

## THE OXIDATION OF IODINATED PHTHALIC AND BENZOIC ACIDS

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In the course of an investigation concerning the mobility of iodine atoms in tetraiodophthalic and tetraiodo-*o*-sulfobenzoic anhydrides, it was discovered that the action of concentrated nitric acid on a suspension of these derivatives in concentrated sulfuric acid produced, not the expected replacement of one or more of the substituents by a nitro group, but an oxidation of the iodine atoms. The resulting compounds were extremely explosive and quantitative analysis showed that, with all the former constituents present, four active oxygen atoms had been added to each molecule of the starting material. The anhydrides were not affected by digestion with concentrated nitric acid, while boiling merely caused a slow destructive oxidation. It was subsequently noted that the same tetraoxy derivatives were obtained, although less conveniently, by treating the anhydrides with a solution of potassium dichromate in dilute sulfuric acid. Furthermore, tetraiodophthalic acid and dimethyl tetraiodophthalate yielded the same oxidation product as the anhydride when subjected to the nitric-sulfuric acid treatment.

It seemed of interest to ascertain where the active oxygen atoms in the oxidation products are located. Their distribution might be such as to affect all four iodine atoms, thus producing a tetraiodoso derivative, or, by involving only two iodine atoms, to yield a diiodoxy derivative. In other words, the new compounds may contain either four—IO groups or two iodine atoms and two—IO<sub>2</sub> groups.

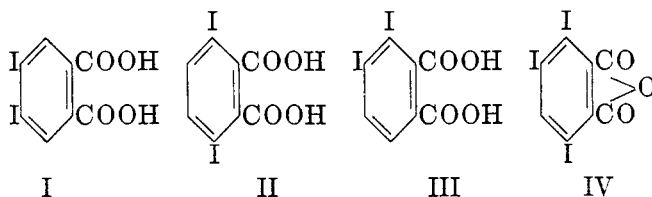
In the investigation presented here, an attempt has been made to solve this problem one way or the other, and it may be stated in advance that our evidence appears to be most favorably interpreted, although by no means conclusively, by assuming the formation of 4,5-diiodo-3,6-diiodoxy derivatives. In order to reach this conclusion it was necessary to extend the work to include a comparative study of the similar oxidation of a number of lower halogenated phthalic and benzoic acids. Although the authors realize that a number of questions remain unanswered, the work is being published in its present form as other activities require their attention for the time being.

In favor of the view that the oxygen atoms are not evenly distributed over the four iodine atoms is the finding that 4,5-diiodophthalic acid (I) and 4-iodophthalic acid are not subject to oxidation under the experimental conditions. From this it may be inferred that in the tetraiodo derivatives the iodine atoms in positions 3 and 6 were oxidized to iodoxy groups while those in positions 4 and 5 had remained unaltered. Our observation that 3,6-dichloro-4,5-diiodophthalic anhydride (1) also failed to take up oxygen, lent added support to this concept.

Apparently contradictory to these conclusions were our observations that 3,6-diiodophthalic acid (II), instead of taking up four active oxygen atoms, added two when subjected to the same oxidation method, 3-iodophthalic acid one in-

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stead of two, while 3,4-diiodophthalic acid (III) alone took up two active oxygen atoms as expected. 4-Iodophthalic acid proved to be unsuitable for this investigation, since it was nitrated to a considerable extent and thereby confused the issue.

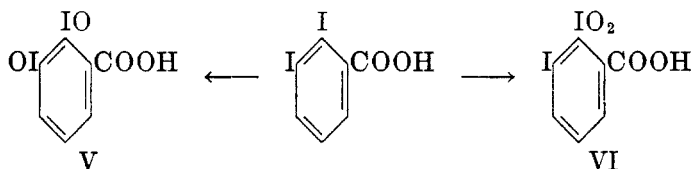


Triiodophthalic anhydride was also included in the investigation. Of the two possible isomers only the 3,4,6-triiodo derivative (IV) is known (1). It proved to be difficult to obtain a sufficient quantity of pure material for experimental purposes. The oxidation of our samples [m.p. 217–225° (cor.)] invariably yielded two substances, the active oxygen contents of which corresponded to triiodophthalic acids which had taken up two and three oxygen atoms per molecule. We therefore concluded that our sample of anhydride consisted of a mixture of 3,4,6- and the unknown 3,4,5-triiodophthalic anhydride, present in the ratio of about 3:1. These anhydrides were actually isolated by reducing the oxidation products and crystallizing the acids so obtained from acetic anhydride. The main fraction [m.p. 217–224° (cor.)] took up three oxygen atoms and corresponded to the 3,4,6-triiodo anhydride, although Pratt and Perkins (1) give a higher melting point. The second fraction, (m.p. 227–229°) obtained from the more soluble oxidation product, took up two oxygen atoms and represented the 3,4,5-triiodo isomer.

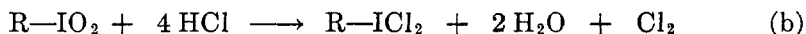
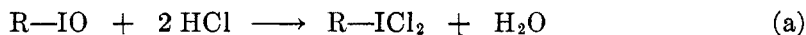
The investigation was then extended to a number of iodobenzoic acids. Previously, Meyer and Wachter (2) treated the three isomeric monoiodobenzoic acids with boiling concentrated nitric acid and found that only the iodine atom situated *ortho* in the carboxyl group could thus be oxidized to form an iodoso group, while the iodine in the *meta* and *para* isomers remained unchanged. The same results were noted with our nitric-sulfuric acid oxidation, and in addition it was found that 2,3-diiodobenzoic acid, like III, took up two active oxygen atoms. The oxidation of 3-chloro-2-iodo-, 3-bromo-2-iodo-, and 2-bromo-3-iodobenzoic acids, prepared for the purpose, yielded resinous products with liberation of iodine in some cases, and were therefore unsuitable for this study.

The general procedure for determining the active oxygen content of the oxidation products consisted of reducing a sample in aqueous sodium iodide slightly acidified with acetic acid and titrating the liberated iodine with sodium thiosulfate using starch as indicator. It is worthy of note that, when titrating the tetraoxy derivative of tetraiodophthalic anhydride without the presence of acetic acid, only an average of 2.5% active oxygen (corresponding approximately to the titration of one active oxygen atom) was found against a theoretical value of 8.72%. A similar observation was made by Willgerodt (3), and it may be stated that the phenomenon is characteristic of iodoso as well as iodoxy derivatives.

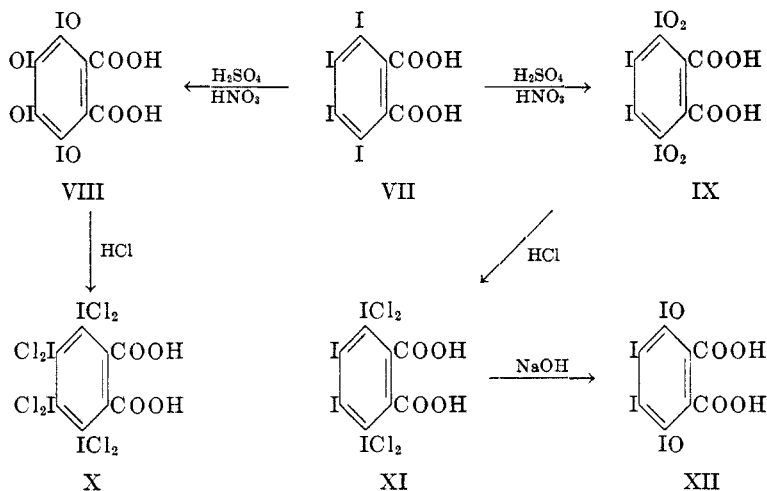
The experimental results obtained by us with the iodinated phthalic and benzoic acids were in good agreement but still left the phenomenon subject to dual interpretation. For example, oxidized 2,3-diiodobenzoic acid could be either a diiodoso derivative (V) or a 3-iodo-2-iodoxy derivative (VI).



It was expected that the problem could definitely be solved with the aid of two known reactions. According to Willgerodt (3,4), hydrochloric acid reacts with an iodoso derivative quantitatively according to equation (a), and with an iodoxy derivative, also quantitatively, according to equation (b),



Applied to the oxidation product of tetraiodophthalic anhydride or acid (VII), treatment with hydrochloric acid would produce an octachloro derivative (X) from the tetraiodoso derivative (VIII), and a tetrachloro derivative (XI) from the diiodoxy derivative (IX).



The spontaneous evolution of chlorine, when hydrochloric acid was added to an ice-cold aqueous suspension of the oxidation product, seemed to decide in favor of formula IX, especially since formation of this tetrachloro derivative (XI) was actually confirmed by analytical data. XI was obtained as a light tan substance, formed in a strongly exothermic reaction. It should be mentioned here that it is dangerous to add hydrochloric acid to the dry tetraoxy derivative. Compound XI is difficult to isolate owing to the fact that it loses chlorine readily to regen-

erate the bright yellow tetraiodophthalic acid. This decomposition takes place within a few hours on standing in the medium in which it was formed and frequently, without apparent reason, in a vacuum desiccator over calcium chloride.

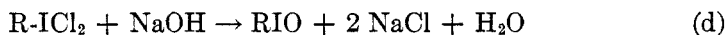
An attempt was made to prepare the tetrachloro derivative (XI) more conveniently by pouring a cold solution of the tetraoxy compound in nitric-sulfuric acid into ice-cold glacial acetic acid saturated with hydrogen chloride. Although chlorine was evolved immediately no spontaneous precipitation occurred, but pure tetraiodophthalic acid crystallized in the course of 12 hours.

The determination of chlorine in compound XI was based on a titration with sodium thiosulfate of the iodine liberated from an acidified solution of potassium iodide according to equation (c).



By this method the average per cent chlorine found was 19.24 compared with a theoretical value of 17.47. On the other hand, a direct determination as silver chloride indicated 16.82% chlorine.

It was anticipated that the decomposition of XI with dilute aqueous alkali would take place with formation of an iodoso derivative (4) [equation (d)],



and that the hypothetical diiodoso derivative (XII) thus formed could be titrated with potassium iodide and sodium thiosulfate. However, taking the conversion factor of 0.8646 into account for the intermediate change of compound XI into XII, the average active oxygen content in the latter was found to be only 2.03, compared with the calculated value of 4.57, probably indicating a more involved decomposition (5).

Masson, Race, and Pounder (6) reported that iodosobenzene may be distinguished from iodoxybenzene by the fact that the former can be titrated quantitatively with sodium thiosulfate by virtue of the iodine liberated from sodium iodide in a saturated borax solution, while iodoxybenzene does not liberate any iodine under these conditions. When applying this test to the tetraoxy derivative to which we have tentatively assigned formula IX, it was noted that iodine was actually freed but not to the full amount (6.9% active oxygen as compared with the theoretical value of 8.7%). We cannot offer a satisfactory explanation for this discrepancy unless it be assumed that the oxidation product really possesses formula VIII, and that, even at low temperatures, a partial conversion into the diiodoxy derivative IX had occurred by intramolecular rearrangement in a manner analogous to the change of simple iodoso compounds into a molar mixture of iodo and iodoxy derivatives under more vigorous conditions (3):



However this hypothesis would necessitate the additional postulate that the four chlorine atoms in the  $\text{-ICl}_2$  groups in positions 4 and 5 (X) are so loosely bound that they are expelled spontaneously under the experimental conditions. Although this view cannot be entirely ignored owing to lack of evidence to the

contrary, it may be pointed out that the difference in behavior of iodoso- and iodoxybenzene in borax solution may not be a general characteristic of the group, and may not hold for acidic derivatives as unstable as the one under discussion; the importance of *pH* will be dealt with in a later paragraph.

In this connection it may be mentioned that the titrations in saturated aqueous borax were carried out with samples of the freshly prepared tetraoxy derivative. Unfortunately, no old preparations were at this time available to ascertain whether under the same conditions the titration result would indicate a shift according to the equation (e).

The spontaneous evolution of chlorine by the action of hydrochloric acid, also on freshly prepared samples of tetraoxy derivative, even under carefully controlled conditions, may either indicate a spontaneous decomposition of compound X or be due to the oxidizing effect of compound IX. Though the reaction cannot decide definitely between the formulas VIII and IX, the authors lean somewhat toward the latter in view of the evidence presented.

It has thus been shown that in the oxidation of iodinated phthalic and benzoic acids with nitric-sulfuric acid an iodine atom between a carboxyl group and a free position is converted into an iodoso group, while iodine atoms *meta* to a carboxyl group and adjacent to two free positions are not susceptible to oxidation. If an iodine atom next to a carboxyl group has another iodine atom in the second adjacent position, our experimental evidence tends to indicate that the first iodine atom is subject to renewed activation and is oxidized to an iodoxy group. However, it should be stated that to date we have no definite proof against the opposite and perhaps less probable contention that the second iodine atom is also converted into an iodoso group. In either case these rules of oxidation completely reconcile the apparently contradictory observations referred to at the beginning of this paper. In view of the remaining element of uncertainty we prefer at present to designate the oxidation products of tetraiodophthalic and tetraiodo-*o*-sulfobenzoic anhydride as tetraoxy derivatives rather than specify iodoxy or iodoso groups.

There still remains to be discussed the fate of the anhydride ring during the oxidation of tetraiodophthalic and tetraiodo-*o*-sulfobenzoic anhydrides. In the latter case a free sulfonic acid group was suggested by the fact that the compound was spontaneously soluble in dilute alkali, apparently without decomposition. However, oxidized tetraiodophthalic anhydride behaves differently. If highly concentrated alkali was added to the oxidation product, previously thoroughly moistened in order to prevent explosion, a rather insoluble sodium salt precipitated. It dissolved upon dilution with water to form a yellow solution, a phenomenon accompanied by destructive changes made noticeable by the distinct odor of iodoform. In concentrated alkali this sodium salt seemed to be stable. It was also formed if dilute alkali was added to an aqueous suspension of the tetraoxy derivative; the suspended particles first became granular, then gradually dissolved. Acidification with dilute sulfuric acid while cooling in ice failed to regenerate any of the starting material. At *pH* 9.5 the solution turned amber and, without liberating iodine, dark brown at *pH* 6.3. Only after the addition of a

large excess of acid was an amorphous chocolate-brown substance precipitated, containing about 76% iodine. It was soluble in aqueous sodium hydroxide, sodium bicarbonate and sodium acetate, also in alcohol and ether, but was not investigated further.

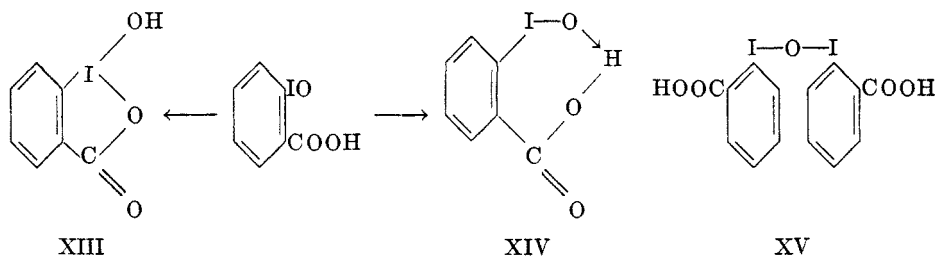
Although the active oxygen values of oxidized tetraiodophthalic anhydride agree better for the acid than for the anhydride structure, the assumption that in the oxidation process the anhydride ring is opened rests mainly on circumstantial evidence; the fact that the same product is obtained from tetraiodophthalic acid and its dimethyl ester, the gradual solution of the anhydride in the medium during oxidation, the spontaneous formation of an alkali salt and, above all, the ready solution in reducing agents such as potassium iodide with formation of tetraiodophthalic acid under conditions sufficiently mild to exclude the possibility of the hydration of a stable anhydride ring.

Tetraoxytetraiodo-phthalic and *o*-sulfobenzoic acids are yellow, very explosive substances, and, being sensitive toward friction and percussion, as well as heat, should be handled with the greatest care. They are soluble in the nitric-sulfuric acid mixture in which they are formed, precipitate quantitatively if the solution is poured on ice and are harmless if thoroughly wet. A solution of the phthalic acid derivative in the concentrated acid mixture may be heated at 130° without decomposition, but at 160–170° it gives off iodine and is gradually destroyed. The compounds are not affected by light, water or alcohols, but in some dry samples a slow loss of oxygen was noted in the course of time, presumably under the catalytic influence of traces of impurities. For example, a sample of the tetraoxy derivative IX, analyzing for 8.69% active oxygen, had 8.31% left after about four months. On the other hand, other samples have completely preserved their active oxygen content after a year under propyl alcohol or carbon tetrachloride or in a desiccator.

Tetraoxytetraiodophthalic acid shows a strong tendency to form a colloidal suspension in water, but not in acetic or sulfuric acids. It is very sensitive toward reducing agents, regenerating tetraiodophthalic acid under the influence of dilute solutions of sulfur dioxide, sodium iodide, sodium thiosulfate or sodium bisulfite at room temperature. The compound possesses very weak acid properties as evidenced by its insolubility in aqueous sodium bicarbonate and ammonia. A sample suspended in 7% sodium bicarbonate had not dissolved completely after standing for eight months at room temperature. The undissolved portion still contained the full amount of active oxygen. That the dissolved fraction had undergone some destructive decomposition was indicated by the crystals of iodoform which had sublimed into the neck of the flask.

The explosive's insolubility in ammonia is difficult to explain. It is interesting to note that Hartmann and Meyer (7) reported *o*-iodoxybenzoic acid to be considerably stronger than *o*-iodosobenzoic acid and that only the latter regenerates the free acid if an ammoniacal solution is evaporated to dryness. This may indicate that iodoso compounds form a chelate structure whereas the corresponding iodoxy compounds cannot do so. In order to interpret the susceptibility to oxidation of *o*-iodo atoms in iodobenzoic acids, as compared with those in other posi-

tions, Meyer and Wachter (2) advanced the view, supported by Lütjens (8), that a five-membered ring may be formed between the iodoso and the adjacent carboxyl group (XIII). While this hypothesis cannot be upheld in the light of more recent knowledge, its more modern equivalent, chelation, seems unlikely as it would involve the formation of a seven-membered ring (XIV). Chelation seems even less probable in *o*-iodoxybenzoic acid, as steric hindrance would prevent the required coplanar configuration of the molecule and this condition would be aggravated by additional iodine atoms (9). The weak acid properties of the carboxyl groups in our tetraoxy compound are undoubtedly at least partially due to the cumulative effect of the massed ring substitution.



To test the possibility that the varying extent of oxidation of the iodine atoms in the isomeric iodobenzoic acids is in some way associated with an adjacent free carboxyl group, dimethyl tetraiodophthalate was prepared and oxidized. Unfortunately, oxidation was accompanied by complete saponification of the ester to give tetraoxytetraiodophthalic acid.

The part which acid plays in the titration for active oxygen is not yet clear (10). The fact that *o*-iodosobenzoic acid gives up half of its active oxygen when no acid is present could be explained by complex formation between a mole of *o*-iodosobenzoic acid as it is produced with a mole of iodoso compound to yield XV. If this explanation were correct, then neutral titration in the presence of excess *o*-iodosobenzoic acid should result in practically no liberation of iodine. Instead of this, all the active oxygen was liberated, just as if acetic acid had been added, indicating that it may be merely a matter of *pH* and that iodobenzoic acid was strong enough to replace the acetic acid usually present. If this is the correct explanation it must also explain why only half the active oxygen is liberated from 2-iodosobenzoic acid while from the analogous iodosophthalic acid all the active oxygen is removed in the absence of acid. While *o*-iodosobenzoic acid is a very weak acid, the iodosophthalic acid has its second carboxyl group free, which may make the molecule acid enough to liberate the active oxygen from itself. When samples of our tetraoxy compound were titrated without addition of acetic acid, one oxygen was removed, and if the titration was then completed after addition of acetic acid the total iodine liberated from the combined titrations was always somewhat less than if the acid had been added at the beginning.

Our hope that a clue in the structure problem might come from these differences in active oxygen titration with and without acid disappeared when the following confusing facts were added to those already encountered. 2,3-Diiodobenzoic acid

can be looked upon as tetraiodophthalic acid which has been bisected by a horizontal line through its center; the oxidized compound would then be expected to act like half an oxidized tetraiodophthalic acid molecule. It was found that two active oxygens may be titrated with, and only one (*i.e.*, half of the total) without acid; on the other hand, in the case of tetraoxytetraiodophthalic acid, one (*i.e.*, a quarter of the total) instead of the two active oxygens predicted by this analogy can be titrated without acid. It is interesting to note that it was found that iodoxybenzoic acid titrated for two active oxygens in the presence of acid but only half an oxygen (*i.e.*, a quarter of the whole) in its absence. Just what the removal of half an oxygen could mean is difficult to imagine.

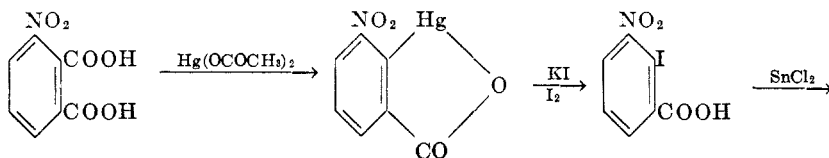
Finally, a few words should also be said about the preparation of the starting materials. Tetraiodophthalic anhydride was prepared according to the original method of Juvalta (11), by iodinating phthalic anhydride in fuming sulfuric acid of high sulfur trioxide content. The process has frequently been described in the literature. For example, Pratt and Shupp (12), using a 50% fuming acid reported an almost quantitative yield. Contrary to our experience, Perkins and Quimba (13) stated that a 60% oleum is essential for insuring a satisfactory reaction, but we also noted excellent results with acids of low sulfur trioxide content. For example, a 90% yield was obtained with a fuming acid containing only 7% sulfur trioxide. We further noted that the reaction also takes place, although somewhat less conveniently, with 100% sulfuric acid. Tetraiodo-*o*-sulfobenzoic anhydride was prepared by the same method (14).

Attempts to prepare 4,5-dibromo-3,6-diiodophthalic anhydride by iodination of the corresponding 4,5-dibromo compound resulted in the formation of a tribromiodophthalic anhydride instead. We were unable to isolate any 4,5-dichlorophthalic anhydride for iodination purposes, but 3,6-dichlorophthalic anhydride was successfully converted to 4,5-diiodo-3,6-dichlorophthalic anhydride.

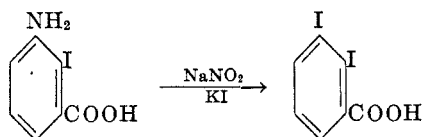
3,4,6-Triiodo-, 3,4-, and 3,6-diiodo-phthalic acids were prepared according to Pratt and Perkins (1), and are by-products of the incomplete iodination of phthalic anhydride in fuming sulfuric acid. The compounds are difficult to obtain pure and the recrystallizations involve a considerable loss of material.

The 3- and 4-iodophthalic acids could not be synthesized by reported procedures (see Experimental), but were prepared from the corresponding dimethylnitrophthalates by catalytic reduction to amino esters, replacement of the amino group by iodine *via* the Sandmeyer reaction, and subsequent saponification of the esters.

The three monoiodobenzoic acids were prepared from the corresponding amino acids by known procedures, but 2,3-diiodobenzoic acid is a new compound, synthesized from 3-nitrophthalic acid following the scheme below.







Attempted catalytic hydrogenation of the intermediate 2-iodo-3-nitrobenzoic acid resulted in elimination of the halogen group due to its extreme lability (15). 3-Chloro-2-iodo-, 3-bromo-2-iodo-, and 2-bromo-3-iodo-benzoic acids, also unreported in the literature, were synthesized by analogous procedures.

*Acknowledgement.* Our thanks are due to Mr. Grant Spurrier for carrying out a portion of the analytical work.

#### EXPERIMENTAL

*General method of oxidation.* The finely powdered iodine derivative (8 g.) was suspended in 60 cc. of concentrated sulfuric acid and 16 cc. of concentrated nitric acid (*d.*, 1.4) was added dropwise with stirring but without cooling. The reaction started spontaneously and the liquid turned brown owing to the liberation of nitrogen dioxide and the formation of nitrosylsulfuric acid. The mixture was heated on the steam-bath until a clear yellow solution was obtained (about 30 to 40 minutes), and poured on cracked ice after cooling. The oxidation product, which precipitated almost quantitatively, was filtered, washed, and dried *in vacuo* over calcium chloride. Deviations from this general outline are mentioned under the compounds concerned.

*Determination of active oxygen.* In a glass-stoppered Erlenmeyer flask containing 0.2 to 0.3 g. of the oxidized material in 100 cc. of water were added in succession 5 g. of potassium iodide in 10 cc. of water and 2 cc. of glacial acetic acid. The suspended particles were broken up mechanically if necessary and the closed flask heated on a water-bath at 60–70° for about 30 minutes. After cooling, the liberated iodine was titrated with 0.1 *N* sodium thiosulfate, using starch as the indicator. Based on the equation:  $\text{RIO}_2 + 4 \text{HI} \rightarrow \text{RH} + 2 \text{H}_2\text{O} + 4 \text{I}$ , the active oxygen content is given by the formula  $[\text{O}] = 8v/100w$ , where *v* is the volume of thiosulfate in cc., *f* the factor of the same, and *w* the weight of the sample in grams.

*Iodine determination.* In a nickel or platinum crucible a small sample of the oxidation product was thoroughly moistened, some concentrated sodium bisulfite solution was added and, after complete reduction, an excess of 40% sodium hydroxide solution. It is dangerous to add the alkali to the dry compound. The mixture was carefully evaporated to dryness, heated for about 15 minutes at dull red heat, the melt dissolved in water, reduced with sulfur dioxide, and the iodine determined with silver nitrate in the usual manner.

*Oxidation of tetraiodo-*o*-sulfobenzoic anhydride.* The oxidation product obtained as described above exploded violently with heat, percussion or friction and should be handled with great care.

*Anal.* Calc'd for  $\text{C}_7\text{H}_2\text{I}_4\text{O}_9\text{S}$ : 4[O], 8.31. Found: [O], 7.73, 7.86, 7.95.

*Oxidation of tetraiodophthalic anhydride.* The resulting product seems to explode even more readily than the previous compound and should be handled accordingly. As it shows a tendency to form a colloidal suspension in dilute acid, the latter cannot be removed completely by washing. In earlier experiments this was accomplished with aqueous sodium bicarbonate but later more conveniently by washing with glacial acetic acid and drying *in vacuo* in the presence of sodium hydroxide.

The average active oxygen content in ten analyses of six different samples was found to be 8.66 with lower and upper limits of 8.32 and 8.75 respectively, while only in one case a value of 9.03 was obtained.

*Anal.* Calc'd for  $\text{C}_8\text{H}_2\text{I}_4\text{O}_8$ : 4[O], 8.72; I, 70.95. Found: I, 70.89.

The same compound was obtained from the oxidation of dimethyl tetraiodophthalate; [O], 8.37, 8.21. On reduction with aqueous potassium iodide the product gave the same titra-

tion curve as did tetraiodophthalic acid and on drying at 110° tetraiodophthalic anhydride was obtained.

Nine titrations of four different samples, carried out with omission of acetic acid gave an average [O], 2.46 (calc'd for 1 [O], 2.23), while slightly less than normal values were obtained if acetic acid was subsequently added (average [O], 8.2). On the other hand, the titration of a sample with [O], 9.03 in the presence of acetic acid, gave [O], 6.96, 6.86, if titrated in a saturated borax solution.

*Reduction.* Tetraoxytetraiodophthalic acid (10 g.) was suspended in 400 cc. of water, 100 cc. of glacial acetic acid was added, and, after cooling in ice, 30 g. of potassium iodide in 100 cc. of water was added dropwise with stirring. After standing for two days, 9.3 g. of dipotassium tetraiodophthalate had crystallized. It was dried at 110°.

*Anal.* Calc'd for  $C_8I_4K_2O_4$ : I, 68.0. Found: I, 67.6.

The free acid was obtained by dissolving the salt in water and precipitating with hydrochloric acid.

*Anal.* Calc'd for  $C_8H_2I_4O_4$ : I, 75.81; Calc'd for  $C_8I_4O_8$ : I, 77.9.

Found: I, 77.53, 78.04.

Evidently the acid had changed into the anhydride on drying. Analogous results were obtained if the reduction was carried out with sodium thiosulfate or sulfur dioxide.

*Action of hydrochloric acid.* A sample of dry tetraoxy derivative was thoroughly moistened, covered with some water and, while stirring and cooling, about 20 volumes of concentrated hydrochloric acid was gradually added. It is dangerous to add the acid to the dry compound. The yellow suspension assumed a light tan color and after about 15 minutes the product was filtered off and dried *in vacuo* over calcium chloride in the presence of sodium hydroxide. The chlorine analysis was carried out by reducing a sample with aqueous potassium iodide in the presence of acetic acid and calculating the chlorine from the amount of liberated iodine as titrated with 0.1 *N* sodium thiosulfate.

*Anal.* Calc'd for  $C_8H_2Cl_4I_4O_4$ : Cl, 17.47. Found: Cl, 19.08.

A direct chlorine determination was carried out as follows: a small sample was decomposed with dilute alkali at room temperature, acidified with acetic acid, filtered, and the chlorine in the filtrate determined with silver nitrate.

*Anal.* Calc'd for  $C_8H_2Cl_4I_4O_4$ : Cl, 17.47. Found: Cl, 16.82.

For reasons not yet known the chlorine derivative frequently decomposes completely on drying *in vacuo*.

*Oxidation of triiodophthalic anhydride.* In order to obtain consistent results the oxidation period had to be extended to about five hours. It was noted that two compounds invariably were formed, one separating spontaneously when the solution in concentrated acid was poured on ice, the other one crystallizing gradually from the dilute acid. Complete separation was effected by washing the first precipitate thoroughly with lukewarm water. The relative amount of the compounds was about 3:1, and the active oxygen content of the first derivative was invariably higher than that of the second.

*Anal.* Calc'd for  $C_8H_3I_3O_7$ : 3[O], 8.1.

Found first fraction: [O], 8.29, 7.82.

Calc'd for  $C_8H_3I_3O_8$ : 2[O], 5.56.

Found second fraction: [O], 6.21, 5.67.

If samples of these two fractions were reduced with potassium iodide, the eliminated iodine removed with sulfur dioxide, and the acids crystallized from acetic anhydride, the corresponding anhydrides were obtained, m.p. 217–224° (cor.) and 227–229° (cor.) respectively.

*Anal.* Calc'd for  $C_8HI_3O_8$ : I, 72.4. Found, both fractions: I, 72.5.

The second fraction obtained from another sample of triiodophthalic anhydride contained [O], 5.46, 5.69, and was converted to the corresponding acid by reduction as before.

*Anal.* Calc'd for  $C_8H_3I_3O_4$ : I, 71.85. Found: I, 71.87.

These data lead to the conclusion that the samples of triiodophthalic anhydride constitute a mixture of isomers.

## OXIDATION OF LOWER IODINATED PHTHALIC ACIDS

*3,6-Dichloro-4,5-diiodophthalic anhydride*, m.p. 252° (uncor.) [literature value (1) 258° (cor.)]. This compound took up no active oxygen and starting material (m.p. 249–250°) was isolated.

*3,4-Diiodophthalic acid*, m.p. 211°. This compound took up two active oxygen atoms.

*Anal.* Calc'd for  $C_8H_4I_2O_6$ : 2[O], 7.11. Found: [O], 6.97.

*4,5-Diiodophthalic acid*, m.p. 222.5–223.5° (cor.). This substance did not take up any oxygen and no nitration occurred.

*3,6-Diiodophthalic anhydride*, m.p. 233.5–235.5° (cor.). This compound took up two oxygen atoms, although the mixture of concentrated acids did not show the temporary dark coloration usually noted. Pouring on to ice did not cause immediate precipitation, but the oxidation product gradually separated in white, shiny crystals.

*Anal.* Calc'd for  $C_8H_4I_2O_6$ : 2[O], 7.11. Found: [O], 6.70, 6.73.

*3-Iodophthalic anhydride*. This compound added one oxygen atom. After the oxidation was completed the concentrated acid solution was poured on to ice and the dilute solution cooled in an ice-salt mixture. The resulting precipitate was washed and dried *in vacuo*.

*Anal.* Calc'd for  $C_8H_5IO_5$ : 1[O], 5.19. Found: [O], 5.17, 5.05.

Similar titration results were obtained without the use of acetic acid.

*4-Iodophthalic anhydride*. This product did not take up any oxygen but was partly nitrated. The reaction product was fairly soluble in dilute acid but separated on cooling in an ice-salt mixture. The compound contained 3.58% N (calculated value for nitroiodophthalic acid, 4.18%).

## OXIDATION OF IODOBENZOIC ACIDS

*2,3-Diiodobenzoic acid*. This compound took up two oxygen atoms, yielding a yellow substance.

*Anal.* Calc'd for  $C_7H_4I_2O_4$ : 2[O], 7.88.

Found, using acetic acid: [O], 7.76.

Found, without acetic acid: [O], 3.73, 4.11.

*2-Iodo-3-chloro-, 2-iodo-3-bromo-, and 2-bromo-3-iodo-benzoic acid*. Each of these compounds yielded resinous products in which no active oxygen could be detected with certainty.

*m- and p-Iodobenzoic acid*. These acids did not take up any oxygen. The former was partly, and the latter almost entirely nitrated under the reaction conditions.

*o-Iodobenzoic acid*. This product took up one oxygen atom.

*Anal.* Calc'd for  $C_7H_5IO_3$ : 1[O], 6.06.

Found, using acetic acid: [O], 5.87.

Found, without acetic acid: [O], 3.03.

For comparison, *o*-iodoxybenzoic acid was prepared by the method of Hartmann and Meyer (16) and analyzed for active oxygen.

*Anal.* Calc'd for  $C_7H_5IO_4$ : 2[O], 11.43; 1/2[O], 2.86.

Found, using acetic acid: [O], 11.62.

Found, without acetic acid: [O], 2.98.

## PREPARATION OF STARTING MATERIALS

*Tetraiodophthalic anhydride*. In a 500-cc. 3-necked flask, fitted with stirrer, mercury seal, air-condenser, and gas absorption tower, were placed 29.5 g. of phthalic anhydride and 725 cc. of 7% fuming sulfuric acid. The temperature was maintained at 80° while 102 g. of iodine was gradually added. The mixture was then heated for 6 hours at 95°, 8 hours at 110–115°, and 12 hours at 135–145°. The heavy yellow precipitate was filtered, stirred into ice-water, washed, and dried. Yield, 119 g. (90%).

*Anal.* Calc'd for  $C_8I_4O_3$ : I, 77.90. Found: I, 77.2.

*Mono- and di-methyl tetraiodophthalate*. Tetraiodophthalic anhydride (20 g.) was heated under reflux for 6 hours with 250 cc. of absolute methanol to which 10 drops of concentrated

sulfuric acid had been added. In the course of the esterification the anhydride slowly dissolved. The solution was then concentrated *in vacuo* and poured into water giving a slightly gummy precipitate which soon became granular. It was purified by solution in 150 cc. of hot alcohol with the addition of hot water dropwise until a slight turbidity appeared, followed by crystallization.

The mono ester thus obtained was dissolved in about the theoretical amount of sodium hydroxide solution, the pH was adjusted to 6.0 with dilute nitric acid, and twice the calculated amount of 5% aqueous silver nitrate was added. The resulting yellow silver salt was filtered and dried. A portion of the dry salt (12.5 g.) was suspended in 80 cc. of dry benzene, 5 cc. of methyl iodide was added slowly and the mixture was refluxed for two hours. After distilling off the solvent, the residue was extracted with 250 cc. of boiling alcohol. Evaporation gave dimethyl tetraiodophthalate in a yield of 6.5 g. (60%). After crystallization from alcohol the alkali-insoluble ester melted at 166.5–167.5° (cor.).

*3,6-Diiodo-4,5-dibromophthalic anhydride.* This compound could not be obtained by iodination of 4,5-dibromophthalic anhydride. 4,5-Dibromophthalic acid was obtained as a by-product in the preparation of tetrabromophthalic anhydride; m.p. 203.5–205.5° (cor.) [literature value, 200° (11)]. This was converted to its anhydride by recrystallization from acetic anhydride, and then from benzene; m.p. 217–220° [literature value 208° (11)].

*Anal.* Calc'd for  $C_8H_2Br_2O_3$ : Br, 52.3. Found: Br, 52.4.

Iodination of the dibromo compound in 60% fuming sulfuric acid in the usual way gave a product which was freed of excess iodine and dried at 110°. It was soluble in cold benzene. Recrystallization from glacial acetic acid containing 1% acetic anhydride gave a product, m.p. 259–261° (uncor.).

*Anal.* Calc'd for  $C_8Br_3IO_3$  (0.3260-g. sample): AgX, 0.5096 g.; Br, 47.0; I, 24.8.

Found: AgX, 0.5098 g.; Br, 49.2; I, 22.0.

Considering the inherent errors in the differential halogen determination, the above analyses indicate the formation of a tribromophthalic anhydride, presumably at the expense of other molecules of the starting dibromo compound.

This tribromo compound on oxidation did not take up any oxygen, but due to uncertainty as to its structure further work on this compound was discontinued.

*3,6-Dichloro-4,5-diiodophthalic anhydride*, m.p. 252° (uncor.). This compound was prepared by iodination of 3,6-dichlorophthalic anhydride (1), in 78% yield.

*Anal.* Calc'd for  $C_8Cl_2I_2O_3$  (0.3838-g. sample): AgX, 0.6174 g.

Found: AgX, 0.6206 g.

*Triiodophthalic anhydride, 4,5-diiodo-, and 3,6-diiodo-phthalic acid.* These compounds were prepared by the method of Pratt and Perkins (1), in which phthalic anhydride is iodinated under suitable conditions.

*3-Iodophthalic acid and 4-iodophthalic acid.* Attempts to prepare the monoiodo compounds by direct iodination in sulfuric acid resulted in the formation of the diiodo compounds instead. When the method of Datta and Chatterjee (17) was followed, using iodine and nitric acid, only unreacted phthalic acid was recovered. Attempted direct reduction of 3-nitrophthalic acid to the corresponding amino compound with zinc dust and acetic acid by the method of Bernthsen and Semper (18) and Kenner and Mathews (19) gave a product which was not soluble in sulfuric acid and which was not the desired amino compound but was probably a polymer. Gisvold (20) reported the formation of much polymeric substance in the reduction of 3-nitrophthalic acid with platinum or Raney nickel at fifty pounds pressure, but reported some of the amine as well. In the present study, catalytic hydrogenation, using platinum and pressures of ten pounds, in 95% alcohol, 50% alcohol or water, invariably resulted in the theoretical uptake of hydrogen but yielded a brown product which could not be diazotized. The literature (21) shows 3-aminophthalic acid to be very unstable, being decomposed by water and alcohol even at room temperature. Our catalytic hydrogenation experiments with 4-nitrophthalic acid met with similar failure. In both cases preliminary esterification of the nitro acids eliminated this difficulty and catalytic hydrogenation to the amino esters went quite smoothly.

Attempts to prepare dimethyl 3-nitrophthalate from the mono ester with dimethyl sul-

fate in the usual manner met with failure. It was made in 83% yield by treating the silver salt of 3-nitrophthalic acid with methyl iodide (22). This dimethyl ester (8.6 g., m.p. 67-69°) was dissolved in 150 cc. of alcohol and hydrogenated over Adams' platinum oxide catalyst, 45 minutes being required for complete uptake of hydrogen. Most of the alcohol was allowed to evaporate to give a colorless oil, wt., 6.6 g., which was dissolved in 100 cc. of 17% sulfuric acid and diazotized as usual. Then 10 g. of potassium iodide in 10 cc. of water was added and the mixture warmed to about 90° for a short time. Extraction with ether and evaporation of the latter yielded 6.3 g. of crude dimethyl 3-iodophthalate, m.p. 77-79°. The ester was saponified by refluxing for two hours with a solution of 3.7 g. of potassium hydroxide in 50 cc. of absolute alcohol; the potassium salt was allowed to crystallize after concentration and cooling in ice. The salt was redissolved in a small amount of water, acidified with sulfuric acid, and the liquid extracted with ether. Vacuum sublimation (in the dark) of the ethereal residue gave 2 g. of slightly yellow needles of 3-iodophthalic anhydride, m.p. 159-161° [literature value (23), 153°].

In contrast to the above, esterification of 4-nitrophthalic acid with absolute methanol gave the desired dimethyl ester (24), m.p. 65°; the ester (5 g.) was hydrogenated catalytically in 100 cc. of alcohol with platinum oxide. Spontaneous evaporation of the solvent left a clear oil which crystallized on stirring. Recrystallization from alcohol gave 3 g. of dimethyl 4-aminophthalate, m.p. 81.5-83° [literature value, 84° (24)]; yield, 70%. The ester was dissolved in 100 cc. of 17% sulfuric acid, cooled to -2°, and a cold solution of 1 g. of sodium nitrite in 5 cc. of water added dropwise until the solution showed an excess of nitrous acid. The addition of 5 g. of potassium iodide in 5 cc. of water produced an oily precipitate which was dissolved in 50 cc. of absolute alcohol containing 2.5 g. of potassium hydroxide and refluxed for an hour. Concentration of the solution yielded a strawberry-colored precipitate. Acidification of a concentrated aqueous solution of the latter gave a precipitate which was washed with ice-water, dried, and sublimed in the dark at 120°/4 mm. Yield, 2.35 g. (60%) of 4-iodophthalic anhydride, m.p. 124.5-126.5° (cor.) [literature value, 123° (24)].

#### IODOBENZOIC ACIDS

*2,3-Diiodobenzoic acid.* Anhydro-2-hydroxymercuri-3-nitrobenzoic acid, prepared from 3-nitrophthalic acid according to Whitmore, Culhane, and Neher (25), was converted into 2-iodo-3-nitrobenzoic acid (26). Attempted catalytic hydrogenation of the latter with platinum resulted in decomposition, but the reduction was successfully carried out in the following manner. A solution of 17 g. of stannous chloride in 20 cc. of hydrochloric acid was added dropwise over an hour to a cooled, stirred solution of 5 g. of 2-iodo-3-nitrobenzoic acid in 100 cc. of glacial acetic acid. The white precipitate, presumably the tin chloride double salt of the amino acid, was filtered off after about 16 hours and washed with a little cold water, in which it was somewhat soluble. A solution of 3.3 g. of the dry compound in 100 cc. of 17% sulfuric acid was diazotized at 0°, and 5 g. of potassium iodide in 5 cc. of water added. The mixture was allowed to warm up to room temperature and then was heated to about 90° for 10 minutes. After standing in the ice box overnight, 2.5 g. of crude 2,3-diiodobenzoic acid had crystallized; yield, 75%. Sublimation in the dark at 4 mm. pressure gave long needles, m.p. 178-181° (cor.). The compound turns yellow on exposure to light.

*Anal.* Calc'd for  $C_7H_4I_2O_2$ : I, 67.9. Found: I, 68.3.

*2-Iodo-3-chlorobenzoic acid.* This acid was synthesized in a similar manner to the previous compound. However in this case the tin double salt was not isolated but the reduction mixture was diazotized directly. The diazotized solution from 10 g. of the corresponding iodonitrobenzoic acid was poured rapidly into a solution of cuprous chloride (27), then 15 cc. of concentrated hydrochloric acid was added, and the mixture was left overnight. After diluting with two parts of water it was cooled in the ice box, whereupon 5.3 g. of crude 2-iodo-3-chlorobenzoic acid separated as a light tan-colored product. The relatively low yield was due to the dissolving action of the acetic acid added in the initial stage of the process. It could be improved slightly by isolating the tin chloride complex and carrying out the Sand-

meyer reaction separately. In another experiment an attempt was made to dissolve the complex in 35% sulfuric acid by heating to 60° prior to diazotization, but this resulted in the elimination of iodine. 2-Iodo-3-chlorobenzoic acid was purified by vacuum sublimation (4 mm.), giving white needles, m.p. 135–138° (cor.).

*Anal.* Calc'd for  $C_7H_4ClIO_2$ , (0.2054-g. sample): Ag halide, 0.2792 g.

Found: Ag halide, 0.2742 g.

*2-Iodo-3-bromobenzoic acid.* To eliminate the possibility of an exchange of halogen atoms during the Sandmeyer reaction, the reduction of 2-iodo-3-nitrobenzoic acid was carried out with stannous bromide, (27), instead of stannous chloride. The tin bromide complex did not precipitate and the diazotization was carried out in the medium in which it was formed. The diazonium solution thus obtained was cooled and poured into a cuprous bromide solution (27), hydrobromic acid was added, the suspension was warmed to 50°, and left overnight in the ice box. After concentration *in vacuo* at 80° to about one-third of its volume the 2-iodo-3-bromobenzoic acid was filtered off from the chilled suspension and purified by sublimation (4 mm.). It formed white needles, m.p. 148–151° (cor.).

*Anal.* Calc'd for  $C_7H_4BrIO_2$ , (0.1513-g. sample): Ag halide, 0.1957 g.

Found: Ag halide, 0.1984 g.

*2-Bromo-3-iodobenzoic acid.* This compound was prepared from anhydro-2-hydroxymercuri-3-nitrobenzoic acid in one continuous operation by reduction with stannous chloride, diazotization, and the Sandmeyer reaction in the cold with potassium iodide. The mixture was finally heated to 70°, concentrated *in vacuo* and, after chilling, the crude acid was filtered off. Sublimation *in vacuo* gave white needles, m.p. 159–162.5° (cor.).

*Anal.* Calc'd for  $C_7H_4BrIO_2$ , (0.1984-g. sample): Ag halide, 0.2566.

Found: Ag halide, 0.2551.

*Monoiodobenzoic acids.* The *ortho* derivative was prepared by reduction of Eastman iodobenzoic acid with potassium iodide, while the *m*- and *p*-iodobenzoic acids were obtained from the corresponding amino acids by diazotization in 17% sulfuric acid and application of the Sandmeyer reaction with potassium iodide.

#### SUMMARY

A comparative study has been made of the oxidation of iodinated phthalic and benzoic acids with nitric-sulfuric acids and some rules were derived from the experimental data.

2,3-Diiodobenzoic acid, 2-iodo-3-chlorobenzoic acid, 2-iodo-3-bromobenzoic acid, and 2-bromo-3-iodobenzoic acid were synthesized from 3-nitrophthalic acid by replacing in succession a carboxyl and a nitro group by the appropriate halogen atom.

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