid could readily be hydrolyzed by 1:1 sodium hydroxide. One of the differences is the greater solubility of the salts of the partially hydrolyzed acid.

The Action of Silver Salts in Pyridine Solution on Iodinated Phthalic Acids.—The partial hydrolysis of 3,6-diiodophthalic acid was easily accomplished by the use of silver salts in pyridine solution. The sulfate was preferred to the nitrate as it gives no oxidizing agent upon acidification.

Since silver salts in pyridine reacted so smoothly with 3,6-diiodophthalic acid a few experiments were made upon other halogenated phthalic acids. The silver sufate reagent (described below) quickly gave silver iodide with tetraiodophthalic anhydride, but the 3,4-diiodo derivative required a more concentrated reagent, either silver nitrate or benzoate dissolved in a very little pyridine. These salts remain fused when almost all of the pyridine has been distilled off, and produce a more energetic action than the sulfate whose solution cannot be made so concentrated. The fused nitrate, however, has the disadvantage of causing explosions.

4,5-Diiodo- and tetrachlorophthalic anhydrides gave almost no silver halide even with the concentrated nitrate reagent.

3-Hydroxy-6-iodophthalic acid was found to be very slowly affected by the concentrated benzoate reagent.

3-Hydroxy-6-iodophthalic Anhydride Acetate.—Five grams of 3,6-diiodophthalic anhydride, and 10 g. of silver sulfate were added to a mixture of 25 cc. of pyridine and 2 cc. of water. The solution was boiled in an atmosphere of natural gas for 1.5 hours. The silver iodide formed remained in solution, only a negligible precipitation perhaps of silver taking place. The golden brown solution was poured slowly into concentrated hydrochloric acid with a constant stirring and cooling. The precipitate of silver chloride and iodide was filtered off and washed with a little water. The filtrate and washings were extracted twice with ether,

from which 3 g. of nearly colorless 3-hydroxy-6-iodophthalic acid crystallized on evaporation.

For complete purification the dried acid was warmed for 15 minutes with 5 cc. of acetic anhydride. 50 cc. of mixed xylene and ligroin were added, and the solution boiled a short time with boneblack. Two and one-half grams of slightly brownish square crystals were obtained which after two recrystallizations from the same solvent, melted at 148.5–152.5° (corr.).

Samples were titrated with sodium hydroxide, boiling to complete saponification.

Subst. (I) 0.1030, (II) 0.1008; cc. 0.1 N NaOH, (I) 9.43, (II) 9.20.
Calc. for $C_{10}H_5O_5I$: Molecular weight, 332.0. Found: (I) 327.7, (II) 328.5.

A dilute solution of 3-hydroxy-6-iodophthalic acid or its acetate gives with very little ferric chloride a blue-violet color changed by more ferric chloride through violet to a red which is destroyed only by a very large excess of the reagent.

3,6-Dihydroxyphthalic Acid.—Ten grams of 3-hydroxy-6-iodophthalic acid were ground in a mortar with 10 g. of pure sodium hydroxide and the mixture added to 100 cc. of 1:1 sodium hydroxide solution in a porcelain dish. The whole was heated rapidly to boiling with constant stirring, and then boiled vigorously for five minutes. A sample was acidified, extracted with ether, and an aqueous solution of the extract tested with ferric chloride. The colors, blue-violet changing to amber with excess, indicated that the second iodine atom had been removed and nearly pure 3-6-dihydroxyphthalic acid[1] was present.

Accordingly the whole product was acidified with hydrochloric acid, extracted with ether, and recrystallized from this solvent. A sample of the nearly colorless product was purified in the form of its acetate by boiling with acetic anhydride and adding boiling ligroin. A mixed melting point with 3,6-dihydroxyphthalic anhydride diacetate previously obtained (*loc. cit.*) was taken and the two samples found to be identical. Thus the position of the iodine atoms in 3,6-diiodophthalic acid was established.

3-Hydroxyphthalic Anhydride.—Fifty grams of 3,6-diiodophthalic anhydride and 50 g. of sodium hydroxide were dissolved in 700 cc. of water. The solution was boiled 20 hours in an atmosphere of natural gas during which it was concentrated to 100 cc. A large excess of hydrochloric acid was then added and the solution extracted with ether. After evaporation of the ether the product was recrystallized from hydrochloric acid and then boiled with 200 cc. of xylene, concentrating to 150 cc. The 3-hydroxyphthalic acid was thus converted to anhydride, which crystallized out on cooling. After two more crystallizations from xylene 5.5 g. of orange-yellow crystals were obtained melting at 198–199° (corr.). This

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[1] See page 226.

product was titrated with standard sodium hydroxide using phenol-phthalein and boiling to remove CO_2.

Subst. (I) 0.1777, (II) 0.0763; cc. 0.1 N NaOH, (I) 21.51, (II) 9.23.
Calc. for $C_8H_4O_4$: Molecular weight, 164.1. Found: (I) 165.2, (II) 165.3.

No recorded melting point of pure 3-hydroxyphthalic anhydride could be found. Jacobsen gives 145–148°[1] and Bentley, Robinson and Weizman[2] 150–190° for samples admitted to be impure. Therefore a sample known to be 3-hydroxyphthalic anhydride was prepared from 3-nitro-phthalic acid. The crude 3-hydroxyphthalic acid, prepared as described by Bernthsen[3] was converted to anhydride by boiling with xylene, crystallized from anhydrous ether to remove amorphous by-products and re-crystallized from xylene. A small yield of brownish yellow crystals were obtained, melting at 198–199°(corr.). Mixed with the anhydride previously obtained it had the same melting point, thus showing the identity of the two samples. Since a dihydroxy, not monohydroxy derivative was de-sired, the hydrolysis was repeated in the manner described for triiodo-phthalic acid, but nothing except 3-hydroxyphthalic could be isolated.

3-Hydroxyphthalic Acid.—One gram of the 3-hydroxyphthalic anhydride was dissolved in 2 cc. of boiling water. Colorless prisms were formed on cooling which melted at about 161–163° (corr.) (with evolution of gas) on rapid heating. The melting point varies with the manner of heating. On very slow heating, crystals of the anhydride were formed, which then melted at about 194° (corr.).

Subst. (I) 0.0778, (II) 0.0709; cc. 0.1 N NaOH, (I) 8.54, (II) 7.87.
Calc. for $C_8H_6O_4$: Molecular weight, 182.1. Found: (I) 182.2, (II) 180.2.

3-Hydroxyphthalic Anhydride Acetate.—One gram of 3-hydroxyphthalic anhydride (obtained from 3,6-diiodophthalic acid) was heated with 10 cc. of acetic anhydride for an hour, most of the solvent evaporating. 50 cc. of ligroin were added, and the solution boiled with boneblack. On further recrystallization from ligroin, using boneblack, 0.9 g. of colorless leaflets were obtained, melting at 113.5–115.5° corr. Titration of the acetate hydrolyzed it rapidly and completely.

Subst. (I) 0.0509, (II) 0.0964; cc. 0.1 N NaOH, (I) 7.37, (II) 13.99.
Calc. for $C_{10}H_6O_5$: Molecular weight, 206.1. Found: (I) 207.1, (II) 206.7.

3-Hydroxyphthalic Anhydride Benzoate.—Half a gram of 3-hydroxy-phthalic anhydride was dissolved in 5 cc. of benzoyl chloride, warmed for an hour and the product crystallized from boiling ligroin without first remov-ing the excess of benzoyl chloride. On recrystallization from the same solvent 0.6 g. of minute colorless crystals were obtained melting at 147.5–

[1] *Ber.*, 16, 1965 (1883).
[2] *J. Chem. Soc.*, 91, 111–112 (1907).
[3] *Ber.*, 19, 166 (1866); cf. Kenner and Mathews, *J. Chem. Soc.*, 105, 2478 (1914).

148° (corr.). The benzoate appears to crystallize also in colorless leaflets, but dimorphism was not definitely established.

This product hydrolyzed on titration even in the cold, but more slowly than the acetate. The hydrolysis was easily completed by boiling.

Subst. (I) 0.0661, (II) 0.0737; cc. 0.1 N NaOH, (I) 7.40, (II) 8.01.

Calc. for $C_{15}H_8O_5$: Molecular weight, 268.1. Found: (I) 268.1, (II) 276.2.

The second sample was first titrated in the cold but it was not found possible to effect complete solution without some hydrolysis. 6.46 cc. 0.1 N were required, representing a molecular weight of 228. The hydrolysis was then completed by adding more sodium hydroxide and boiling. The final result is recorded above.

3,6-Diiodophthalanil.—Eighty grams of 3,6-diiodophthalic anhydride dissolved in about a liter of boiling acetic acid were treated with 40 g. of aniline. After boiling a minute the solution was allowed to cool. The product, 82 g., an 86% yield, was twice recrystallized from xylene, having then a melting point of 233.5–234° (corr.) unchanged by another crystallization.

Subst. (I) 0.3402, (II) 0.3806; cc. 0.1 N AgNO$_3$, (I) 14.35, (II) 16.05.

Calc. for $C_{14}H_7O_2NI_2$: I, 53.44. Found: (I) 53.54, (II) 53.52.

3,6-diiodophthalanil crystallizes in colorless rectangular plates, 1 g. of which is dissolved by 7 cc. of boiling xylene.

On heating the anil in excess of aniline 20 hours at 140° a deep red color was produced but only unchanged anil could be isolated. The anilino derivative was not obtained.

4,5-Diiodophthalic Acid.—The acid obtained as previously described was purified by recrystallization from glacial acetic acid, in which it is quite soluble and from which it always separated in the form of colorless needles. These effloresce on exposure to air, probably losing acetic acid of crystallization. From acetic acid containing some water leaflets are often formed. The acid is slightly soluble in hot water from which it crystallizes in needles or leaflets. The leaflets are the stable form at room temperature but the needles require long standing in contact with water before conversion to leaflets is complete. A sample of the *leaflets* prepared in this way, melted at 221–222° (corr.) on rapid heating, giving off water and forming the anhydride. The sample was analyzed by titrating with sodium hydroxide to determine its molecular weight.

Subst. (I) 0.2029, (II) 0.1998; cc. 0.1 N NaOH, (I) 9.71, (II) 9.57.

Calc. for $C_8H_4O_4I_2$: Molecular weight, 417.9. Found: (I) 417.8, (II) 418.4.

4,5-Diiodophthalic acid both dissolves in acetic acid and crystallizes out on cooling much more rapidly than the 3,4-isomer. The acid is almost insoluble in boiling benzene and its mono-sodium salt is very slightly soluble in water. All of these facts were of assistance in separating the 4,5-acid from its concomitants.

4,5-Diiodophtbalic Anhydride.—4,5-Diiodophthalic acid obtained as described on page 229, was dehydrated with acetic anhydride, using acetic acid or benzene as solvent. It was obtained from either of these in poorly formed prisms which became nearly colorless after several recrystallizations and melted at 216.5–217° (corr.). It is fairly soluble in hot benzene, less so in acetic acid.

Subst. (I) 0.2759, (II) 0.4241; cc. 0.1 N AgNO₃ (I) 13.85, (II) 21.26.
Calc. for $C_8H_2O_3I_2$: I, 63.48. Found: (I) 63.71, (II) 63.62.

Hydrolysis of 4,5-Diiodophthalic Acid.—Twenty-five grams of 4,5-diiodophthalic anhydride, and 25 g. of sodium hydroxide were dissolved in 200 cc. of water and boiled in an atmosphere of natural gas for 18 hours, concentrating to about 50 cc.

The solution was strongly acidified with concentrated hydrochloric acid and thoroughly extracted with ether. The ether extract was crystallized from concentrated hydrochloric acid, yielding 10 g. of light brown product which melted at 137–47°. On recrystallization from dilute hydrochloric acid using boneblack, the melting point was raised to 148–9°. The product was a mixture of two substances, one of which was extracted by a liter of boiling xylene in several portions. The xylene extract was recrystallized from the same solvent, giving 1 g. of silvery leaflets with a slight brownish cast. They melted at 250.5–252.5° (corr.). The colors which ferric chloride gave with an aqueous solution of the substance were almost exactly the same as those obtained with protocatechuic acid although varying more with conditions. The product was therefore 4,5-dihydroxyphthalic anhydride, for which a melting point of 247–248°[1] is recorded, and with which ferric chloride gives the same colors[2] as with protocatechuic acid.

To demonstrate further the identity of the substance it was treated with ethyl alcohol containing hydrochloric acid. The resulting diethyl 4,5-dihydroxyphthalate crystallized from water in colorless blades melting at 148.5–150° (corr.) Rossin records 152°.[3]

The hydrolysis product from 4,5-diiodophthalic acid which was not dissolved by boiling xylene was recrystallized from water, yielding about 0.5 g. of slightly brownish crystals which did not contain halogen, and melted slowly with decomposition, beginning at about 280° (corr.). It gave a greenish blue with a little ferric chloride and a yellow-green with excess. It was probably 3,4,5-trihydroxyphthalic acid for which Senhofer and Brunner[4] give a melting point of "over 270°, with evolution of CO_2." These authors state that ferric chloride when very dilute gives a violet, when concentrated a greenish brown color.

[1] Freund, *Ann.*, **271**, 385 (1892).
[2] *Loc. cit.*
[3] *Monatshef. Chem.*, **12**, 493 (1891).
[4] *Ibid.*, **1**, 474 (1880).

4,5-Diiodophthalanil.—The use of 4,5-diiodophthalic acid for this preparation was attempted, since it happened that not much of the corresponding anhydride was at hand. The 4,5-acid was dissolved in acetic acid and acetic anhydride added. The solution was then treated with aniline, but the resulting crystals consisted of a mixture. On boiling in aniline, however, they gave off water and yielded nearly pure anil. This was recrystallized three times from xylene using boneblack, then having a melting point of 241.5–243° (corr.), unchanged by recrystallization from xylene and acetic acid. The reason for the last crystallization was a softening noticed at about 231° especially on rapid heating. This is not due to impurity, however, or solvent of crystallization but to the dimorphism, as explained below.

Subst. (I) 0.3344, (II) 0.4041; cc. 0.1 N AgNO₃, (I) 14.19, (II) 17.11.
Calc. for $C_{14}H_7O_2NI_2$: I, 53.44. Found: (I) 53.86, (II) 53.74.

Dimorphism.

4,5-Diiodophthalanil is soluble in about 8 parts of boiling xylene or 50 of boiling acetic acid. It crystallized from these solvents in pale yellow needles which melt as stated above, if the usual method of powdering the substance and heating it slowly is employed. If the unpowdered crystals, however, are heated fairly rapidly they melt about 10° lower, *i. e.*, at 231.5–233.0° (corr.). This is then the true melting point of the needles, that is, of the modification stable at temperatures below the boiling point of xylene. This form is not stable at its melting point, but especially when powdered changes slowly to the modification melting at 241.5–243° (corr.). This modification is not obtained, as might be expected, when a sample of the other form is melted and allowed to cool fairly rapidly. The formation of the needle modification under these conditions is due to the greater tendency toward supersaturation of the other form. By very slow cooling the melted anil was crystallized in pale yellow hexagonal plates. These showed no tendency to melt or change at 231°, but melted at the higher temperature. Attempts by the use of seeding to crystallize the anil from xylene and ethyl acetate in the form showing the higher melting point were unsuccessful. Only needles were obtained.

It is evident that 4,5-diiodophthalanil has a transition point somewhere between room temperature and 231°.

3,4,6-Triiodophthalic Anhydride.—The benzene extract[1] containing triiodophthalic anhydride was treated with acetic anhydride and concentrated. The product was recrystallized several times from benzene and acetic acid yielding bright yellow rhombic pyramids melting at 230–231° (corr.).

Subst. (I) 0.3442, (II) 0.4569; cc. 0.1 N AgNO₃, (I) 19.65, (II) 26.00.
Calc. for $C_8HO_3I_3$: I, 72.41. Found: (I) 72.46, (II) 72.22.

[1] Page 222.

3,4,6-Triiodophthalic anhydride is dissolved by about 5 parts of boiling benzene or 20 parts of boiling acetic acid. When it is dissolved in sodium hydroxide solution and precipitated carefully with an excess of hydrochloric acid minute needles are formed which are probably the triiodo-acid, but efforts to isolate this substance were unsuccessful due to the ease with which it loses water even in aqueous suspension. The mono-sodium salt is only slightly soluble in water but not quite so readily precipitated as that of 4,5-diiodophthalic acid.

Hydrolysis of 3,4,6-Triiodophthalic Acid.—Forty grams of 3,4,6-triiodophthalic anhydride with 80 g. of sodium hydroxide were dissolved in 700 cc. of water and boiled for $2^3/_4$ hours, concentrating to about 150 cc. The solution was acidified with a large excess of hydrochloric acid and extracted with ether. On concentration and cooling the extract gave about 2 g. of crystals which proved to be 3,6-dihydroxyphthalic acid. After recrystallization from acetone and then water, the product, which was partly colorless and partly a greenish brown, melted at about 216–218° (corr.), (rapid heating) giving off water and forming impure anhydride. Brunner[1] records a melting point of 219–220° and mentions the two colors. The colors given by ferric chloride with an aqueous solution of the acid agree with those observed by Brunner, $i. e.$, a blue-violet changing nearly to black with excess, but when dilute solutions are used excess of ferric chloride gives an amber color.

More of the 3,6-dihydroxyphthalic anhydride was obtained by adding concentrated hydrochloric acid and xylene to the concentrated ether extract mentioned above. The mixture was then boiled until all of the aqueous hydrochloric acid had distilled off. The hot xylene was filtered off and the process repeated with the residue until 1500 cc. of xylene solution were obtained which was then boiled with boneblack and concentrated to 200 cc., yielding 3 g. of crude 3,6-dihydroxyphthalic anhydride on cooling. This was purified by two recrystallizations from anhydrous ether, melting then at 234.5–236.5° (corr.) with very slight evolution of gas. Brunner gives 232–233°.

As an additional test of its identity a sample of the anhydride was warmed an hour with acetic anhydride. A large excess of hot ligroin was added which caused the diacetate to separate on cooling in colorless leaflets. Two recrystallizations from ligroin deposited each time small compact colorless prisms that apparently represented a polymorphic modification more stable at room temperature than the leaflets. The melting points of the crystals from each of the three crystallizations were practically the same, that of the final product being carefully determined as 155.5–156.5° (corr.). Brunner gives 156–156.5° (corr.).

In addition to 3,6-dihydroxyphthalic acid small amounts of other sub-

[1] *Monatshef. Chem.*, **34**, 924 (1913).

stances were found among the hydrolysis products of the triiodophthalic acid. Crystals of a substance containing halogen were obtained by concentrating the xylene mother liquor from which the dihydroxy anhydride had separated. A substance almost insoluble in xylene but soluble in ether was also found. It contained no halogen, gave no precipitate with lead acetate, practically no color with ferric chloride, gave the anthrachrysone test, and showed a melting point of about 230–235° (corr.). These properties agree with those recorded for 3,5-dihydroxybenzoic acid[1].

3,4,6-Triiodophthalanil.—Eighty grams of 3,4,6-triiodophthalic anhydride dissolved in two liters of boiling acetic acid were treated with 40 g. of aniline. The mixture was boiled about a minute longer and then allowed to cool. A yield of 82 grams, 89% of the theoretical, was obtained. This was recrystallized three times from xylene using boneblack. The product then had a melting point of 254.5–255.5° (corr.), unchanged by a recrystallization. The anil is soluble in about 18 parts of boiling xylene from which it crystallizes in light yellow microscopic needles.

> Subst. (I) 0.3524, (II) 0.3161; cc. 0.1 N AgNO$_3$, (I) 17.56, (II) 15.74.
> Calc. for $C_{14}H_6O_2NI_3$: I, 63.37. Found: (I) 63.24, (II) 63.20.

3,4-Dichloro-5,6-diiodophthalic Anhydride.—Fifty-four grams of 3,4-dichlorophthalic anhydride and sixty-four grams of iodine were dissolved in 250 g. of 50% fuming sulfuric acid and heated for 20 hours at 100°, 4 hours at 150°, and $1/2$-hour at 200°. The mixture was transferred to a porcelain dish and treated when cold with 500 cc. of water. Sodium sulfite was added to remove free iodine and the yellow crystalline anhydride then filtered off. The product was freed from sulfuric acid by digestion with water at 100°. The yield was 106 g., 90% of the theoretical. This was recrystallized twice from acetic acid using boneblack, after which recrystallization did not change its melting point of 229.5–230.5° (corr.). One gram of the anhydride dissolves in 9 cc. of acetic acid, from which it crystallizes in yellow prisms. The substance was analyzed for iodine and chlorine by heating with lime, titrating the soluble halides formed, and weighing the resulting silver halides.

> Subst. (I) 0.4101, (II) 0.2331; cc. 0.1 N AgNO$_3$, (I) 34.59, (II) 19.79; weight of AgCl + AgI, (I) 0.6538, (II) 0.3766.
> Calc. for $C_8O_3Cl_2I_2$: Cl, 15.13; I, 54.15. Found: Cl, (I) 14.98; (II) 14.65; I, (I) 53.47, (II) 55.31.

3,4-Dichloro-5,6-diiodophthalanil.—The anhydride dissolved in boiling acetic acid was treated with its own weight of aniline. After two minutes boiling the mixture was allowed to cool and then filtered. On recrystallization from xylene light yellow needles were obtained having a melting point of 242.5–243.5° (corr.), unchanged by recrystallization. One gram dissolves in about 9 cc. of boiling xylene.

[1] Beilstein, 1746.

Subst. (I) 0.4177, (II) 0.2475; cc. 0.1 N AgNO₃, (I) 30.85, (II) 18.33; weight of AgCl + AgI (I) 0.5774, (II) 0.3431.

Calc. for C₁₄H₅O₂NCl₂I₂: Cl, 13.04, I, 46.67. Found: Cl, (I) 13.65, (II) 13.68, I, (I) 44.92, (II) 45.08.

3,6-Dichloro-4,5-diiodophthalic Anhydride.—A solution of 217 g. of 3,6-dichlorophthalic anhydride and 254 g. of iodine in 1 kg. of 50% fuming sulfuric acid was heated to 100° for 20 hours. The temperature was gradually raised to 170° during the next 6 hours. At this point the mixture was poured out and allowed to cool. The crude anhydride was separated as described for the product from 3,4-dichloro anhydride. It weighed 453 g., representing a 97% yield, but was found to contain a considerable amount of tetraiodophthalic anhydride. This impurity was easily removed by extracting with boiling benzene, after conversion of the main product into the acid, and identified by a mixed melting point. This conversion was effected by digesting the mixture with water at 95° for about 10 hours. The tetraiodophthalic anhydride was not affected by this treatment but the 3,6-dichloro-4,5-diiodophthalic anhydride was slowly acted on by the hot water, giving colorless leaflets of the corresponding acid. After complete extraction with boiling benzene, the residue was reconverted into anhydride by recrystallization from acetic acid containing an excess of acetic anhydride. It formed yellow prisms melting at 258–258.5° (corr.).

Subst. (I) 0.2265, (II) 0.2705, cc. 0.1 N AgNO₃, (I) 19.45, (II) 23.17; weight of AgCl + AgI, (I) 0.3646, (II) 0.4357.

Calc. for C₈O₃Cl₂I₂: Cl, 15.13; I, 54.15. Found: Cl, (I) 15.77, (II) 15.52; I, (I) 52.57, (II) 53.25.

One gram of 3,6-dichloro-4,5-diiodophthalic anhydride dissolves in 20 cc. of boiling acetic acid, readily taking up water if any is present in the solvent. One gram dissolves in 3 cc. of boiling xylene from which it crystallizes in nearly colorless needles containing xylene of crystallization shown by their efflorescence when exposed to air.

3,6-Dichloro-4,5-diiodophthalanil.—This was prepared as described for 3,4-dichloro-4,5-diiodophthalanil. Light yellow needles were obtained melting at 232–232.5° (corr.).

Subst. (I) 0.2842, (II) 0.4332; cc. 0.1 N AgNO₃, (I) 20.95, (II) 31.90; weight of AgCl + AgI, (I) 0.3945, (II) 0.5995.

Calc. for C₁₄H₅O₂NCl₂I₂: Cl, 13.04; I, 46.67.   Found: Cl, (I) 13.29, (II) 13.38; I, (I) 46.00 (II) 45.55.

One gram of the anil dissolves in 6 cc. of boiling xylene or 40 cc. of boiling acetic acid.

The attempt was made to replace halogen in the anil by boiling in aniline for 2 hours. Only tarry products were obtained except a small amount of impure substance, evidently unchanged anil, melting at 211–217° (corr.).

4,5-Dichloro-3,6-diiodophthalic Anhydride. — The details of this

preparation were the same as given for the iodination of 3,4-dichloro-phthalic anhydride. The yield was 110 g., 93% theoretical. After three recrystallizations from acetic acid using boneblack, the product melted at 232.5–233.5° (corr.). One gram dissolves in 8 cc. of boiling acetic acid, separating on cooling in the form of large jagged yellow blades.

Subst. (I) 0.3063, (II) 0.2372; cc. 0.1 N AgNO$_3$, (I) 25.80, (II) 20.13; weight of AgCl + AgI, (I) 0.4863, (II) 0.3841.

Calc. for C$_8$O$_3$Cl$_2$I$_2$: Cl, 15.13; I, 54.15. Found: Cl, (I) 15.13, (II) 14.48; I, (I) 52.78, (II) 55.93.

4,5-Dichloro-3,6-diiodophthalanil.—This substance was made like its above mentioned isomers, and after two recrystallizations from xylene and one from acetic acid melted at 282.5–284° (corr.). One gram of the anil dissolves in 18 cc. of boiling xylene or 140 cc. of boiling acetic acid. It crystallizes from these solvents in very pale yellow needles.

Subst. (I) 0.2573, (II) 0.1615; cc. 0.1 N AgNO$_3$, (I) 18.79, (II) 12.03; weight of AgCl + AgI, (I) 0.3529, (II) 0.2250.

Calc. for C$_{14}$H$_5$O$_2$NCl$_2$I$_2$: Cl, 13.04, I, 46.67. Found: Cl, (I) 13.30, (II) 13.80; I, (I) 45.09, (II) 45.20.

3,6-Dianilino-4,5-dichlorophthalanil.—Twenty grams of 4,5-dichloro-3,6-diiodophthalanil were heated with 100 g. of aniline for 24 hours at 130°. The temperature was then kept at about 175° for four hours. A very small yield of orange-red crystals was obtained by the treatment described in the case of the isomeric product from tetrachlorophthalanil[1].

The product melted at 181.5–185° (corr.). Its isomer obtained from tetra-chlorophthalanil melted at 182.5–183.5° (corr.), and a mixture of the two at about 156–173° (corr.). These melting points show that the sample was impure but entirely distinct from the previously obtained product. Unfortunately the amount in hand was insufficient for further purification, but qualitative tests showed that the substance contained no iodine, and a lime combustion showed that it had approximately the composition of a dianilino dichlorophthalanil:

Subst. (I) 0.1088; cc. 0.1 N AgNO$_3$, 5.39.

Calc. for C$_{26}$H$_{17}$O$_2$N$_3$Cl$_2$: Cl, 14.96. Found: 17.57.

Summary.

(I) The partial iodination of phthalic anhydride has been effected, an easy method of separating the four products worked out, and their structures established.

(II) The iodination of three dichlorophthalic acids has been effected.

(III) Silver salts in pyridine solution have been found to act readily on certain iodinated phthalic acids, forming 3-hydroxy-6-iodophthalic acid from the corresponding diiodo derivative.

(IV) Sodium hydroxide solutions hydrolyze the iodinated phthalic acids, often yielding at the same time both oxidation and reduction prod-

[1] This Journal, **40**, 198 (1918).

ucts.   In this way a number of hydroxyl derivatives have been prepared by new methods, in particular 3-hydroxyphthalic acid.   The anhydride of this substance has been obtained in much purer condition than samples previously recorded, and several of its derivatives prepared.

(V)   The anils of the new iodinated phthalic acids have been prepared and one of them found to exhibit dimorphism.

(VI) Iodine in the nucleus of phthalic acid does not react smoothly with aniline, but a small yield of 3,6-dianilino-4,5-dichlorophthalanil has been obtained from the corresponding iodinated derivative.

(VII) A spectroscopic study of the new iodinated phthalic acids will be reported in a later paper.

PITTSBURGH, PA.

PHTHALIC ACID DERIVATIVES CONSTITUTION AND COLOR. VIII.[1] TETRAIODOFLUORESCEIN AND SOME OF ITS DERIVATIVES.

BY DAVID S. PRATT AND ARTHUR B. COLEMAN.

A large and important class of dyes resulting from introducing chlorine into the phthalic acid residue of fluorescein with or without halogens in the resorcin portions of the molecule is recognized at the present time.   Among these might be mentioned eosin, erythrosin, phloxine and a variety of their chorine derivatives.   Some are especially valuable as stains and indicators, others for dyeing silks delicate shades of red and pink.

Tetraiodofluorescein, or fluorescein with four atoms of iodine substituted in the phthalic anhydride molecule, had never been prepared.   The substitution of iodine in such a colored substance, especially iodine in large amount, might be expected to show some interesting results.   As is well known the effect of substituting halogen for hydrogen in many compounds especially dyes, is frequently to increase the period of molecular vibration, or, in other words, to shift the absorption of light toward the longer wave lengths.   This modifies the shade of color and might result in producing desirable new dyestuffs.

Iodine is an unsaturated atom possessing considerable residual affinity and chemical activity in excess of that shown by other halogens.   This activity should result in various proximity effects modifying the tendency to produce a lactone ring and altering the equilibrium between benzenoid and quinoid condition depending upon this ring.   It was also with the view of obtaining information relating color and chemical constitution that we undertook the study of these derivatives.

Fluorescein itself and its related compounds exist in either of two isomeric