

DIRECT MONO-IODINATION  
OF  
PHTHALIC ANHYDRIDE

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Introduction to the Subject

The halo-aryl compounds are well known for their commercial uses in dyeing and in medicine, the latter either for actual medicinal properties, or for staining effects (e.g. phenoltetrachlorophthalein and tetraiodophenolphthalein).

This thesis had for its general purpose, then, the production of iodo-phthalic anhydride compounds by means of new and better methods. An extensive search of the literature was made as preliminary work on the subject, and several articles pertaining to the various iodophthalic anhydrides and acids were disclosed. Summaries of the significant ones follow.

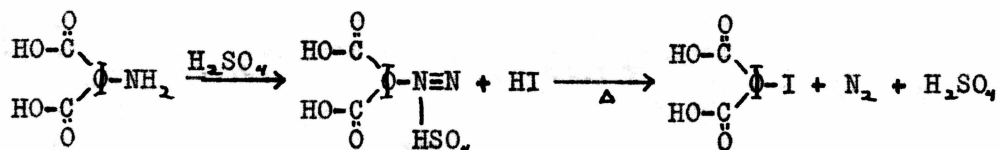
The tetra-iodo phthalic anhydride can quite readily be prepared by heating phthalic anhydride and an excess of crystalline iodine in 50% oleum at 65° until the reaction is complete, and then raising the temperature to 175° for fifteen minutes (1).

The various di- and tri-iodo phthalic acids and

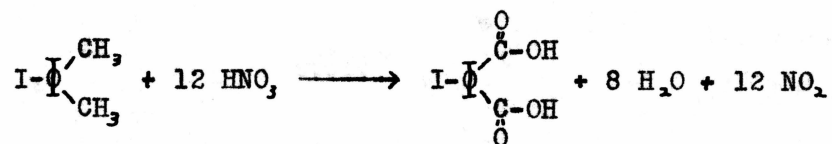
anhydrides, 3,6-diiodo-anhydride, 3,4-diiodo-acid, 4,5-diiodo-acid, and 3,4,6-triiodo-anhydride, are formed in a similar manner, again using phthalic anhydride and crystalline iodine, with 50% fuming sulphuric acid, and heating from 110°-120° for one and one-half hours, from 140°-160° for one hour, from 160°-200° for fifteen minutes, and at 200° for five minutes (2).

No mention of the mono-iodo compounds was to be found, however, in these sulphuric acid-iodine discussions. Other references, though, did help to throw some light on the picture, and gave the following data:

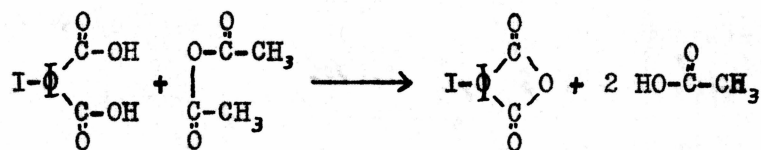
1. In 1879, a paper by Edinger was published in the Journal für Praktische Chemie, on the preparation of the 3- and 4-iodophthalic anhydrides by the sublimation of the 3- and 4-iodophthalic acids (3). The 3-iodophthalic acid is prepared by diazotization of 3-aminophthalic acid in dilute sulphuric acid, forming the diazonium hydro-sulphate, which is warmed with hydroiodic acid to yield the desired product (4) :



The 4-iodophthalic acid may be prepared either in a similar manner from 4-aminophthalic acid (4), or by the oxidation of 4-iodo-1,2-dimethylbenzene, using nitric acid as the oxidizing agent (5):



2. In 1929, just fifty years later, there appeared in the Journal of the American Chemical Society a paper by Blicke and Smith, in which they describe the preparation of the 3- and 4-iodophthalic anhydrides by heating the respective acids for ten minutes with an equal weight of acetic anhydride (6) :



Upon further exploration, the literature refused to divulge any further basic information or other important methods concerning aryl iodination. Thus it would appear that direct iodine mono-substitution onto the phthalic anhydride nucleus has never been successfully carried out. Also, since the JACS, 40, papers concerning iodination by means of fuming sulphuric acid and crystalline iodine, failed to note the formation of any such products, this



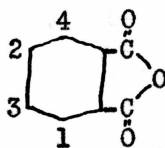
method obviously does not lend itself readily to monosubstitution.

Thus, after this preliminary literature research, the specific primary purpose and object of this thesis became the attempted preparation of either 3- or 4-iodophthalic anhydride by direct iodination of the anhydride ring, and, if successful, the secondary object was the condensation of the product with resorcinol to give a fluorescein containing an iodine in the acid residue. (Those fluoresceins mentioned above contain halogen atoms on the resorcinol residues.)

The iodinating agent decided upon was iodine chloride,  $\text{ICl}$ . This is a dark, wine-colored liquid, analogous in molecular structure to  $\text{I-I}$  ( $\text{I}_2$ ) or  $\text{Cl-Cl}$  ( $\text{Cl}_2$ ), which is formed by passing chlorine gas over iodine crystals. Iodine chloride is a good iodinating agent because it acts simultaneously as reagent and as catalyst. Since the hydrogen to be replaced on the nucleus carries with it a positive charge, the replacing element must likewise have a positive charge: iodine chloride consists of a positively charged iodine, and a negatively charged chlorine.

The sketch below shows the probable order in which the first, second, third and fourth substituents, respectively, are commonly believed to enter the phthalic

anhydride ring when substitution is complete:



Since iodine, however, is a large atom, it may not enter the nucleus at the usual position of mono-substitution, due to steric hindrance resulting from the close proximity of the adjacent carbonyl group, but may instead enter at position number three (identical with position number two).

Carbon disulphide was chosen as the solvent to be used.

## Experimentation on the Subject

The object of this thesis, as pointed out in the introduction, was the production of either 3- or 4-iodophthalic anhydride by the use of iodine chloride as the iodinating agent, and carbon disulphide as the solvent.

Since iodine chloride is quite unstable, it cannot be obtained commercially, and thus has to be freshly prepared for each attempted iodination, unless the time-interval between experiments is short enough so that the reagent is still usable. The first thing to be carried out, therefore, was the manufacture of a sample of iodine chloride. Chlorine was generated by the action of hydrochloric acid, from a dropping-funnel, on manganese dioxide in a stoppered flask equipped with a safety tube. The chlorine gas was then conducted through the outlet tube, bubbled through sulphuric acid (d.1.84), and introduced into another stoppered flask, equipped with exhaust tube, containing crystalline iodine. When the iodine crystals had disappeared and been replaced by a heavy, dark wine-colored liquid, iodine chloride, generation of chlorine was stopped.

Equimolar amounts of iodine chloride (m.w. 162.38)

and phthalic anhydride ( m. w. 148.11 ) were weighed out and the latter placed in an Erlenmeyer flask. Carbon disulphide, equal in volume to about twice that of the crystalline anhydride, was added to the flask, and the contents shaken. The iodine chloride, in carbon disulphide, was added, three or four drops at a time, to the phthalic anhydride in partial solution. The reagent was added slowly so that, if substitution took place, there would never be an excess of iodine. For, if the rate of substitution were greater for the substitution of the second iodine than for that of the first, any slight excess of reagent would produce a diiodo- instead of the desired moniodo-compound.

After all of the iodine chloride had been added, the flask and the contents were shaken and warmed slightly, but many of the anhydride crystals refused to dissolve. After a time-interval sufficient to allow the reaction, if any, to go to completion, these crystals were filtered off and dried. They were found to give a melting point of about  $190^{\circ}$ , or about that of phthalic acid, and a negative halogen test upon sodium fusion. This high melting point was considered unusual, since no water had been present in the reaction flask, by which the anhydride could have been hydrolyzed to the acid. The filtrate from the above filtration was distilled in order to conserve the solvent. During the process, heating was periodically stopped to

allow opportunity for crystallization. No crystals were formed, however, until the last of the solution had been removed; at that time, a small mass of crystals composed partially of crystalline iodine, was left behind in the distillation flask. After the iodine had been removed by sodium bisulphite, the unpurified crystals were dried and were found to give a melting-point of about  $125-6^{\circ}$ , which is the recorded melting-point of 4-iodophthalic anhydride(7). Since the mass of crystals was so small ( about 0.115 g.), they were tested microscopically for a suitable recrystallization medium. Acetic acid was found to dissolve them fairly well, and to give up fine white crystals upon evaporation. After recrystallization from acetic acid in this manner, the crystals still gave a melting point of  $125-6^{\circ}$ . Because of the small amount of the substance that had been made, however, no decisive tests (sodium fusion, molecular weight determination, etc.) could be made. The distillate from above was extracted three times with sodium hydroxide in order to obtain a larger yield of the substance if possible. The extraction removed all color from the solution, but yielded no more crystals.

Hoping to obtain a reasonable amount of product, so that analyses and further reactions could be carried out on it, the experiment was repeated using acetic acid instead

of carbon disulphide as a solvent; a few milliliters of acetic anhydride were added to prevent any possible hydrolysis of the phthalic anhydride to the acid. Chlorine, for the manufacture of iodine chloride, was generated this time by the action of concentrated sulphuric acid on a mixture of sodium chloride and manganese dioxide; this was a considerable improvement over the first method. About ten times as much iodine chloride and phthalic anhydride were used in this experiment. As before, anhydride, solvent and reagent were added to a flask, which was stoppered and shaken for about an hour, by which time all crystals had dissolved. Upon standing, new crystals began to form; when these were filtered off and dried, they gave a melting point of  $130-31^{\circ}$ , which is the melting point recorded for unchanged phthalic anhydride. (Since the unchanged anhydride and the 4-iodo anhydride melt fairly close together, the thermometer was checked against any possible error in calibration by taking the melting point of the phthalic anhydride on the reagent shelf. When this sample, as well as samples from all other available sources, gave melting points of  $180-200^{\circ}$ , it became apparent that the anhydride had undergone atmospheric hydration to the acid, and that reconversion to the anhydride would be required before any future undertakings. This also explains the "yield" of acid in the first experiment.) Sodium fusion gave a negative halogen test, although a little sodium bisulphite was added to the solution of fusion

products in order to prevent possible oxidation of iodine to iodate, in which form it would escape detection.

When a small portion of the filtrate from above was poured into cold water, a dark precipitate was thrown out, which, upon drying, turned white and gave a melting point of 130-31°. After standing, the remainder of the filtrate yielded another set of crystals upon decantation which, when dried, gave a melting point of 210-12°, melting with decrepitation. A sodium fusion gave negative halogen tests, so this latest crystal mass was evidently composed of phthalic acid containing water of occlusion. When the liquor decanted from these crystals was evaporated, yet another set of crystals was obtained. They were refined by trituration in a clean mortar with distilled water, and when dry, gave a melting range of about 125-190°. The melting seemed to take place exclusively at the ends of the range, and not in between. This would indicate that possibly some iodination had succeeded, but that most of the anhydride had been converted into the acid. No means of separation of the two crystalline compounds possibly present was found, and a sodium fusion was run on the sample as a whole, with the subsequent confirmatory tests for the presence of iodine turning out negative.

After some good phthalic anhydride had been manufactured, a third attempt at iodination was made, the solvent

being a mixture of half acetic acid and half carbon disulphide.

The sample of phthalic anhydride was prepared from the acid on hand by the method of Koenigs and Hoerlin (8): "Equimolecular amounts of acetic anhydride and the dibasic acid are heated together with dissolved zinc chloride the size of a pea for ten minutes." The mixture was heated until a homogeneous melt was formed; upon cooling, the melt yielded a greyish mass of crystals. These were washed with water, filtered, and washed alternately with water and sodium bicarbonate. After drying, the crystals gave a clean melting point at 130-31°.

The mixed solvent, together with equimolar weight of the new phthalic anhydride and iodine chloride, was shaken in the reaction flask for a little over an hour, then was gently heated in a warm water bath. For promotion of possible nuclear reaction, a few granules of antimony were added to the contents of the flask, which was then stoppered and allowed to stand in strong sunlight. After several days, the contents of the flask were filtered. The original crystals had disappeared, and a new mass, made up of small fine needles, had formed, colored by the solution. The crystal mass obtained contained several crystals of iodine, which sublimed out of the mass upon exposure to air; the remaining crystals had lost most of their color, turning a light brown. The unpurified crystals gave a melting point of 125-28°; trituration with water and chloroform yielded



an almost white product, which gave a melting point of 124-5°. This was quite close to the melting point recorded for the 4-iodo phthalic anhydride (125-6°). After sodium fusion, a definite cloudiness was obtained for the halogen test, although it was not the usual halogen curdy precipitate. These more or less positive signs seemed to indicate that perhaps the desired compound had at last been produced. A molecular-weight determination by the Rast method (9), however, gave a value of only about 130, which nowhere approached the molecular weight of the monoiodophthalic anhydride, which is 274.02. Thus, all conflicting evidence to the contrary, the anhydride had escaped unscathed, and another attempted iodination had failed.

The filtrate obtained above was evaporated, yielding another set of crystals. After purification by means of trituration with distilled water, however, they gave a melting point of about 190°, showing that the anhydride had evidently been converted into the acid.

From the results of these last two attempts at iodination, the apparent success of the first experiment is drawn into the shadow of doubt.

### Summary of the Subject

As can readily be seen from the foregoing pages, all attempts at iodination of phthalic anhydride, made by means of iodine chloride, have failed. Fuming sulphuric acid was not used in these experiments because it had already proven its worth as a general substituting agent in the preparation of the various di-, tri-, and the tetra-iodo phthalic anhydrides and acids, using crystalline iodine. Also, as noted before, the papers discussing the above preparations made no mention of obtaining mono-iodo compounds, so it can probably be safely assumed that no such compounds are formed by this method.

Some indications of partial success of the iodination process were given, however, mainly through melting points. Several times sharp melting points were observed which were quite low enough to be given by compounds in which iodine had substituted in the number four position. Two or three times, the compound under observation could definitely be seen starting to melt at about 125°, and then remaining mostly in the solid state until temperatures around 130°, or even 190°, were reached. This would indicate that probably a small amount of the anhydride had been converted into the 4-iodo compound, with most of it remaining unchanged. If some method of separation were to be worked out, the

compound could probably be obtained in this manner, the percentage yield, however, would undoubtedly be quite small. A better method of production would be the use of a catalyst of some kind which would promote reaction to a much greater extent than iodine chloride, antimony, and sunlight apparently do.

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