[Contribution from the Frank C. Whitmore Laboratory of the Pennsylvania
State College]

THE PARTIAL, DIRECT IODINATION OF PHTHALIC ANHYDRIDE AND PHTHALIMIDE[1]

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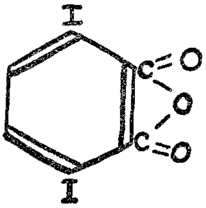
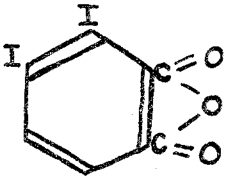
In the course of several investigations carried out in this laboratory, it became desirable to obtain fairly large quantities of pure diiodophthalic anhydrides. The procedure for the iodination of phthalic anhydride is due to Pratt and Perkins (1). The original investigators carried out the reaction in two different ways. One method involved heating at a high temperature for a short period of time. The other involved heating at a lower temperature for a longer period. Higgins and Suter (2) found the low-temperature method to be the more satisfactory of the two. Therefore, only the low temperature (75–80°) method was utilized during the course of this investigation. In the partial, direct iodination of phthalic anhydride by the existing procedure, the following products are obtained:



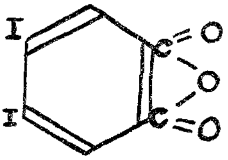
I

3,6-Diiodophthalic anhydride



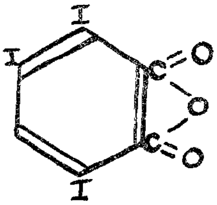
II

3,4-Diiodophthalic anhydride



III

4,5-Diiodophthalic anhydride



IV

3,4,6-Triiodophthalic anhydride

Compounds I and II are obtained in considerably larger amounts than III and IV. The original authors also reported obtaining small amounts of 4-iodophthalic anhydride. No attempt was made, however, to isolate this product from the phthalic anhydride iodination during the course of this investigation.

In view of the fact that nitration of phthalimide yields chiefly 4-nitrophthalimide (3) while nitration of phthalic anhydride gives a mixture of 3- and 4-nitrophthalic acids (4), the partial, direct iodination of phthalimide might be expected to be a better potential source of III. Such has been shown to be the case. The relative yield of III with respect to the other products of iodination has been

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increased from 11% in the case of the iodination of phthalic anhydride to 55% in the case of phthalimide.

Inasmuch as the original separation of the iodinated phthalic acids and anhydrides was based on fractional precipitation with hydrogen ion, the separation by carefully bringing the solution to a lower *p*H was investigated. A pure sample of each of the compounds I to IV, inclusive, and also a sample of tetraiodophthalic anhydride, were tested separately by dissolving in 20% sodium hydroxide solution, neutralizing, heating to 80°, and then gradually adjusting the solution to a lower *p*H. Figure 1 illustrates the results of this preliminary investigation.

From these results, it appeared that a separation of the various iodinated products by gradually adjusting the solution to lower and lower *p*H values should be comparatively easy. An attempted separation of a mixture of each of the four products, however, yielded a series of impure fractions. Figure 2 shows the percentage of the total amount precipitated at each *p*H value.

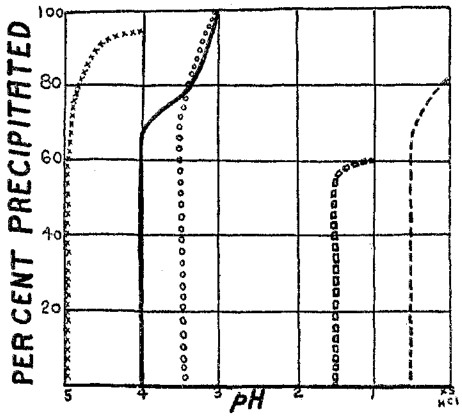

FIGURE 1. FRACTIONAL PRECIPITATION OF IODINATED PHTHALIC ANHYDRIDES WITH ACID. 4,5-Diiodophthalic anhydride, xxxx; 3,4,5,6-tetraiodophthalic anhydride, ————; 3,4,6-triiodophthalic anhydride, ○ ○ ○; 3,4-diiodophthalic anhydride, □ □ □; 3,6-diiodophthalic anhydride, - - -.

A further modification was suggested by the fact that I and IV are formed from the corresponding acids on digestion with excess hydrochloric acid, while II and III remain as the free acids. Thus, extraction of the crude dried product after such treatment yields I and IV in the benzene extract and the acids of II and III in the residue. After evaporation of the benzene, the two fractions are treated separately with cold 20% sodium hydroxide; and separation is effected by gradually bringing the solution to a lower *p*H. The *p*H values for complete precipitation are as follows: III and IV, 3.5; and II, 1.0. Precipitation of I is accomplished only after digestion with excess hydrochloric acid for an extended period of time. Since I and IV are found in one fraction and II and III in the other, separation is considerably easier than by the original method.

The iodination of phthalimide was carried out in a similar manner. In order to render the iodinated mixture more soluble in dilute sodium hydroxide solution, the iodinated phthalimides were hydrolyzed by treatment with concentrated sulfuric acid for a period of three hours at 130°. The mixture was stirred continuously throughout this period. Although the phthalimides should be converted directly to the disodium salts of the phthalic acids by digestion with more concentrated alkali, the increased concentration of sodium hydroxide was avoided in order to prevent loss of iodine. The products of hydrolysis were treated in the manner described in the iodination of phthalic anhydride. In this case, however, some 4-iodophthalic acid was obtained by concentration of the filtrates and recrystallization from water.

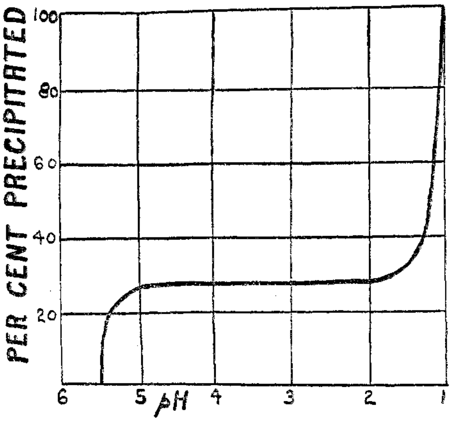

FIGURE 2. ATTEMPTED FRACTIONAL PRECIPITATION OF A MIXTURE OF IODINATED PHTHALIC ANHYDRIDES, COMPOUNDS I–IV.

TABLE I

PARTIAL, DIRECT IODINATION OF PHTHALIC ANHYDRIDE AND PHTHALIMIDE

IODINATED DERIVATIVE	FROM PHTHALIC ANHYDRIDE (5 moles), G.	RELATIVE PER CENT	FROM PHTHALIMIDE (4 moles), G.	RELATIVE PER CENT
Impure 4-Iodophthalic acid	None	—	100	13.3
II	338	35.0	130	17.0
I	375	38.7	70	9.1
III	109	11.3	420	55.0
IV	145	15.0	45	5.7

Table I summarizes the results of these two reactions.

EXPERIMENTAL[4]

The partial, direct iodination of phthalic anhydride. A mixture of 780 g. (5.2 moles) of *o*-phthalic anhydride, 1270 g. (5.0 moles) of iodine, and 2400 g. of 50% oleum was heated

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[4] All melting points are uncorrected.

in a 5-liter round-bottomed flask for six days at 70 to 80°. The temperature was controlled with a Glas-Col mantle and a Variac. At the end of this heating period, the reaction mixture was permitted to cool to room temperature. It was then poured into a large evaporating dish and exposed to the air overnight. Approximately 2500 g. of crushed ice was added. After the ice had melted and the mixture had been thoroughly stirred, the precipitated iodinated phthalic anhydrides were removed by filtration. After washing with sodium sulfite solution to remove unreacted iodine, a yellow solid remained.

The solid residue was treated with cold 20% sodium hydroxide. Although the solubility is limited in cold alkali, heat had to be avoided to prevent loss of iodine from the product. The solution was brought to *p*H 6 to 7 with concentrated hydrochloric acid, warmed, filtered to remove insoluble impurities, and gradually brought to *p*H 0.5. Digestion with excess hydrochloric acid for 48 hours on the steam-bath converted I and IV to the anhydrides, leaving II and III unaffected. The mixture was stirred vigorously during this period.

The mixture was filtered and the precipitate thoroughly dried. Extraction with benzene dissolved the anhydrides, but not the acids. The benzene-insoluble fraction, Fraction A, was redissolved in cold 20% sodium hydroxide; and the solution was lowered to *p*H 3.5 by the gradual addition of glacial acetic acid. At this point, substantially all of compound III had been precipitated as the monosodium salt. This was removed and converted to the acid by digestion with excess hydrochloric acid; total yield, 120 g. Conversion to the anhydride with benzene and acetic anhydride yielded 109 g. of pure III, m.p. 215–216°.

The filtrate from the precipitation at *p*H 3.5 was then brought to *p*H 1.0 in increments of 0.5 *p*H units. Only slight amounts of impure products were obtained between *p*H 3.5 and *p*H 1.0. These were discarded. At *p*H 1.0, the precipitation of II as the monosodium salt was virtually complete. Conversion to the acid gave 375 g. of product, m.p. 210–211°. Treatment with benzene and acetic anhydride left 338 g. of pure II, m.p. 195–196°.

The benzene extract was evaporated to dryness. The residue, Fraction B, was treated in the same manner as Fraction A. However, this time IV precipitated as the monosodium salt at *p*H 3.5. This was converted directly to the anhydride by digestion with excess hydrochloric acid. A total of 145 g. of IV, m.p. 220–224°, was obtained. Compound I precipitated as such after prolonged heating with excess hydrochloric acid. After recrystallization from benzene, 375 g. of I (m.p. 233–236°) resulted. If the yields are calculated on the basis of the entire amount of available material going either to the diiodo- or triiodo-phthalic anhydrides, the percentage yields of these products are: I, 18.8; II, 16.8; III, 5.7; and IV, 5.7.

The partial, direct iodination of phthalimide. A mixture of 588 g. (4.0 moles) of phthalimide, 1016 g. (4.0 moles) of iodine, and 2000 g. of 50% oleum was heated for six days at 90 to 100°. The temperature was controlled as before. The procedure was identical with that given above, except that it was necessary to heat the crude product for three hours with concentrated sulfuric acid at 130° in order to convert the iodinated phthalimides to the corresponding iodinated phthalic anhydrides and/or acids before carrying out the separation. In addition to compounds I–IV, 100 g. of impure 4-iodophthalic acid was obtained by concentration of the filtrates and recrystallization from water. By treatment with benzene and acetic anhydride 45 g. of 4-iodophthalic anhydride, m.p. 124–126°, was obtained.

SUMMARY

1. The partial, direct iodination of phthalic anhydride and of phthalimide have been carried out.

2. The ease of separation and purification of the reaction products has been greatly improved by careful control of the *p*H, after first separating the anhydrides and the acids by extraction of the former from the latter with benzene.

3. Iodination of phthalimide is superior to the iodination of phthalic anhydride for the production of 4,5-diiodophthalic anhydride.

4. Iodination of phthalic anhydride is superior to the iodination of phthalimide for the production of 3,4- or 3,6-diiodophthalic anhydride.

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