# CERTAIN IODO AND OTHER DERIVATIVES OF DIPHENYL ETHER

by

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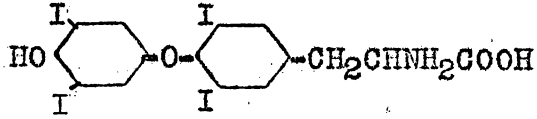
## INTRODUCTION AND HISTORICAL

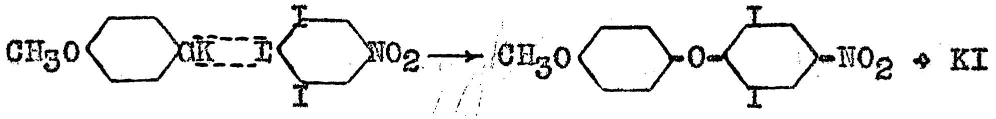
The following consists of a description of studies made on certain iodo and other derivatives of diphenyl ether, particularly on the mono and diiodo substitution products of this substance, with intermediate compounds through which these iodo derivatives were synthesized. Also is included a description of an extension of the work on certain iodo and other derivatives of carboxy diphenyl ethers, a portion of which has been described in the foregoing Master's thesis (K.U. 1931)[47], with particular reference to derivatives of 2-phenoxy benzoic acid.

Diphenyl ether, obtained as a by-product from the preparation of phenol through the interaction of chlorobenzene and sodium hydroxide, has recently become readily available, and an increasing number of its derivatives and substitution products have been synthesized. Some of these such as amino and substituted amino derivatives are of possible commercial importance, notably in the field of dye intermediates. Many of these compounds have been synthesized directly from diphenyl ether, among which are products of nitration obtained by Mailhe and Murat[1], Ryan and Drumm[2], and more recently and satisfactorily by Suter[3]; products of sulfonation by Suter[4]; and of bromination by Mailhe and Murat[5] and also by Suter[3]. Most of the numerous synthesized diphenyl ether derivatives, however, have been obtained by the reaction of an alkali salt of a phenol with an aromatic halogen compound, which components contain in their nucleii, substituents desired in the resultant ether. (Compare Ullmann[7], Haeussermann[8], and collaborators of each, Jones and Cook[9], Raiford and Colbert[10], and others)

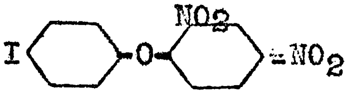
Of great interest has been the recent proof by analysis and synthesis[11] (1926-7) by Harington and Barger, that thyroxine, a normal constitutent of the thyroid gland and used in the treatment of deficiencies of this gland, is a tetra-iodo derivative of a substituted diphenyl ether with the following structure:



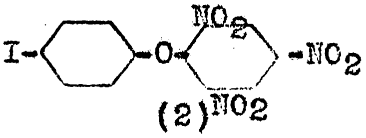
The iodo derivatives of diphenyl ether obtained by Harrington and Barger in the above synthesis and proof, with two other iodo ethers previously synthesized (1909) by Willgerodt and Wiegand[18], were the only iodo-diphenyl ethers appearing in the literature when this investigation was begun. The simplest iodo derivative obtained by Harington was the ether synthesized as represented by the following equation:



From this compound were obtained the ethers with the nitro group in the product above replaced by $-NH_2$, $-CN$, $-CHO$, and $-COOH$. By further reactions the aldehyde was condensed with hydantoin or hippuric acid, the resulting product reduced, hydrolyzed, and demethylated at once with hydriodic acid; then finally iodinated to give thyroxine. The ethers obtained by Willgerodt and Wiegand consisted of the two represented below, with a number of polyvalent iodo derivatives of each.



(1)



(2)

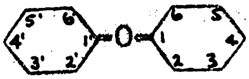
The simple monoand higher iodo substitution products of the parent substance, diphenyl ether, thus being unreported, an extension of the knowledge of the properties of diphenyl ether derivatives to include these compounds has seemed desirable. This investigation has also been made to include several of the possible unknown carboxy-iodo diphenyl ethers, as simple iodo substituted compounds more soluble in aqueous solutions than the other relatively insoluble iodo ethers synthesized; inasmuch as such soluble compounds might form useful, assimilable, thyroxine-like sources of iodine.

A few of the iodo compounds obtained as original syntheses in this investigation have been reported in the literature in connection with other recent researches. Where duplication exists, experiments carried out previous to the knowledge of the results of these other investigations had given results corroborative and in most cases more complete than those which have appeared in the literature.

The compounds synthesized in this investigation, for convenience, may be divided into two general classes. Those of the first class consist of the mono-iodo derivatives of diphenyl ether with some of their nitration and iodination products, certain of the possible diiodo-diphenyl ethers, and other intermediate compounds found necessary in synthesis and proof of constitution of these ethers. The second class includes some of the iodo derivatives and nitration products of certain carboxylic diphenyl eithers (substituted benzoic acids), with intermediate compounds in synthesis and proof of constitution. For simplification in the following discussion, these two classes are treated separately.

### Class I. Derivatives of Diphenyl Ether

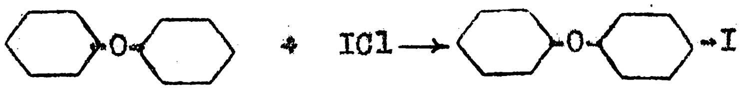
Numbering the positions of possible substitution in diphenyl ether as in the following,



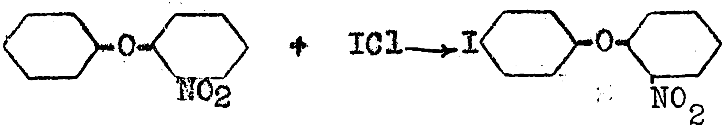
the simple mono-substitution iodo derivatives will include three separate compounds, with iodine atoms substituted for hydrogen in position 2,3, and 4, respectively. These were the first objects of this investigation. Examination shows that there are twelve possible diiodo diphenyl ethers, with iodine atoms substituted in positions 2-3, 2-4, 2-5, 2-2', 2-3', 2-4', 3-4, 3-5, 2-6 3-3', 3-4', and 4-4', respectively. Five of these diiodo ethers were synthesized in this work. These include namely the 3-4, 2-4, 2-4', 3-4', and 4-4' diiodo diphenyl ethers, which are all the compounds possible keeping one iodine atom constant at position 4, while varying the second in all possible positions.

Two general methods, or some combination of these, have been used in synthesizing these mono and diiodo compounds. These were:

(1) Direct iodination of diphenyl ether, or a substituted diphenyl ether, using iodine monochloride in glacial acetic acid solution, which produced the desired iodo product or a partly iodinated one from which it could be obtained by further reactions. Examples of this method are the syntheses of 4-iododiphenyl ether and 2-nitro-4'-iododiphenyl ether represented respectively by the reactions:



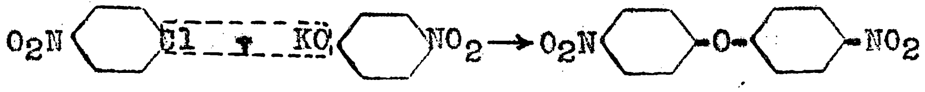
and



The 2,4'-diiododiphenyl ether could then be obtained by reactions described below, from the 2-nitro-4'-iododiphenyl ether. By the same method of iodination as given above, a second iodine atom was introduced into each of the three mono-iodo diphenyl ethers after these compounds had been obtained.

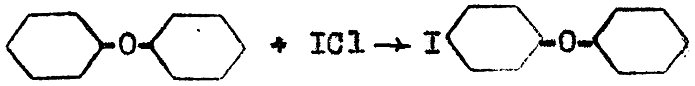
(2) Synthesis of a nitrodiphenyl ether, with one or more nitro groups in the desired position or positions, from which the iodo derivatives were obtained by subsequent reduction to the amine and replacement of the

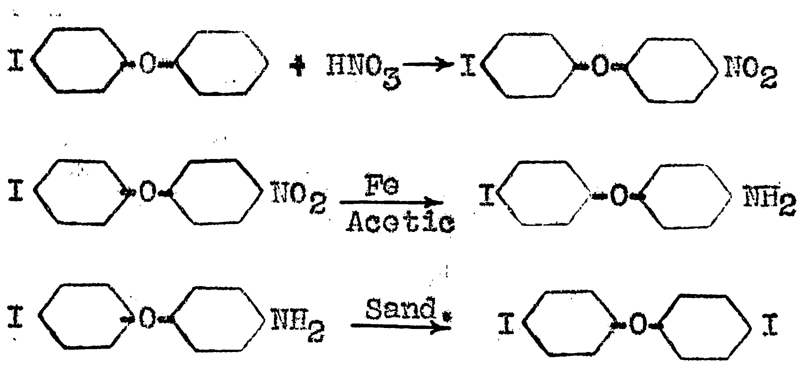
amino group by iodine through the Sandmeyer reaction. An example of this is the synthesis of 4,4'-dinitrodiphenyl ether after the method of Haeussermann and Teichmann[12], by a reaction represented by the following equation:



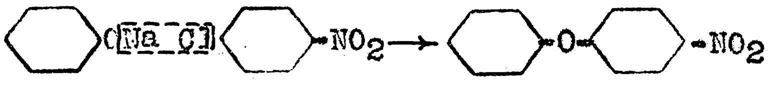
From this dinitro product a known sample of 4,4'-diiododiphenyl ether was obtained. This was found to be identical with the diiododiphenyl ether formed in the direct iodination of diphenyl ether, thus establishing the constitution of the latter.

A combination of the two methods of preparation of the iodo derivatives, in which the nitro compound was obtained by direct nitration (see further discussion below on methods of synthesizing nitro compounds) of an already substituted mono-iodo ether, is pepresented by a synthesis of 4,4'-diiododiphenyl ether according to reactions represented by the following equations. These equations also illustrate the methods used in establishing the constitution of the nitration products of the mono-iodo diphenyl ethers.





Nitro compounds from which the iodo derivatives were synthesized, were obtained either by direct nitration, as indicated just above, or by the mush used reactions of the type employed by Ullmann in the synthesis of aromatic ethers (referred to pages 1 and 2), using an alkali salt of a phenol and a halogenated benzene with desired substituents in one or both nucleii and with an excess of the phenol or halogenated benzene as solvent. An example of this reaction has been given (page 7), and may be further illustrated by the following equation which represents the method by which 4-nitrodiphenyl ether (also 2- and 3-nitrodiphenyl ethers) were obtained.



Raiford and Colbert[10] have concluded that this reaction, when occurring between a halogenated nitrobenzene and a phenol, is influenced most noticeably by the substituents in the phenol; and that when the latter contains a nitro radical, the reaction will fail unless the halogenated benzene contains more than one nitro group. However, the reaction given on page 7 between p-nitrochlorobenzene and the potassium salt of p-nitrophenol gave small but appreciable yields of the dinitro ether, as has previously been described by Haeussermann and Teichmann[12]; although much higher temperatures were necessary than in cases where the phenol contained no nitro group. It is well known that a nitro group in an aromatic nucleus loosens a halogen in the ortho position to some extent, still more in the para position, but hardly at all if the halogen is in the meta position to the nitro group.[7,8,9] Ullmann[13] has also found the reaction to give highest yields if the halogen is iodine, lowest if bromine, and still lower if chlorine. Although the fluorine atom in fluorobenzene is more tightly bound than in the case of the other halogens[14], the loosening effect by a nitro group is much in excess of that the other halogens, as was first observed by Holleman and Beekman[15]. These investigators easily obtained p-nitro-anisole frompp-nitrofluorobenzene and sodium methylate, and found that 2,4-dinitrofluorobenzene reacted with sodium methylate to form the corresponding anisole almost 600 times as rapidly as the corresponding chlorine derivative. Utilizing this reactivity of the fluorine atom in p-nitrofluorobenzene and 2,4-dinitrofluorobenzene, some of the ethers in this investigation have been easily obtained, as recently have been a larger number of diphenyl ethers by Rarick, Brewster, and Dains[16] in this laboratory with p-nitrofluorobenzene, and who found that some ethers difficultly obtained using chlorine compounds (as 4,4'-dinitrodiphenyl ether previously mentioned, page 7), were easily produced by this method. The reactivity of 2,4-dinitrochlorobenzene, however, is sufficiently great that there is little advantage in using the much more difficultly obtained 2,4-dinitrofluorobenzene.

Various procedures for synthesis of a number of the nitrodiphenyl ethers prepared in this investigation are given in the literature, usually utilizing the fusion reaction described above. These include 2-, 3-, and 4-nitrodiphenyl ethers, 4,4'-dinitrodiphenyl ether, and 2,4-dinitrodiphenyl ether.

Haeussermann and Teichmann[12] have obtained both 2- and 4-nitrodiphenyl ether by heating one part of the appropriate nitrochlorobenzene with two parts of potassium phenate, in two parts of phenol, for five hours at 150°. The ortho nitro ether was described as a yellow oil of peculiar odor, boiling at 205° at 45 mm. pressure, and remaining liquid at -20°; the para compound, crystalline and melting at 61°, (b.p. 220° at 30 mm.)

Yields were not stated.

F. Ullmann[13] prepared 2-nitro diphenyl ether by a similar method comparing the yields using o-chloro-, o-bromo-, and o-iodonitrobenzenes (referred to page 9) and found them to be 65%, 68%-70%, and 96.2% respectively. In 1906, Ullmann and Sponagel[27] reported reduced copper to be an effective catalyst for this reaction, and again found the yields to be in the same order as above, using potassium phenate and the three halogenated benzenes in the preparation of diphenyl ether. Potassium phenate gave a much better yield (78.2%) than the sodium salt (33%) in the fusion with bromobenzene. These investigators have also obtained 2-nitrodiphenyl ether (Ref. 27, p. 103) by the following method: To a solution of 0.8g. of metallic potassium in 10g. of phenol, were added 4g. of m-bromonitrobenzene, and the mixture heated for three hours at 150°, then 30 minutes at 180°, When cool, the resulting oil, dissolved in ether, washed with alkali, and distilled at 14 mm. pressure gave 4.3 grams of m-nitrodiphenyl ether, boiling at 202-4°.

Raiford and Colbert[10], have prepared a large number of diphenyl ethers including 4-nitrodiphenyl ether, by a slight modification of this method. Para-nitrochlorobenzene (10g.) was heated with phenol (7.5g.) and potassium hydroxide (4.25g. in 15 cc. $H_2O$), at a temperature of 160° for six hours, then steam distilled to remove the unchanged nitrochlorobenzene. The yield of 4-nitrodiphenyl ether was 66.4%.

Recently Miss. Henley[28] has ascertained, by varying the temperature and proportions of the reactants, that the best yields are produced (95% of o-nitrodiphenyl ether) if 1 mol. of the halogen-nitro compound, 1.75 mols of phenol, 1.33 mols of pôtassium hydroxide (molten), and 0.1 mol of water are heated together at 200°-210° for 1 hour. The addition of copper bronze gave no improvement in the yields.

Attempts have been made by various investigators to obtain nitro derivatives[1,2] by direct nitration of diphenyl ether, usually a difficulty separable mixture of products being obtained. Suter[3] (see also page 1) has been most successful, nitrating a well stired solution of the ether (340g., 2 mols) in acetic anhydride (400 cc.), by adding a solution of a slight excess of fuming nitric acid of density 1.52 (100 cc. = 2.4 mols) in glacial acetic acid over a period of two hours, the temperature being maintained between 25°-30°. The products (mostly 2- and 4-nitrodiphenyl ethers) were noteasily separated by distillation, their boiling points being only 4° apart at 20 mm. pressure, but could be partially separated by freezing out the para isomer.

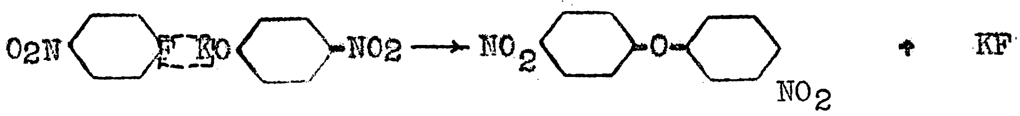
However, since the amines, which could be readily separated by the difference in solubility of their sulfates (ortho salt easily soluble, para only slightly so), were desired, the mixture was usually separated after reduction. The yield of the nitro products by this method of nitration was 370 grams (86% of theoretical), 54% of which proved to be the para isomer.

For the synthesis of 4-4'-dinitrodiphenyl ether, the following method is given by Haeussermann and Teichmann[12] (previously mentioned page 7). To four times the calculated amount of p-nitrochlorobenzene, heated in a metal bath to 225-235°, was added the finely powdered potassium salt of p-nitrophenol in small portions, and that temperature maintained for several hours. The product was them washed with water and steam distilled to remove unchanged nitrochlorobenzene. The melting point was given as 142-3°, no yield being stated. This compound has also been obtained as one of the products of nitration of diphenyl ether by Hoffmeister[29], and also by Mailhe and Murat[1]. As has been previously mentioned page 10, Rarick, Brewster and Dains[16] of this laboratroy have recently found the yield to be excellent and the reaction used by Haeussermann and Teichmann to proceed at a considerably lower temperature of p-nitrofluorobenzene is used instead of p-nitrochlorobenzene.

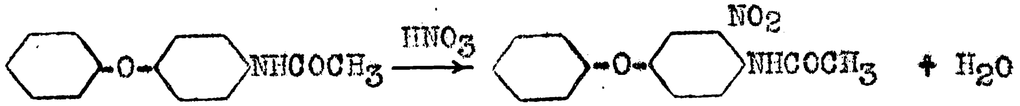
Willgerodt[30] in 1879, obtained 2,4-dinitrodiphenyl ether from 2,4-dinitrochlorobenzene and the equivalent quantity of potassium phenate in alcohol solution. The melting point of the product was given as 71°. Later Cook[23] synthesized this dinitro ether by heating 2,4-dinitrobromobenzene with potassium phenate on the water bath. More recently Bogert and Evans[21] have produced this compound by grinding together in a mortar, *in small portions*, 400 grams of 2,4-dinitrochlorobenzene with 300 grams of sodium phenate, which, after the reaction was complete, yielded 500 grams of the 2,4-dinitrodiphenylether, which represents a yield of 97.5%. Raiford and Colbert[10] have obtained this ether in 92.6% yield by a method analogous to that for their synthesis of 4-nitrodiphenyl ether (page 11).

The preparation of these nitrodiphenyl ethers for use in this investigations was accomplished by methods given above, or slight modifications, which are discussed in the appropriate places in the record of experimental work.

The 3,4'-dinitrodiphenyl ether, previously unreported, was easily obtained (see page 78 for experimental details), using the potassium salt of m-nitrophenol with p-nitrofluorobenzene, according to the following equation:



In the synthesis of 3,4-diiodo diphenyl ether, instead of using the corresponding dinitro compound, (3,4-dinitrodiphenyl ether, also previously obtained by fusion, m.p. 89° *C. I*, 74 (1915)) as a source of 3,4-diaminodiphenyl ether, it was found more convenient to prepare this latter compound from 3-nitro-4-acetaminodiphenyl ether. In this work nitration of 4-acetaminodiphenyl ether at ordinary temperatures, using glacial acetic acid as a solvent (see page 142 ), as shown in the following equation,



had yielded this compound, but the constitution of the product was yet unproved when it was reported by Scarborough[31], who used a similar method, nitrating the 4-acetaminodiphenyl ether in the same solvent but at a higher temperature (80°), and reported the product to melt at 100°. The constitution of the nitro compound was established by Scarborough by the following facts: (1) conversion by deacetylation and deamination to a product with properties identical with the 3-nitrodiphenyl ether, previously reported by Ullmann and Sponagel[27];

further reduction and acetylation yielding 3-acetaminodiphenyl ether melting at 83°, also previously described by Ullmann and Sponagel; (2) the mono-bromination product of the 3-nitro-4-acetaminodiphenyl ether was found to be identical with the nitration product of 4-bromo-4'-acetoamino diphenyl ether; (3) the 3-nitro-4-aminodiphenyl ether obtained from the nitro compound did not form a salt with a mineral acid; (4) other experiments had shown a nitro group in one nucleus to direct entering substituents to the other nucleus independent of groups other than nitro, present. The hydrolysis to the nitro-amine (3-nitro-4-aminodiphenyl ether) was carried out by Scarborough by boiling in a solution of alcohol and hydrochloric acid. The producy was a black oil, which when crystallized from dilute methyl alcohol yielded bright red prisms melting at 82°. Attempts to obtain the diamine from this, and to condense with benzil were described as unsuccessful. The 3-nitro-4-acetaminodiphenyl ether has since been reported by Oesterlin[32], who carried out the nitration of the p-acetoaminodiphenyl ether in 10 parts of acetic acid, adding fuming nitric acid (1.1 mols) diluted slightly with glacial acetic acid, and warming two hours on the water bath. The melting point of the product after crystallization from alcohol was reported by this investigator to be 104°. Oesterlin has reduced the 3-nitro-4-acetaminodiphenyl ether in 50% alcohol with sodium hydrosulfite, obtaining

0.9 g. of 3-amino-4-acetaminodiphenyl ether, m.p. 124°, but states that most of the product was unfortunately lost. By hydrolysis of the 3-nitro-4-acetaminodiphenyl ether using alcoholic barium hydroxide, this investigator also obtained 3-nitro-4-aminodiphenyl ether (obtained by Scarborough, see above) and reported two melting points for this substance (47-8° and 81°). Hydrolysis of the 3-amino-4-acetaminodiphenyl ether by the same method, or reduction of the 3-nitro-4-aminodiphenyl ether with sodium hydrosulfite, yielded 3,4-diaminodiphenyl ether, which was obtained as an ether soluble oil, becoming crystalline on short rubbing and melting at 66°. Oesterlin, however, was more successful in condensing this diamine with benzil (3,3'-dinitro-) that was Scarborough, amd assigned the formula given above because of the ease with which this reaction was found to occur. With the exception of the 3-amino-4-acetaminodiphenyl ether which was mostly lost no yields were given.

The constitution of the nitration product of the 4-acetaminodiphenyl ether obtained in this investigation, has thus been accepted from the work of these investigators, and from this compound the 3,4-diiododiphenyl ether has been synthesized. The compounds obtained from 3-nitro-4-acetaminodiphenyl ether by Scarborough and Osterlin, have also been synthesized, in this work, by slightly different methods in some cases. (See experimental part). The melting point of 3-amino-4-acetaminodiphenyl ether, of which Osterlin obtained only 0.9g., and of 3,4-diaminodiphenyl ether, have been found to be slightly higher than reported by this investigator.

Reduction of nitrodiphenyl ethers to produce amines has usually been accomplished by reducing agents generally employed for aromatic nitro compounds. Haeussermann and Teichmann[12] prepared 4-aminodiphenyl ether 9 (m.p. 84°, b.p. 187-189° at 14 mm., acetyl m.p. 127°), and 4,4'-diaminodiphenyl ether (m.p. 186-7°) by reduction of the corresponding nitro compounds in alcohol solution, with tin and hydrochloric acid, removing the tin salts after reduction by means of hydrogen sulfide. Ullmann (Ref. 13, p. 1878) reduced 2-nitrodiphenyl ether (10g.) in alcohol (40 cc.) by adding this solution to a warm solution of stannous chloride (31g.) in concentrated hydrochloric acid (100 cc.) and boiling for a short time. The amine (m.p. 42.5-43°; b.p. 307-8° at 728 mm.; 172-3° at 14 mm.) was recovered by extracting the solution with ether, after rendering strongly alkaline with sodium hydroxide.

Other investigators have used such reducing agents as iron powder and hydrochloric acid[3,21]; stannous chlor- in glacial acetic acid, ether, or alcohol while pas ing in dry hydrogen chloride[11,19,31]; and sodium hydrosulfite[32]. The last mentioned agent was tried in some cases in this investigation but was generally found to produce as the main product, aromatic sulfamates, compounds of the type $R-NHSO_3Na$, as described by Seyewetz and collaborators[33], while although yielding some amine on boiling with 30% hydrochloric acid, were not completely hydrolyzed by this treatment after an hour or even longer. Exception to this formation of sulfamates was found by Seyewetz, in the reduction of m-dinitrobenzene. The reductions carried out by Oesterlin (page 17) on 3-nitro-4-acetamino and 3-nitro-4-aminodiphenyl ethers, apparently constitute similar cases.

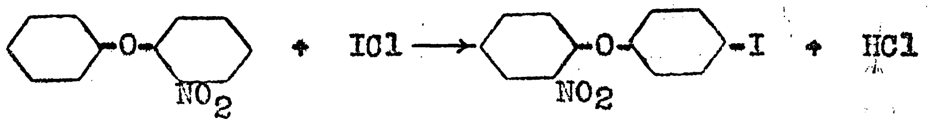
Suter[3] has obtained best results in the reduction of 2-and 4-nitrodiphenyl ethers by slowly adding zinc dust (80g.) to a gently boiling solution of the nitro compound (43g., 0.2 mol), and calcium chloride (20g.), in a mixture of ethyl alcohol (200 cc.) and water (75 cc.) The solution was kept boiling gently for an hour after all the zinc had been added, cooled, filtered from any of the hydrazo compound that had been formed, then diluted with water to precipitate the amine. The yield was practically theoretical. The previously unobtained 2-acetaminodiphenyl ether was reported by Suter to melt at 81°.

Ullmann and Sponagel[27] have obtained 4-aminodiphenyl ether (also 3-aminodiphenyl ether) in 64.6% yield, directly, by fusion of p-bromoaniline with potassium hydroxide and phenol, with copper powder as a catalyst, and heating for three hours at a temperature of 180°. The reaction was carried out in an atmosphere of hydrogen, otherwise the product was highly oxidized. The amine was recovered by extraction with ether, washed with alkali, the ether evaporated then the product recrystallized from a mixture of carbon disulfide and ligroin, which yielded colorless crystals melting at 84°. The 3-aminodiphenyl ether was obtained by a similar methld in 57% yield, and purified by vacuum distillation, boiling at 190-1° at 14 mm., melting at 37°, its acetyl derivative melting at 83°.

The methods of reduction of nitrodiphenyl ethers used in this investigation were similar to those given above, with a number of reductions using iron or zinc and acetic acid, or hydrogen under pressure with platinum catalyst. The construction of the apparatus and preparation of the catalyst necessary in the last method given, was according to the directions specified by Adams, Vorhees, and Shriner[17].

The constitution of compounds obtained by direct iodinatiom or nitration was established either by synthesis by some other method in which the positions occupied by the substituents in the ether produced were known, or by conversion by chemical reactions to a known compound. Examples of these methods have been given (1) in the proof of constitution of the diiodo ether obtained from direct iodination of diphenyl ether, through synthesis of this substance from 4,4'-dinitrodiphenyl ether (page 7); and (2) the proof of the constitution of 4-iodo-4'-nitro diphenyl ether produced by nitration of 4-iodo-diphenyl ether, by the conversion of the iono-nitro ether by reduction and the Sandmeyer reaction into the then known 4,4'dinitrodiphenyl ether (page 8).

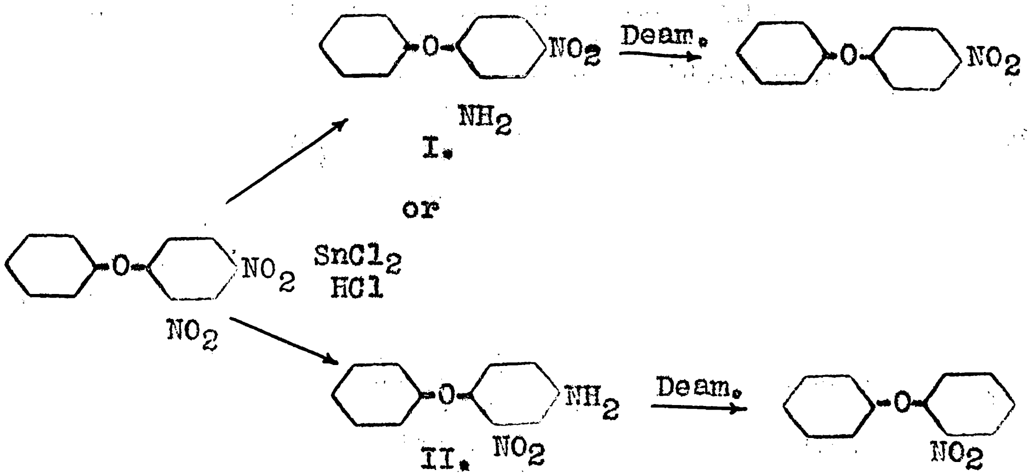
Iodination of 2-nitrodiphenyl ether, with iodine monochloride in glacial acetic acid, yielded a product (page 6) which has been recently reported by McCombie, Macimillan and Scarborough[19], being obtained by them by the same method, which is represented by the following equation:



These investigators assigned the structure indicated, from analogy with the products of chlorination in which the halogen was found to enter at position 4', and report that in the attempted deamination of the amine obtained by reduction of this nitro iodo ether they were unsuccessful in obtaining a pure specimen of 4-iododiphenyl ether. In this investigation, deamination was found to be successful yielding a good sample of 4-iododiphenyl ether, thus proving the iodine atom to be in position 4 or 4'. By conversion of the amine to 2,4'-diiodo diphenyl ether, the constitution of which had been established by another method, the structure indicated above, and which was assigned by the above investigators, was positively proved to be correct.

In the synthesis of 2,4-diiodo diphenyl ether, it was found that the corresponding diamino compound (2,4-diamino diphenyl ether), by the Sandmeyer reaction, gave relatively low yields of the desired diiodo product accompanied by considerable by-products, mostly in the form of tar (see page 138 ). This is in accordance with other experience with diazotization of aromatic amino groups in the meta position to each other, as described by Cain[20]. Since a corresponding nitro amine (2-nitro-4-amino diphenyl ether) had been described by Bogert and Evans[21], it was expected that synthesis of the diiodo compound from this in steps, by replacing first the one amino group by iodine, then reduction and replacement by the remaining nitro group, would produce the desired product in better yield than had been obtained previously using the diamine.

This expectation was found to be true; and the reactions were accompanied by less tarry by-products than before. In the case of 3,4-diamino diphenyl ether, no appreciable yield of the desired diiodo product was obtained from the diamine (see page 158 ), which further agrees with previous experience with ortho aromatic diamino compounds as recorded by Cain. It has been found (compare Vignon[22]) that an intramolecular reaction occurs as soon as one amino group is diazotized yielding azimino derivatives, which prevents the formation of the tetraazo compound. For this reason it was found necessary to synthesize the 3,4-diiododiphenyl ether in steps, from a nitro-amine, as indicated from 2,4-diiododiphenyl ether above (see page 160). In the synthesis of the 2,4-diiodo ether from the nitro amone which had been prepared by a method following quite closely that indicated by Bogert and Evans, it was observed that the solubility of the sulfates of the amines obtained preliminary to diazotization was in reverse order to that previously experienced, and which has also been observed by Suter[3]. These salts with the amino group in the 2(ortho) position were found to be easily soluble in aqueous solutions while those in the 4(para) position were not nearly so much so. Bogert and Evans assigned the structure of 2-nitro-4-aminodiphenyl ether to the nitroamine on the basis that deamination yielded an oily product which after distillation with superheated steam did not solidify at $-20^{\circ}C$; hence which they supposed to be 2-nitro diphenyl ether, since this substance does not dolidify at this temperature[12], while the alternative product, 4-nitro diphenyl ether, melts at 61° (the latter was believed by them, however, to melt at 123.5° because of the erroneous observations made by Cook[23]). These reactions, including the formation of the nitro-amine by reduction of 2,4-dinitrodiphenyl ether with stannous chloride-hydrogen chloride in alcohol solution, are represented by the following equations, which allow also for the possible formation of the alternative nitro-amine.



For the reasons stated above there was some doubt that the conclusions of Bogert and Evans were correct. and the possibility was entertained that I. above might have been the correct formula to be assigned rather than II.

In support of this is the fact that Anschutz and Heusler[24] found the nitro group in position 2, of 2,4-dinitrotoluene to be reduced by stannous chloride in preference to the one in position 4. Since the constitution of the derivatives obtained from the nitro-amine intermediate in the synthesis of the desired diiodo ether (an iodo-nitro ether, iodo-amino ether, and acetyl derivative), depended on the correctness of the formula which had been chosen (I or II), deamination was again carried out on a sample of the nitro-amine, whose melting point and other properties checked with that observed by Bogert and Evans, and the oily product which failed to dolidify when cooled in an ice salt mixture distilled under reduced pressure. The distilled product solidified on cooling and was shown (page 131) by melting point and mixed melting point to be 4-nitro-diphenyl ether, which proved formula I to represent the correct structure rather than formula II. A number of derivatives obtained from this nitro-amine by Bogert and Evans are thus incorrectly named[21].

Two of the three mono-iodo derivatives obtained, 2, and 4-iododiphenyl ethers have been successfully nitrated and the constitution of the products established. The nitration was found to proceed smoothly under proper conditions for the ortho isomer, but the 4-iododiphenyl ether lost iodine quite easily under all conditions of nitration. In this latter case a study of the products appearing during the reaction indicated (see pages 102 and 103 for complete discussion) that the iodine atom was at least partially removed, being replaced by a nitro group; the free iodine resulting then acting as an iodinating agent. Under certain conditions of nitration, both atoms of iodine were also found to be removed from 4,4'-diiododiphenyl ether, yielding 4,4'-dinitrodiphenyl ether. Fox and Turner[34] have recently found that 4-chloro-4'-bromodiphenyl ethers eliminate halogen atoms on nitration, but that the corresponding ortho substituted compoundsdo not do so unless the nitration is drastic, which is essentially the behavior observed for iodine atoms in this investigation.

Certain of the compounds obtained in this rerearch have been found to be oils, which did not crystallize after purification by reduced pressure distillation even after standing several months, and which on strong cooling became very viscous but still did not crystallize. In cases where only a few grams of the product were obtained, small distilling flasks of approximately 5 cc. capacity were blown from pyrex glass for the distillation of the liquid. These were constructed with

with fractionating columns approximately 2 cm. long by the method described by Noyes and Skinner[25], and with a low flame from a small burner, gave an even distillation which, with a few cc. of liquid in all respects approximated distillation of ordinary laboratory proportions. For most of these oily compounds specific gravities ($\frac{25^\circ}{4^\circ}$ with reference to water), and indices of refraction were determined, the latter with an Abbe refractometer using sodium light. The specific gravity determinations were made using small capillary pyknometers with capacities of 0.2-0.3 cc., blown from pyrex. With these, specific gravities were easily peproducible on a given sample to one part in the second decimal place, and often to 1-2 parts in the third. Corrections for air buoyancy were found to amount to about 0.2 mg in most cases, which is significant if the results are to be expressed in the third decimal place, hence the observed weights were corrected in all cases. The formula used fnr this calculation was the following,

$$W_v = W_a\left(1+\frac{s}{L}-\frac{s}{D}\right)$$

where $W_v$=wt. in vacuo, $W_a$=observed wt. in air, s = density of air (0.00114 g. per cc.), L=density of the liquid (must first be approximated for calculation), and D =

density of weights (aluminum =2.7). Incidentally it may be stated that these specific gravities ($\frac{25^{\circ}}{4^{\circ}}$ with reference to water) give numerically the absolute density of the liquid, in vacuo, in grams per milliliter. To obtain the absolute density in grams per cubic centimeter (since 1 liter of water at 4°C is unequal to 1 decimeter) it would be necessary to multiply the values obtained by 0.999973, which in these results is entirely insignificant. Hence the numerical values obtained for specific gravities may be considered to represent, also absolute densities (in vacuo) in grams per cc. or ml.

It is interesting to note that three of the diiododiphenyl ethers obtained as oils were very nearly of the same specific gravity, and had almost precisely the same indices of refraction. The two iodo-amines remaining liquid showed a close similarity of those physical properties also, which is to be expected from the physical theory of molecular refraction. (See texts on Physical Chemistry.)

Synthesis of some of these iododiphenyl ether derivatives by the methods described, require the preparation of a number of amino compounds from which acetyl derivatives were usually also obtained. In the case of 4-iodo-4'-aminodiphenyl ether, the urea and urethane were also synthesized (see pages 110 and 111 ). Both the acetyl and urethane derivatives of 4-amino diphenyl ether were iodinated giving mono-iodo derivatives, the position of the iodine atom in each of which was proved to be at 4', by synthesis from 4-iodo-4'aminodiphenyl ether mentioned above. Attempts to iodinate the urea from 4-amino-diphenyl ether, previously obtained by Lange and Reed[45] were unsuccessful, this substance being unable to withstand the methods used in introduction of iodine in the other derivatives.

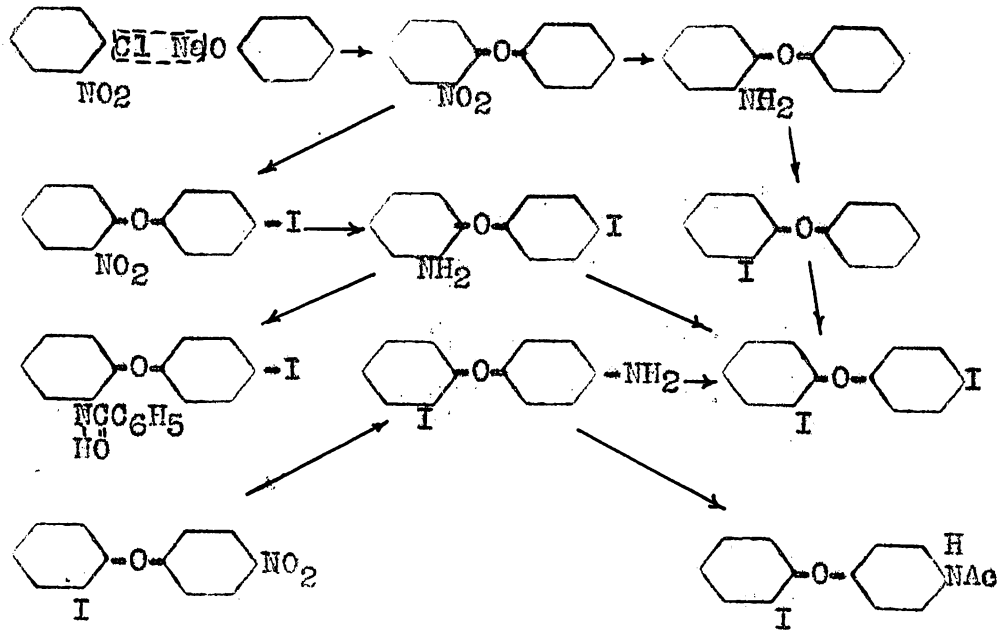
For convenience in description, the diphenyl ether derivatives synthesized are placed in the following groups, based on positions of substitution in the ether, the numerals indicating the positions occupied:

A. 2 or 2 and 4'.
B. 3 or 3 and 4'.
C. 4 or 4 and 4'.
D. 2 and 4.
E. 3 and 4.

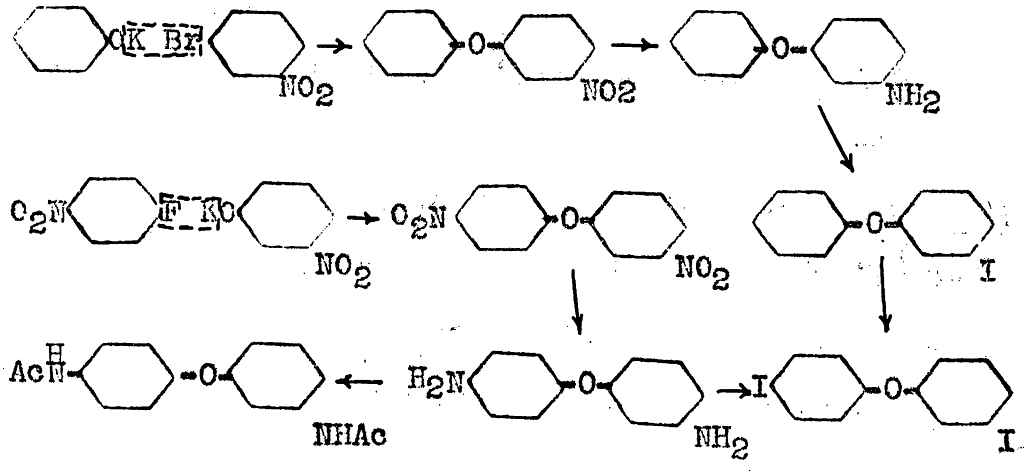
These groups are shown in the following diagrammatic representation of syntheses in this investigation:

## SERIES I. DIPHENYL ETHER DERIVATIVES

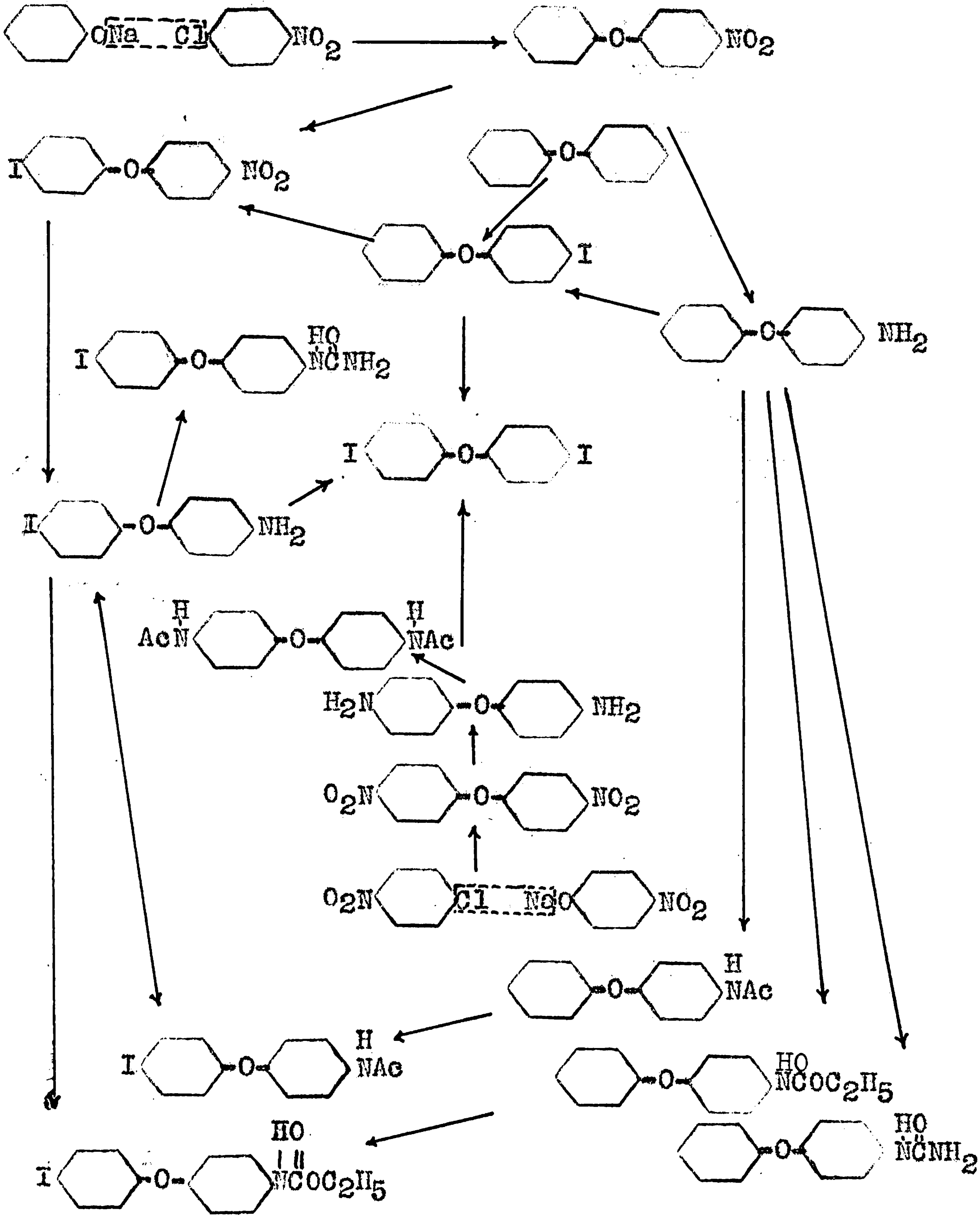
**Group A.** Substituents in positions 2, or 2 and 4'.



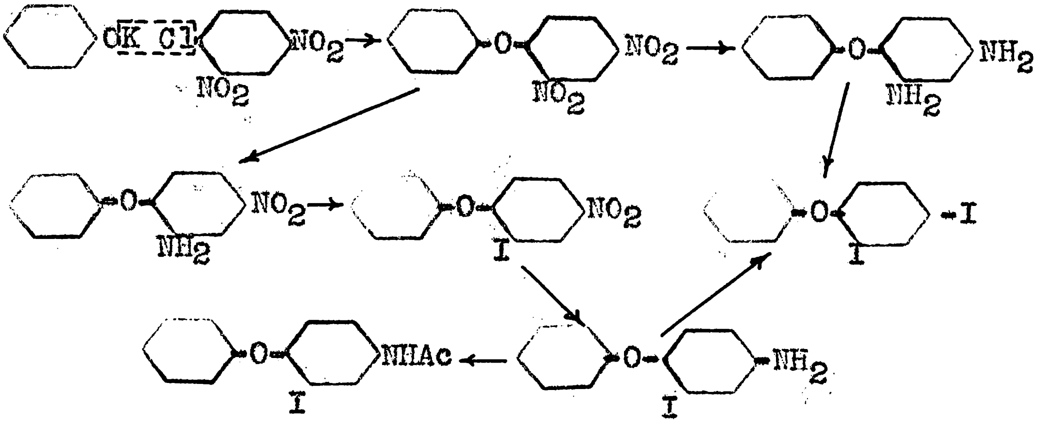
**Group B.** Substituents in positions 3, or 3 and 4'.



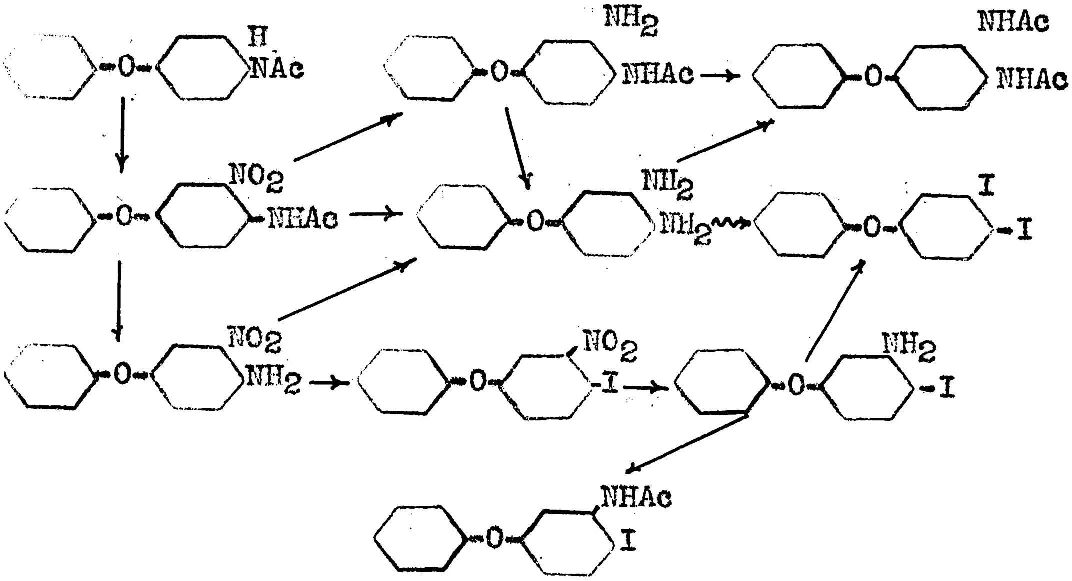
**Group C.** Substituents in positions 4, or 4 and 4'.



**Group D:** Substitutents in positions 2 and 4.

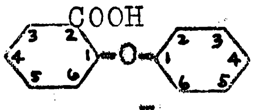


**Group E:** Substitutents in positions 3 and 4.



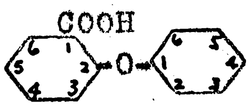
## II. Derivatives of Carboxylic Diphenyl Ethers.

In the preceding Masters thesis[47] (mentioned page 1) a study was made of certain iodo and other derivatives of 2-phenoxy-benzoic acid,



I

or



II

*

also called ortho-carboxydiphenyl ether, phenyl ether of salicylic acid, etc. The compounds synthesized consisted of two general types:

(A) Derivatives in which a substituent group or atom (nitro,- amino acetamino,- or iodo-) was in the same aromatic nucleus as the carboxyl group and occupied the position 4 of the formula I indicated above; and

(B) Derivatives in which the substituent group, or atom was in the nucleus not containing the carboxyl group, but occupied position 4' of formula I above.

This formed two parallel series of compounds with substituent groups in one nucleus in one series and on the other nucleus in the other series.

* These carboxylic diphenyl ether derivatives are usually named as substituted benzoic acids.

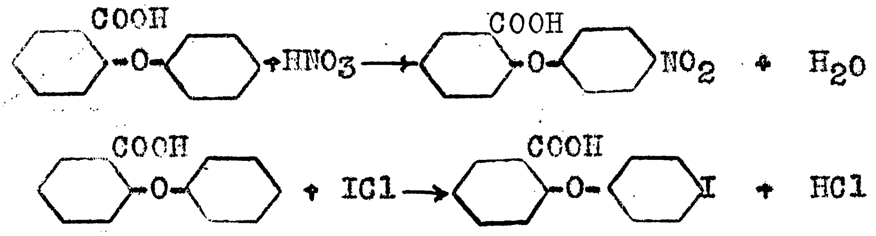
The 2-phenoxy-benzoic acid has been synthesized in small quantities by various investigators, (See Master's thesis- page 9 and seq.) and the nitro compound under series (A) above has been obtained by Haeussermann and Bauer[26]. With this exception the compounds prepared in both series were new.

The nitro compounds from which amino-, acetyl-amino-, and iodo derivatives were obtained, were synthesized by the same two general methods, which have previously been given (page 8) for other derivatives of diphenyl ether, i.e. direct nitration, or fusion of an alkali salt of a phenol with a halogenated aromatic compound.

The amino-, acetamino-, and iodo derivatives in series A were obtained by successive reactions from the nitro compound (2-phenoxy-5-nitro benzoic acid), for which a method for preparation of a large quantity by fusion was developed, carrying out a slight modification of the procedure given by Haeussermann and Bauer (Master's thesis- page 17). This substance, however, has been further used in studies described in this present thesis, amd an improved method giving superior yields to that described in the Master's thesis has been found. (See page 173 ).

A large scale method was also developed in the

Master's thesis for the preparation of 2-phenoxy-benzoic acid, the parent substance of these compounds. By direct nitration and direct iodination according to the two equations given below, the nitro and iodo derivatives in series B were obtained.

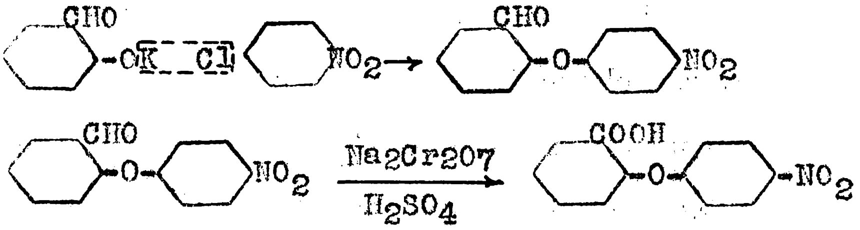


It was first thought nitration might yield the nitro derivative of series A (2-phenoxy-5-nitro-benzoic acid), but a comparison of the properties of the product with this known substance, proved the two to be different, although the analysis showed the nitration product to be a mono nitro derivative. By reduction and the Sandmeyer reaction, the nitration product was converted into the same iodo derivative as was obtained by direct iodination showing that the two substitutents entered the same position in the 2-phenoxy benzoic acid on nitration and iodination.

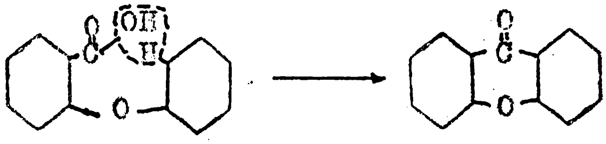
The constitution of the mono-nitro compdund from direct nitration, and hence the iodo derivative also, was established by the following two independent methods.

(1) By a study of the product formed when the compound of unknown constitution was converted into a xanthone.

(2) By synthesis of 2-(4-nitrophenoxy)-benzoic acid (the nitro derivative under series B) which proved to be identical with the nitration product. This synthesis was accomplished by methods indicated by the following equations (see Master(s thesis pages 27-29):

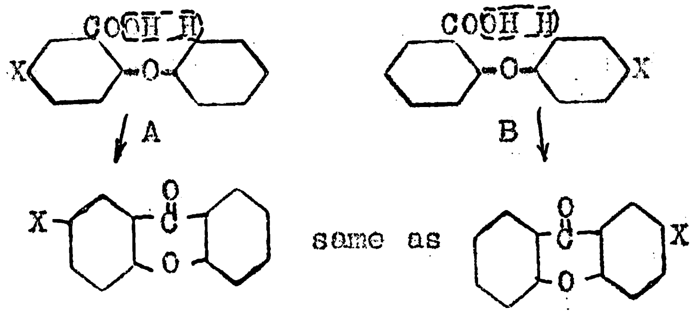


Compounds which are derivatives of 2-phenoxy-benzoic acid have been used in synthesizing substituted xanthones by Graebe[35], Arbenz[36], Ullmann and Wagner[37], and others, employing the following reaction in which concentrated sulfuric, hydrochloric, hydriodic acids, or phosphorus pentachloride were used as dehydrating agents:



Graebe[35] found xanthone to be formed slowly from 2-phenoxy-benzoic acid, in accordance to the above reaction, when this acid is dissolved in cold concentrated sulfuric acid. At the temperature of the water bath the yield of xanthone was practically quantitative in a few minutes. In a similar reaction using a dinitro-derivative, Arbenz[36] found ring closure to the dinitroxanthone to take place much more slowly, and that yields approaching quantitative were obtained only at temperatures of 150° to 180°. Experiments with the mono-nitro derivatives in this investigation showed these compounds to be converted almost completely into nitroxanthones, by heating at 100° in sulfuric acid, for fifteen minutes to one half hour.

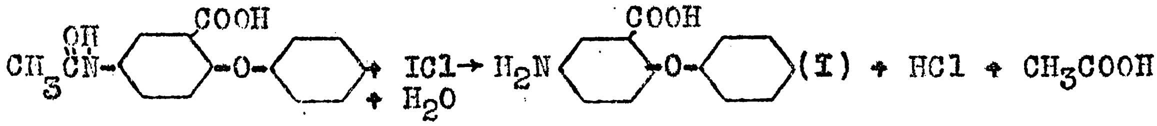
Inspection of the following equations shows that compounds of types A or B (see page 33) will yield identical substituted xanthones if the substitutent X is the same in each case.



Although the mono-nitro product from direct nitration of 2-phenoxy-benzoic acid was shown to be different from the known 2-phenoxy-5-nitro-benzoic acid (series A), both compounds were found to yield the same xanthone on ring closure; hence the nitration product was 2-(4-nitrophenoxy)-benzoic acid, or the nitro compound under series B.

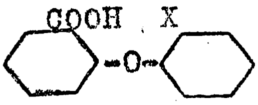
Similarly, 2-phenoxy-5-iodo-benzoic acid, obtained by reduction and Sandmeyer's reaction from 2-phenoxy-5-nitro-benzoic acid, and the mono-iodo-product from direct iodination of 2-phenoxy-benzoic acid, although different, were found to yield identical iodi-xanthones; which gave an added proof that the iodination product was 2(4-iodophenoxy)-benzoic acid. (Master's thesis, page 43).

In the Master's thesis iodination of the acetyl derivative under series A (2-phenoxy-5-acetamino-benzoic acid) was attempted, using iodine monochloride and glacial acetic acid as a solvent. The product of this reaction, however, was found to be a mono-iodo derivative of the corresponding amine, hydrolysis of the acetoamino grouping having taken place according to the following reaction:

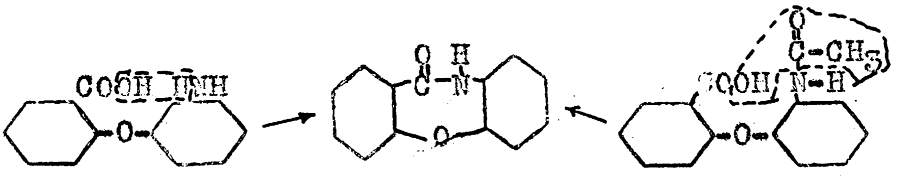


The orientation of the iodine atom in the above remained unproved in the Master's thesis, but has been shown in the present investigation to be in the position indicated as a possibility. The means of this proof will be explained in the following discussion of further research on carboxylic diphenyl ethers, made in this thesis.

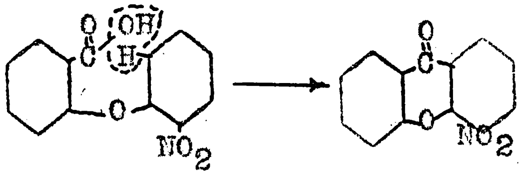
An extension of these studies on the derivatives of 2-phenoxy benzoic acid has been made in this present investigation, to a third type of compounds (designated as Type C), with substitutent groups X (nitro,-amino-, acetamino,- and iodo-) in the nucleus not containing the carboxyl group, and occupying a position ortho to the ether-oxy grouping as:



Compounds of this third type all have been synthesized by the same general methods as have been described for derivatives of Types A and B. The amine and its acetyl derivative of this type were found to lose water or acetic acid respectively, on heating slightly above their melting points, forming the lactam with a seven membered ring, as shown in the equation. (See pages 167 and 168 ):



The nitro derivative of this type, 2-(2-nitrophenoxy)-benzoic acid has been readily converted into 4-nitroxanthone by warming in concentrated sulfuric acid, as have been the other nitro derivatives of types A and B previously obtained in the Master's thesis. (Referred to page 33). The following reaction represents this formation of 4-nitroxanthone:

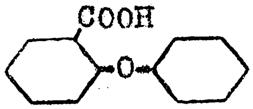


Ullmann and Wagner[37] have synthesized 2-nitroxanthone (m.p. 176°) by an analogous reaction. The 2-nitroxanthone was likewise obtained in the Master's thesis as fine colorless needles melting at 203°-4°. 2-nitroxanthone has been produced by Purgotti[38] by the same method, but no melting point was reported.

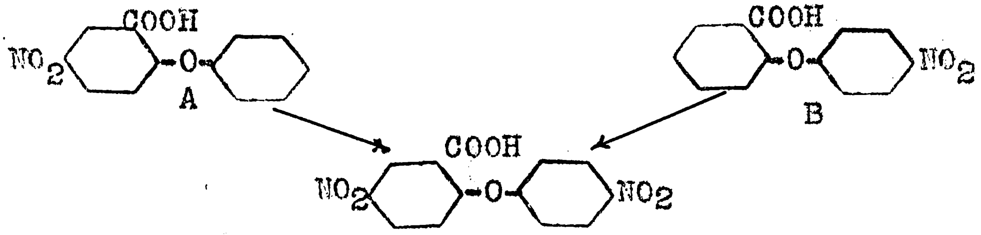
Dhar[39] has reported all four of the mono nitroxanthones, obtaining them by a different method. Three of these (the 1-, 2-, and 3- isomers) were obtained by heating the alkali salts of a nitrophenol and o-chlorobenzoic acid with a small amount of copper powder for a short time at a temperature of 140°-160°, then cooling and extracting at $100^{\circ}$ with concentrated sulfuric acid, from which the product was precipitated by dilution with water. The products were reported as "slender brown needles) with melting points of the 1- and 2- isomers at $210^{\circ}$ and $200^{\circ}$ respectively, the 3-nitroxanthone not being obtained in sufficient purity to melt at $176^{\circ}$, the value previously reported by Ullmann and Wagner. Unsuccessful attempts were made by Dhar to synthesize 4-nitroxanthone by the same method. Finally, however, supposedly this compound, was obtained by him by the following method: "Fifty grams of salicylic acid and 50g. of o-nitrophenol were boiled with 100g. of acetic anhydride for 10 hours, then the whole distilled, a tarry material passing over at a very high temperature." This latter, when boiled with alcohol with decolorizing charcoal, yielded from the extract "about 2.5g. of yellow needles melting at $127^{\circ}$". One analysis gave 5.71% nitrogen against a theoretical percent of $5.8^{0}$for nitroxanthone.

The 2-nitroxanthone obtained by Dhar, thus evidently was not quite pure, melting three to four degrees below that observed in the Master's thesis. The melting point reported above for 4-nitroxanthone $127^{\circ}$) differs widely from the value of $190^{\circ}$ obtained n this investigation, Considering the method of preparation and results of analyses, there can be no doubt as to the constitution of the product obtained in this work. Some source of error, perhaps in the method employed by Dhar, by which a mixture of several products might easily have been obtained, must be responsible for the wide divergence in melting points.

Also included in this extension of studies on derivatives of 2-phenoxy benzoic acid, are several compounds in which both of the positions which were substituted in derivatives of types A and B (page 33), are occupied at once; i.e., both positions 4 and 4' in the formula:

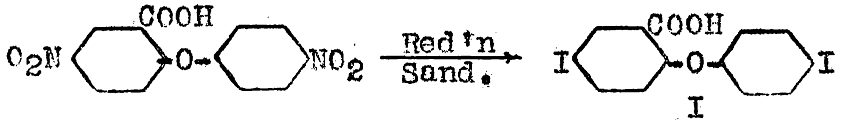


Thus by slightly different methods of nitration both of the mono-nitro derivatives (Types A and B) have yielded 2-(4-nitrophenoxy)-5-nitro-benzoic acid. (2-carboxy-4,4'-dinitrodiphenyl ether.

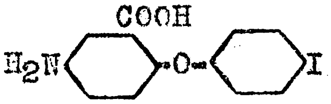


This dinitro acid has been obtained by Arbenz[36] along with nitrophenols, and nitrosalicylic acid, by allowing five parts of ice cold concentrated nitric acid to react with 2-phenoxy-benzoic acid for half an hour. This investigator found purification of the product to be best accomplished through fractional crystallization of the barium salts of the two acids produced in the nitration, the salt of dinitrosalicylic acid being the more soluble of the two; and reported the melting point of the 2-(4-nitrophenoxy)-5-nitrobenzoic acid to be 153°. In this present investigation samples of this compound from the separate sources represented in the above equation, or a mixture of the two, on slow heating showed a transition point at 158° and melted finally at 170-171°. (See pages 175 and 177 ).

By reduction and the Sandmeyer reaction, this dinitro derivative has been converted to 2-(4-iodophenoxy)-5-iodobenzoic acid, as represented by the equation:

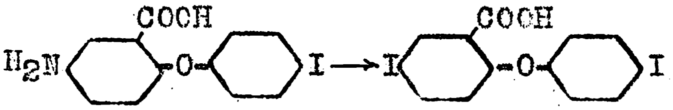


The 2-phenoxy-5-nitrobenzoic acid (A above) has been iodinated to give a mono-iodo substitution product, which on reduction easily yielded the corresponding amine, represented by the following formula:



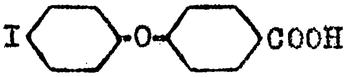
II.

This compound was found to be identical in melting point with the product of iodination of 2-phenoxy-5-acetamino-benzoic acid obtained in the Master's thesis[47] (referred to page 38). The structure of this substance, represented by the above formula, was established by conversion to the then known 2-(4-iodophenoxy)-5-iodo-benzoic acid (formula I above) as represented by the equation:



This same diiodo acid has also been obtained by iodination of 2-phenoxy-5-iodo benzoic acid (page 184 ).

For comparison with the mono-iodo derivatives of 2-phenoxy-benzoic acid which have been obtained, the mono-iodo substitution product of 4-phenoxy benzoic acid with the following structure has been synthesized.



This compound, 4-(4-iodophenoxy)-benzoic acid, was obtained from the corresponding nitro compound by similar reactions as have been used in synthesis of the other iodo derivatives.

Haeussermann and Bauer[49] first obtained 4-(4-nitrophenoxy)-benzoic acid by stiring the di-potassium salt of p-hydroxy-benzoic acid into an excess of p-nitrochlorobenzene, the latter at 160°, then raising the temperature to 235° where it was held for 6 hours. The product, slightly soluble in hot alcohol, ether, and chloroform, and insoluble in water, was reported to melt at 236-7°. These investigators also reduced the nitro acid to 4-(4-aminophenoxy)-benzoic acid, using tin and hydroshloric acid, and found the amino acid to melt at 193-4°.

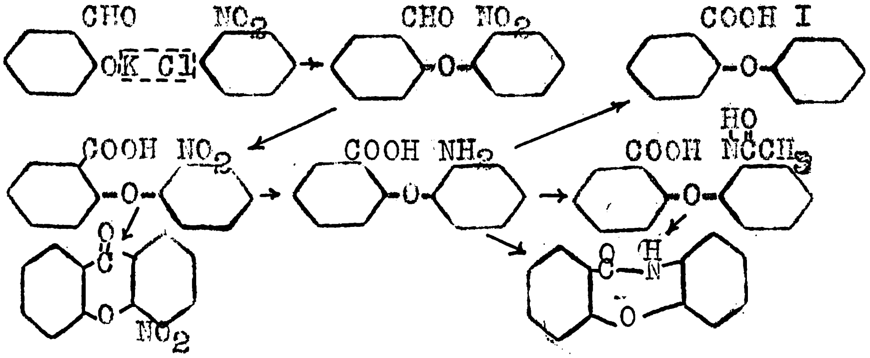
Recently Suter and Oberg[40] have synthesized this nitro compound by fusion of the potassium salt of p-hydroxy benzaldehyde with an excess of nitrochlorobenzene, and subsequent oxidation of the 4-(4-nitrophenoxy)-benzaldehyde obtained (75% yield), using sodium dichromate and sulphuric acid (yielded 79% of theoretical of the nitro acid. For temperatures and proportions of reactants used in this synthesis by Suter and Oberg, see the paralled synthesis in this investigation of the isomeric 2-(2-nitrophenoxy)-benzoic acid, (page 162).

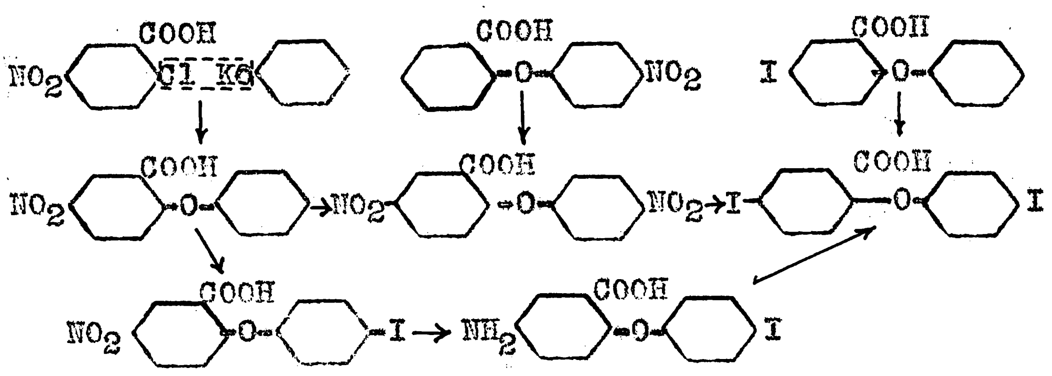
The 4-(4-nitrophenoxy)-benzoic acid used in this work, however, was obtained more conveniently by using reactions (see experimental part) similar to those above, with nitrofluorobenzene substituted for nitrochlorobenzene, the use of which has been previously mentioned, pages 10 and 14. (See also the work of Rarick, Brewster and Dains[16].) The product has been reduced to the amine most satisfactorily using hydrogen under pressure with platinum catalyst. (page 186 ).

These syntheses in the carboxylic-diphenyl ether series in this present investigation, which are a continuation of those described in the Master's thesis, are represented diagrammatically in the following scheme.

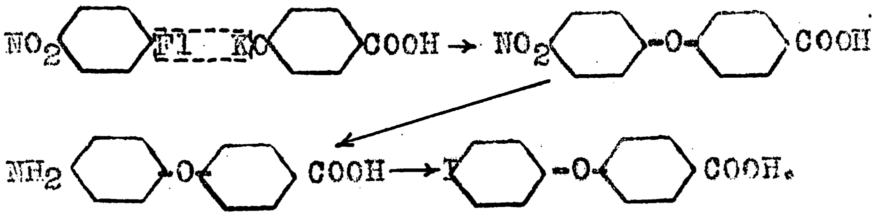
## SERIES II. CARBOXY-DIPHENYL ETHERS

### A. Derivatives of 2-phenoxy benzoic acid.





B. Derivatives of 4-phenoxy benzoic acid.



Considerable research has recently been done to determine the relative directive or orienting powers of various substituent groups, when further substitution occurs in the presence of one or more of these groups in one or both nucleii of diphenyl ether.

Lea and Robinson[41] have concluded (1926) from their studies that a method group has much greater directive power tham either phenoxy or p-tolyloxy radicals.

More recently Scarborough and collaborators[31,19] have ascertained that hydroxy, amono-, and acetamino-groups are of greater influence than halogens or alkyl radicals. Acetamino- groups are also found to be stronger ortho or para directing than phenoxy-, for entering nitro groups or halogens, except that the latter there seems to be a strong steric factor preventing substitution in the ortho position to acetamino- group. Hence the p-acetaminophenoxy- radical is found to be of greater influence than the acetamino- group if the entering substituent is halogen. It is further concluded that the presence of a nitro group in one nucleus directs entering substitutents to the other nucleus regardless of groups, other than nitro, present in the nucleus.

Nitration, bromination, and chlorination of diphenyl ether and derivatives (by the above investigators, those mentioned page 2, also Henley and Turner[42], and others), have shown in general that such entering groups or atoms ($-NO_2$, -Cl, -Br) tend to substitute in the para (4 and 4') rather than the ortho (2,2', 6 and 6') positions; and that the presence of one of these substituents in one nucleus renders further substitution in that nucleus much more difficult, and also slightly more so in the other nucleus. The effect is such that further substitution although slightly more difficult than the first, takes place in the other ring. Nitro groups are found to be of greater influence in inhibiting this substitution than halogens, but the latter show much greater tendency to enter para to contrast to ortho positions. Thus Suter[3] has found in the nitration of diphenyl ether, that 54%, or slightly more than half of the mono-nitro products consisted of the para isomer, but on bromination the halogen entered only the para positions. Mono-bromination with the calculated amount of bromine in glacial acetic acid yielded 47% of the para-bromo- compound (4-bromodiphenyl ether), most of the remainder of the bromine going to form 4,4'-dibromodiphenyl ether. It is interesting to note that in this present investigatinn the iodination of diphenyl ether, by a similar method using iodine monochloride as iodinating agent, resulted in somewhat higher yield of mono-iodo product (59%) than was obtained bt Suter in bromination.

From the results of this present work, it may be concluded, with respect to directive effects and substitution, that iodine partakes of the nature of the other halogens. Also that the presence of an iodine atom in one nucleus makes substitution by a nitro group more difficult in that nucleus, so that the nitro group enters the other ring, which in this case has been unsubstituted. The acetamino- and urethane radicals appear to have like influence in directing the entrance of iodine atoms.

The carboxyl group is of similar directing influence as has been described for the nitro, but slightly weaker than the latter. This is shown by the facts that on iodination and nitration of 2-phenoxy benzoic acid, the entering group occupies the para position in the nucleus not containing the carboxyl group, and that on further nitration of the mono-nitro product, the second nitro group enters the nucleus containing the carboxyl rather than the one containing the nitro group.

Throughout the experimental work, a thermometer which had been calibrated with a standard thermometer from the Bureau of Standards, was used in observing meltimg points. All melting points recorded, are uncorrected for the exposed thermometer stem. If the corrected value is desired, since the level of the bath liquid was at $0^o$, and the room temperature ususlly at approximately $26^o$, the following formula may be used,

$$\text{Correction} = 0.00016\ T\ (T-t)$$

where $T$ = the observed melting point; and $t$ = the mean temperature of the emergent stem, usially taken as the mean of $T$ and the room temperature.

Analyses for nitrogen have been made by the

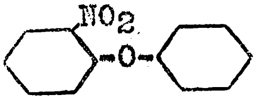
Kjeldahl method, slightly modified for nitro compounds, by the addition of zinc dust and salicylic acid. (See ref. 43.). Iodine in iodo compounds has been determined by the Parr bomb method in which a sample of about 0.2g was fused in a bomb with 15g. of sodium peroxide, 0.4g. of cane sugar, and 1.0 to 1.5g. of potassium nitrate. The bomb was then cooled, the contents dissolved out with hot water, boiled to remove excess $H_2O_2$, 30 cc. of saturated solution of hydrazine sulphate added, the solution cooled, acidified with nitric acid, the iodides determined by precipitation with standard silver nitrate solution (Volhard method), using an excess and titrating back with standard potassium thiocyanate solution with ferric alum as an indicator. In preparation for analyses all samples were dried at 105° for an hour, or over calcium chloride in a desicator for several days.

# EXPERIMENTAL

## SERIES I: DIPHENYL ETHER DERIVATIVES

### GROUP A: SUBSTITUENTS IN POSITIONS 2, or 2 and 4'.

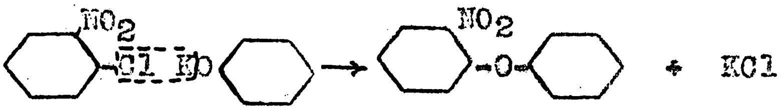
### (1) Preparation of 2-Nitrodiphenyl Ether.



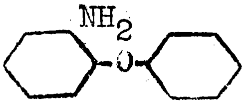
The first portions of this substance prepared in this investigation were produced according to the following method, a slight modification of that described by Haeussermann and Teichmann[12] (see also page 10):

One hundred grams (1.8 mols) of potassium hydroxide were dissolved in 400 grams (4.3 mols) of phenol by warming, 250 grams (1.5 mols) of o-nitrochlorobenzene, and approximately 5 grams of copper powder added, then the resulting mixture boiled gently over an air bath, using an air reflux condenser, for 6-7 hours. Water was gradually eliminated during the reaction and the temperature rose from approximately 140° at the beginning of heating until 175° at the end. The mixture was then cooled, excess phenol washed out with dilute alkali, and the product steam distilled to remove unchanged nitrochlorobenzehe. The residual oil was then separated and distilled at 30-40 mm. pressure, boiling at 200-205°. The yield of distilled product was 245 grams, or 72% of the theoretical.

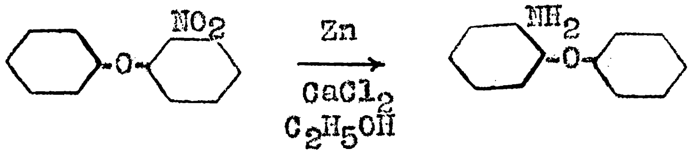
Slightly higher yields (80-85%) have later been obtained by a method which has been found best by Dr Brewster, and which is somewhat similar to that described by Miss Henley[28] (see page 12), except that no extra water was added. In this, the proportions were 1 mol of a nitrochlorobenzene, 1.7 mols of phenol, 1.4 mols of potassium hydroxide with approximately 1 g. of copper powder. Heating as before, gradually at first until the spontaneous reaction which began about 140° had subsided, the temperature was maintained at approximately 160° for an hour; then the product recovered in a manner similar to that described above.



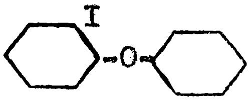
(2) Preparation of 2-Aminodiphenyl Ether.



This amine was best obtained using the method of reduction given by Suter[3] on page 19. Following this procedure, 245 grams of o-nitrodiphenyl ether yielded 175 grams (83% of the theoretical) of the amine. The product was further purified by distillation, boiling at 175° at 15mm pressure.

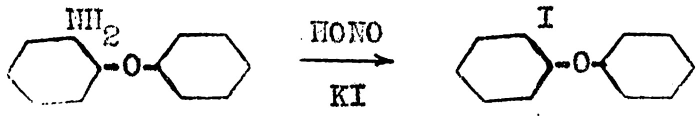


(3) 2-Iododiphenyl Ether.



To a cooled solution of 40 cc. of concentrated sulfuric acid in 150 cc. of water, were added 37g. (0.2 mol) of 2-aminodiphenyl ether, and the mixture stirred and warmed on the steam bath until the amine had dissolved. The resulting solution was then cooled to 0° and diazotized by the addition, drop by drop, during 10 minutes, and with constant stirring, of an ice cold solution of 14g. of sodium nitrite in 40 cc. of water. After allowing to stand for 15 minutes, the diazo solution was poured with rapid stirring into a solution of 33g. of potassium iodide in 50 cc. of water to which approximately 50g. of ice had been added. The addition product formed was exceedingly unstable and partially decomposed immediately, even in the presence of ice. After allowing to warm to room temperature, the resulting mixture was heated to 60° on the steam bath to insure complete decomposition; then cooled and the oily product extracted from the solution with ether, separated, the ether layer washed with dilute alkali, and dried over calcium chloride. The ether was then evaporated and the residual oil distilled under reduced pressure, boiling at 158-60° at 4mm. (187-9° at 15 mm.), with a residue of approximately 10g. of higher boiling tar remaining in the distillation flask. The distilled product 36-38 grams (61-64% of the theoretical), solidified immediately on cooling, and melted at 54-56°. Recrystallization from 95% ethyl alcohol yielded colorless irregular plates, melting at 56°.

This compound has recently been reported by Clarkson and Gomberg[44], and by Buchan and McCombie[6], neither of whom give the yields obtained. The melting point is recorded as 54-6° (b.p. 198-202° at 32 mm.) by the former and 55-6° by the latter, who separated the product by steam distillation. Lesslie and Turner[46], in the past year, have also repported this iodo-ether, obtaining 90-100g. yield from 93g. of 2-aminodiphenyl ether. These investigators report the melting point to be 55-55.5° and boiling point 180-185° at 15 mm.



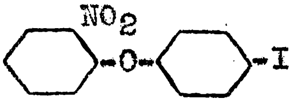
Analysis:

Calculated percent iodine (for $C_{12}H_9OI$; mol. wt. = 296.0)
= 42.9%

Found = 42.9%

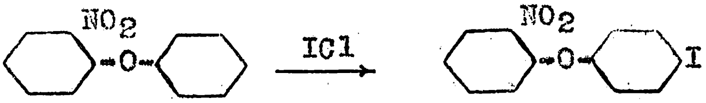
(1) Wt. of sample----------------------------------------.3075g.
Std. $AgNO_3$ sol'n. used (1cc≑.006345 g. I)-----20.80 cc
Wt. of iodine in sample---------------------------.1320g.
Percent iodine in sample--------------------------42.9%

(4) 2-Nitro-4'-Iododiphenyl Ether.



To a cooled solution of 32.3g. (.15 mol) of 2-nitrodiphenyl ether in 75 cc. of glacial acetic acid, were added 24.8g. (0.5g. excess) of iodine monochloride, and the resulting solution boiled gently under reflux for one hour. The solution was then cooled, poured into 500 cc. of a dilute solution of sodium sulfite, containing ice, which removed excess iodine, and precipitated the product as an oil which soon became solid. After standing a short time the aqueous portion was decanted, the product pressed free from water, then dissolved in 200 cc. of boiling heptane (b.p. approximately 95°) using a small amount of decolorizing charcoal. On filtering, and cooling the heptane solution in ice, the product separated in nearly colorless needles, which after filtering and drying weighed 40g. (78% of the theoretical) and melted at 85-86°.

This compound has recently been reported by McCombie, McMillan, and Scarborough[19], who obtained it by allowing a solution of 2-nitrodiphenyl ether to stand for 12 hours with excess iodine monochloride, and reported the product to melt at 86°, but gave no yield.



Analysis:

Calculated percent iodine (for $C_{12}H_8O_3NI$; mol. wt. = 341.0) = 37.2%

Found 37.2%

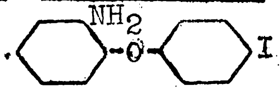
(1) Wt of sample-----------------------------------.2081 g.

Std. $AgNO_3$ sol'n. used (1cc ≎ .006345 g. I)----12.21 cc.

Wt. of iodine in sample--------------------------.0775g.

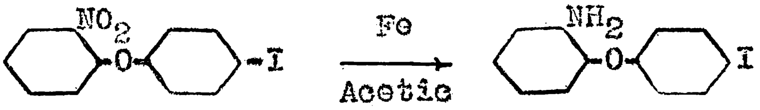
Percent iodine in sample----------------------37.2%

(5) <u>2-Amino-4'-Iododiphenyl Ether.</u>



A solution of 20g. of 2-nitro-4'-iododiphenyl ether in 200 cc. of glacial acetic acid containing 1 cc. of water, was heated to the boiling point in a 500 cc. flask, fitted with a reflux air condenser and adaptor, and 25 g. of iron powder added slowly and in small portions, shaking the flask continuously during the operation. The reaction was strongly exothermic and it was necessary to allow boiling to cease after the addition of each small portion of iron powder. After all the iron had been added, the solution was refluxed gently for 10 minutes, then filtered rapidly while hot through a Buchner funnel to remove unchanged iron and the crystallized iron acetates. These latter were washed with a small amount of acetic acid, then the filtrates diluted with water containing crushed ice to approximately 800 cc. The solution became cloudy but the amine did not separate readily, so a slight excess of cold 40% sodium hydroxide was added and the mixture shaken out with ether. A tendency toward emulsification, due to the small amounts of iron hydroxides present, caused separation of the ether layer to be unusually slow. After standing several hours the layers were separated, the ether extracted dried over solid sodium hydroxide, ether evaporated, and the residual oil distilled under reduced pressure. The product was a pale yellow oil, boiling at 195° at 2mm. pressure, and weighed 13.6 grams (75% of the theoretical).

This compound has also been obtained by McCombie, McMillan and Scarborough[19], by reduction of the 2-nitro-4'-iododiphenyl ether with stannous chloride in ethereal hydrogen chloride solution; and who reported the boiling point to be 240° at 20°mm., but record no yields.



Analysis:

Calculated percent iodine (for $C_{12}H_{10}ONI$; mol. wt= 311.0) = 40.8

(1) Wt. of sample------------------------.2249 g.

Std. $AgNO_3$ sol'n. used (1cc≑.0063465 g I)------ 14.40 cc.

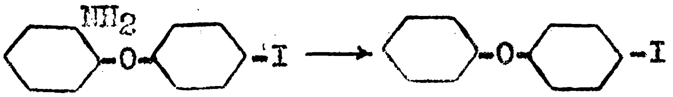
Wt. of iodine in sample-------------.0914 g.

Percent iodine in sample------------40.6

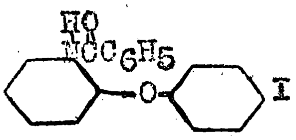
### (6) Deamination of 2-Amino-4'Iododiphenyl Ether.

To a cooled solution of 3.0 grams of 2-amino-4'-iododiphenyl ether in 30 cc. of 95% alcohol contained in a 150 cc. flask, were added 3.0 cc. of cold concentrated sulfuric acid. The resulting solution was then cooled to

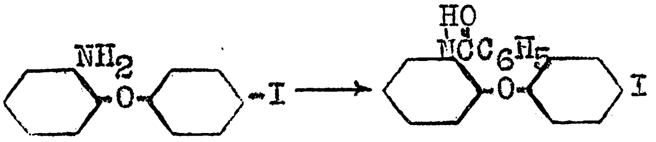
0°, and diazotized by the addition, drop by drop with stirring, of an ice cold solution of 1.0 g. of sodium nitrite in 2.5 cc. of water. After standing for 15 minutes, the flask was attached to a reflux condenser and gently warmed until the contents boiled. The odor of acetaldehyde was immediately distinguishable at the top of the condenser. After boiling for 15 minutes the flask was cooled and its contents poured into 250 cc. of water and crushed ice. A dark oil was immediately precipitated but did not solidify readily. The aqueous portion was then decanted, the oil taken up in ether, transferred to a small distillation flask, the ether evaporated, and the residual oil distilled under reduced pressure. The product distilled mostly between 150-65° at 3-4mm. and after distillation was a clear pale yellow oil weighing 1.8 g. (63% yield of 4-iododiphenyl ether.) The distilled oil, dissolved in a small amount of 95% ethyl alcohol and stirred while cooling in ice, soon crystallized. Filtered and dried, the product melted at 44-45°; mixed with known 4-iododiphenyl ether (of m.p. 47°) the melting point was 45-47°, showing the two to be identical.



## (7) 2-Benzoylamino-4'-Iododiphenyl Ether.



To a cooled suspension of 2.0 grams of 2-amino-4'-iododiphenyl ether in 30 cc of 10% sodium hydroxide were added 4.0 cc. of benzoyl chloride, and the resulting mixture warmed gently to approximately 70°, stirred meanwhile. After the excess benzoyl chloride had disappeared, the white solid was filtered off and washed with water. The yield was practically theoretical. Recrystallization from boiling 95% ethyl alcohol yielded colorless needles, melting at 105-6°.



Analysis:

Calculated percent iodine (for $C_{19}H_{14}O_2NI$; mol. wt. = 415.1) = 30.6%

Found: 30.5%

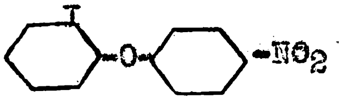
(1) Wt. of sample---------------------------------.2272g.

Std. $AgNO_3$ sol'n used (1cc ≎ .0063465 g I) 10.91 cc.

Wt. of iodine in sample------------------------.0692g.

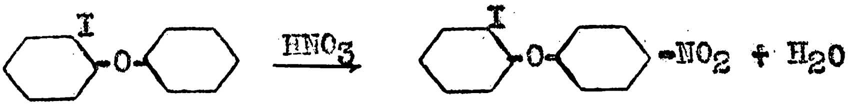
Percent iodine in sample--------------------30.5%

## (8) 2-Iodo-4'-Nitrodiphenyl Ether.



Twenty three grams of 2-iododiphenyl ether were dissolved at room temperature in a mixture of 35 cc. of glacial acetic acid and 35cc. of acetic anhydride. To the resulting solution, while stirring with a thermometer, were slowly added during ten minutes, 8.0 cc fuming nitric acid (sp. gr. 1.5) in 15 cc. of acetic acid, allowing the temperature to rise slowly to not above 50° and cooling in a bath of cold water near the end of the addition to keep at this temperature. After all the nitrating acid had been added, the mixture was kept at 50° for 10 minutes, then allowed to stand at room temperature for 45 minutes by which time the thermometer reading was 35°. Dilution at this point with 500 cc. of water and crushed ice precipitated a yellow oil which soon became semi-solid. After standing for a short time the aqueous portion was decanted and drained from the product, the latter washed by stirring with two separate 50 cc. portions of cool ligroin (heptane) which removed most of the unchanged oily 2-iododiphenyl ether. The crystallized product after this treatment when dry weighed 13-14g. (50-53% of the theoretical) and melted at 97-99°. Recrystallization from heptane, then 95% ethyl alcohol yielded faintly yellow elongated prisms melting at 104°.

The constitution of this product was shown to be as indicated above through its synthesis, by fusion of p-nitrofluorobenzene with the potassium salt of o-iodophenol, by Rarick, Brewster and Dains, in this laboratory[16]. Melting points and a mixed melting point were identical, as also was the appearance of the two products.



Analysis:

Calculated percent iodine (for$C_{12}H_8O_3NI$; mol. wt. =341.0) = 37.2%

Found: 37.2%

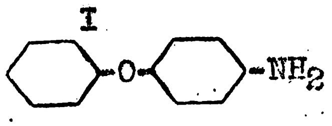
(1) Wt. of sample---------------------------.2052 g.

Std. $AgNO_3$ sol'n used ( 1cc. ⇔ .0063465 g. I)------- 12.01 cc.

Wt. of iodine in sample---------------------------.0762 g.

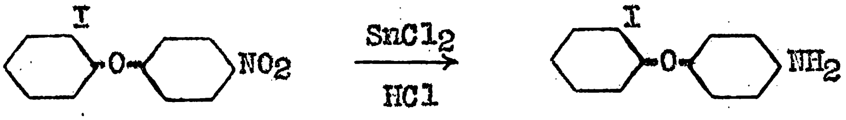
Percent iodine in sample---------------------37.2%

(9) 2-Iodo-4'-Aminodiphenyl Ether.



This compound was obtained by reduction of 2-iodo-4'-nitrodiphenyl ether, using as reducing agents, either stannous chloride-hydrogen chloride with alcohol as a solvent, or iron powder and glacial acetic acid. The percentage yield by both methods was practically the same, but since the similar procedure using iron and acetic acid has been given for the reduction of 2-nitro-4'-iododiphenyl ether (page 58), that using stannous chloride will be described here.

To a gently refluxing solution of 10.0g. of 2-iodo-4'-nitrodiphenyl ether in 100 cc. of 95% ethyl alcohol contained in a 500 cc. flask was slowly added during 10 minutes, a solution of 24g. of stannous chloride (hydrated) in 40 cc. of concentrated hydrochloric acid, and the resulting mixture boiled for fifteen minutes after the addition was complete. Excess alcohol was then evaporated off under reduced pressure, until the tin double salt had crystallized, the flask cooled, then its contents transferred to a beaker containing approximately 100g. of crushed ice. Cold 40% sodium hydroxide was then slowly stirred into the mixture until the precipitate of tin hydroxides produced had completely dissolved after which the solution was extracted with ether. After washing with a small amount of water, the ether extract was evaporated, removing the last traces of ether over the steam bath. The product, a reddish oil after this treatment, weighed 8.5g. (94% of the theoretical) and solidified on rubbing, after short cooling with ice. Recrystallization from petroleum ether (heptane b.p. approximately 95°) yielded colorless monoclinic prisms melting at 69°. Purification was also conveniently effected by distillation under reduced pressure, the product boiling at 198° at 2-3mm. The hydrochloride salt of the amine was hydrolyzed in aqueous solutions except at fairly high concentrations, from which it crystallized in colorless needles melting at 216-217°.



Analysis:

Calculated percent iodine (for $C_{12}H_{10}ONI$; mol. wt. = 311.0) =40.8%

Found: 40.9%

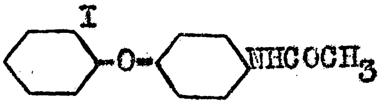
(1) Wt. of sample----------------------------------.2327 g.

Std. $AgNO_3$ sol'n used ( 1 cc.≏ .0063465 g. I)----------- 14.99 cc.

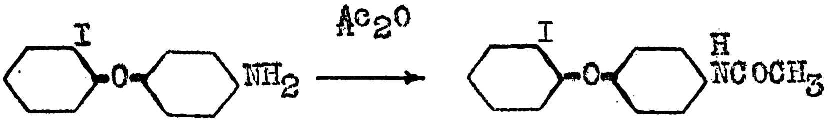
Wt. of iodine in sample----------------------------.0951 g.

Percent of iodine in sample---------------------40.9%

## (10) 2-Iodo-4'-Acetaminodiphenyl Ether.



A solution of 1.5g. of 2-iodo-4'-aminodiphenyl ether in a mixture of 15 cc. of glacial acetic acid and 10 cc. of acetic anhydride was refluxed gently for 30 minutes then poured into 300 cc. of ice water. A white solid formed immediately, which when filtered off and dried weighed 1.6g. (95% of the theoretical). When crystallized from aqueous solutions this product retained water of crystallization which was not removed in a dessicator, and which caused the product from these solutions to melt a few degrees above 100°, with the evolution of water. However, recrystallization from boiling petroleum ether (heptane b.p. approximately 95°), in which the product was sparingly soluble, yielded colorless needles melting at 149-50°.



Analysis:

Calculated percent iodine (for $C_{14}H_{12}O_2NI$; mol. wt. = 353.0) = 36.0%

Found: 35.9%

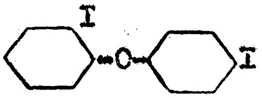
(1) Wt. of sample---------------------------------.2055 g.

Std. $AgNO_3$ sol'n used (1cc.≑ .0063466 g. I)--------
11.63 cc.

Weight of iodine in sample-------------------.0738 g.

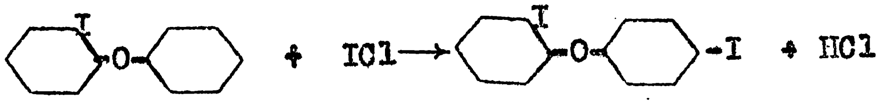
Percent of iodine in dample---------------35.9%

(II) 2,4'-Diiododiphenyl Ether.



This compound was obtained by the following three different methods: (a) By direct iodination of 2-iododiphenyl ether in glacial acetic acid, using iodine monochloride as iodinating agent. (b) By the Sandmeyer reaction, from 2-iodo-4'-aminodiphenyl ether, (page 58) which had been synthesized from 2-iodo-4'-nitro diphenyl ether, the constitution of this latter substance having been established as described on page 63. Since the substance here obtained was identical with that from (a), the constitution of the iodination product is therefore established. (c). By the Sandmeyer reaction, from 2-amino-4'-iododiphenyl ether (page 58); hence with the product of deamination of this latter substance (page 60), establishes the constitution of the iodination product of 2-nitrodiphenyl ether (page 56) (see also page 22). The methods used for the preparation of the 2,4'-diiododiphenyl ether were as follows:

(a) To a cooled solution of 15g. of 2-iododiphenyl ether in 25 cc. of glacial acetic acid were added 10g. of iodine monochloride, and the resulting mixture boiled gently under reflux for 15 minutes. Evolution of hydrogen chloride, which was rapid at first, had practically ceased at the end of this time. The solution was then poured out into approximately 400 cc. of cold water which precipitated the product as an oil. The latter was diluted slightly by the addition of a small amount of chloroform, separated, washed with dilute sodium hydroxide, dried over calcium chloride, then distilled under reduced pressure. The distilled product, a faintly yellow oil boiling at235-40° at 20 mm., weighed 15 grams (70% of the theoretical). By cooling a solution of the oil, in a mixture of ether and alcohol, in a bath of liquid ammonia while stirring rapidly, colorless crystals were obtained which after filtering and drying melted at 46-48°. The index of refraction of the oily product before crystallization was 1.695 at 20° using sodium light.



Analysis:

Calculated percent iodine (for $C_{12}H_8OI_2$; mol. wt. = 421.9) = 60.2%

Found 60.3%

(1) Wt. of sample---------------------------------.2139 g.

Std. $AgNO_3$ sol'n used (1cc≎.0063465gI)

20.33 cc.

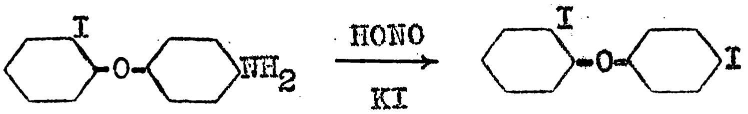
Wt. of iodine in sample--------------------.1290 g.

Percent of iodine in sample-------------60.3%

(b) To a solution of 3.2 g. of 2-iodo-4'-amino-diphenyl ether in 20 cc. of glacial acetic acid, was added a cooled solution of 10 cc. of concentrated sulfuric acid in 10 cc. of water. The resulting solution was then cooled in an ice salt bath to 0°, and diazotized by the addition, drop by drop with stirring, during ten minutes, of an ice cold solution of 0.72g. of sodium nitrite in 5 cc. of water. The diazonium solution resulting was cherry red in color. After standing for five minutes to insure complete diazotization, this was poured into a solution of 1.8g. of potassium iodide in 50 cc. of cold water containing 50g. of crushed ice. After the solutions were well mixed, the orange colored addition product was decomposed by heating to a temperature of 65°

on the steam bath (most of the decomposition occurred at approximately 25°). The resulting mixture containing the oily product was then cooled, the aqueous portion separated, and the oil remaining boiled with 75 cc. of petroleum ether (heptane b.p. approximately 95°). This dissolved all but a small amount of carbonaceous material, and after boiling with charcoal, cooling , and shaking with a sm all amount of sodium sulphite solution to remove a trace of iodine, was cooled well in ice for an half hour. No crystallization occurred, however, so the heptane was evaporated off over the steam bath, leaving a residue of 3.3g. of a yellow oil. (Crude yield 76% of the theoretical). The product was purified by dissolving in 50 cc. of ethyl alcohol to which was added just sufficient ether to cause solution, then allowing the ether to evaporate slowly, while the whole was immersed in an ice bath. The beaker was covered with a watch glass to prevent too rapid evaporation, and after about 12 hours a small globule of oil had precipitated which carried down most of the impurities. The supernatant liquid was then decanted into a clean evaporating dish and allowed to evaporate further. After about 24 hours most of the product had separated in rosettes of colorless needles. A total of 2.5 grams of the purified product which melted at 48° was obtained in this manner. Mixed with the product from iodination of 2-iododiphenyl ether (of m.p. 46-48°), the melting point was 47-8°, showing the two to be identical. For small quantities, the method of purification by crystallization, as given above, was more convenient than distillation; the latter, however, was better when larger quantities were involved, and gave higher percentage recovery of product.

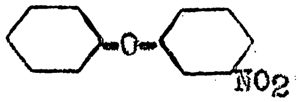
Equation:



(c) Five grams of 2-amino-4'-iododiphenyl ether were dissolved with stirring in a cooled solution of 20 cc. of glacial acetic acid and 35 cc. of water to which 10cc. of concentrated sulfuric acid had been added. The resulting solution was then cooled to 0° and diazotized by the addition, drop by drop with stiring, during ten minutes, of an ice cold solution of 1.3g. of sodium nitrite in 10 cc. of water. After standing for 30 minutes, stirring frequently, the diazo solution was poured rapidly, with stirring, into a solution of 3.1g. of potassium iodide in 30 cc. of water, to which a small quantity of crushed ice had been added. After the solutions were well mixed, the orange colored addition product was decomposed by heating slowly to a temperature of 65° on the water bath. The product separated as a dark oil, from which the aqueous portion was separated after cooling. The oil was then shaken with a small amount of warm, dilute sodium sulphite solution to remove a trace of iodine, then separated, dissolved in a small quantity ofa warm mixture of 95% alcohol and ether, boiled under reflux with a small amount of decolorizing charcoal, and filtered. When cold, sufficient ether was added to remove any cloudiness present, then the solution allowed to evaporate slowly, while cooling in an ice bath, in the same manner has been described in (b) above. After several hours, the supernatant liquid was decanted from the small globule (about .5g.) of precipitated oil, to a clean dish, then further cooled and evaporated, finally yielding 3g. of needles, which separated in rosettes, as did the 2,4'-diiododiphenyl ether obtained from 2-amino-4'-iododiphenyl ether in (b) above. The melting point of the product was 48°, and was undepressed when mixed with the diiodo ether in (b) above, showing the two to be identical.

## GROUP B: SUBSTITUENTS IN POSITIONS 3 or 3 AND 4'

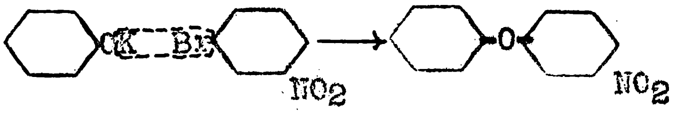
### (1) Preparation of 3-Nitrodiphenyl Ether.



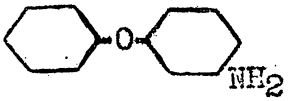
The method described by Ullmann and Sponagel[27] (see page 11) was used in obtaining this substance. A typical experiment in its preparation was the following:

To a solution of 6g. of metallic potassium dissolved in 50g. of phenol, were added 20g. of m-bromonitrobenzene and 1g. of copper powder, the resulting mixture heated in an oil bath for 3 hours at 150-60°, then 1 hour at 180°. When cool the resulting oil was washed with water, taken up in ether, dried over calcium chloride, and distilled under reduced pressure. The yield was 16 grams (75% of the theoretical) of a pale yellow oil, boiling at 180-185° at 15 mm.(Ullmann and Sponagel report 202-4° at 14 mm). Following the same procedure and using the same quantities as given above, except that the metallic potassium was replaced by an equivalent quantity of potassium hydroxide, the yields were somewhat lower (about 55-60°).

Equation:



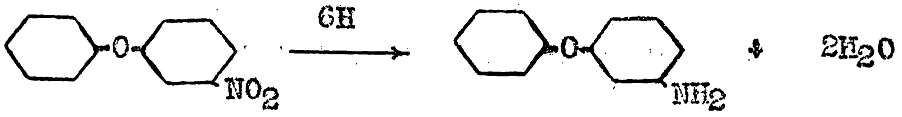
## (2) Preparation of 3-Aminodiphenyl Ether.



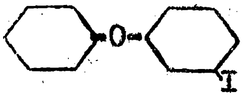
The 3-nitrodiphenyl ether was reduced most conveniently using hydrogen under pressure, with platinum catalyst. (See page 20).

Forty-three grams (0.2 mol) of 3-nitrodiphenyl ether was dissolved in 175 cc. of 95% ethyl alcohol, warmingslightly; then reduced by shaking with gaseous hydrogen under a pressure of 40 pounds per sq. in., in the presence of .2g. of platinum catalyst. Absorption of the calculated amount of hydrogen (0.6 mols) was complete in about 45 minutes. The alcohol was then distilled off and the residual oil vacuum distilled, boiling at 201° at 20mm. (Ullmann and Sponagel[27] report the boiling point to be 190-1° at 14 mm.). The yield of distilled product was 33 grams or 89% of the theoretical.

Equation:



(3) 3-Iododiphenyl Ether.



To a cooled solution of 20cc. of concentrated sulfuric acid in 75 cc. of water, were added 14g. of 3-aminodiphenyl ether, and the mixture stirred and warmed on the steam bath until the amine had dissolved. The resulting solution was then cooled to $0^{\circ}$ and diazotized by the addition drop by drop, during ten minutes, and with constant stirring, of an ice cold solution of 5.3g. of sodium nitrite in 15 cc. of water. The sulfate salt separated to some extent on cooling, but dissolved during the addition of the sodium nitrite to give a clear orange solution. After allowing to stand for fifteen minutes, the diazo solution was poured with rapid stirring into a solution of 12.5g. of potassium iodide in 25 cc. of water, to which approximately 25g. of crushed ice had been added. Decomposition of the orange addition product partially occurred immediately, and was complete by warming the solution on the steam bath to 60°. The product precipitated as a dark oil, which after cooling was separated from the aqueous portion, diluted slightly with chloroform, washed with water, then with dilute sodium sulfite solution to remove a trace of iodine; then dried over calcium chloride, the chloroform evaporated, and the residual oil distilled under reduced pressure, using a 10 cm. fractionating column. (Constructed as described by Noyes and Skinner[25]). The product, a pale yellow oil, was collected between 150-160° (boiling mostly at 155°) at 3 mm. pressure, and weighed 15.2.g. (68% of the theoretical), with a small residue of approximately 5g. of higher boiling tar remaining in the distilling flask. At 20 mm, pressure, the boiling point of the 3-iododiphenyl ether was 195-6°. A small fraction of the oil (b.p. 155° at 3 mm.), collected from the middle of the distillation was used in the specific gravity determination below. At 20° the index of refraction of this sample of the product was 1.643 ,using sodium light.

Equation:

Specific Gravities:(See page 27 for description of determinations).

| <u>Calibration of pylmometer bulb:"A".</u> | <u>Trial I</u> | <u>Trial II</u> |
|---|---|---|
| Wt. of pyk. filled with $H_2O$ @25° | 2.3234g. | 2.3234g. |
| " " " empty @ 25° | 2.0002 | 2.0002 |
| Observed wt. of water @ 25° | 0.3232 | 0.3232 |
| Buoyancy correction (see page 27) | 0.0002 | 0.0002 |
| Corrected wt. of water at 25° | 0.3234 | 0.3234 |
| Vol. of pyk.(Sp.gr.$H_2O$ $\frac{25^\circ}{4^\circ}$=0.99707 | 0.3243ml. | 0.3242ml. |

| | | |
|---|---|---|
| (1) | Wt. of pyk. filled with 3-iododiphenyl ether @ 25° | 2.5243g. |
| | " " " empty | 2.0002g. |
| | " " 3-iododiphenyl ether at 25° | 0.5241 |
| | Buoyancy correction | 0.0002 |
| | Corr. wt. of 3-iododiphenyl ether @25° | 0.5243 |
| | Calc. sp. gr. $\frac{25^\circ}{4^\circ}$ of " " | 1.616 |
| (2) | Wt. of pyk. filled with 2-iododiphenyl ether at 25° | 2.5242 |
| | " " " empty | 2.0002 |
| | " " 3 iodo-diphenyl ether @ 25° | 0.5240 |
| | Buoyancy correction | 0.0002 |
| | Corr. wt. of 3-iododiphenyl ether @ 25° | 0.5242 |
| | Calc. sp. gr. $\frac{25^\circ}{4^\circ}$ of " " | 1.616 |

Analyses:

Calculated percent iodine (for $C_{12}H_9OI$; mol. wt. = 296.0) = 42.9%

Found: 42.9%, 42.6%

(1) Wt. of sample--------------------------------.3187g.

Std. $AgNO_3$ sol'n. Used (1cc. ≏ .01269g I)10.78 cc.

Wt. of iodine in sample---------------------.1368g.

Percent of iodine in sample---------------42.9%

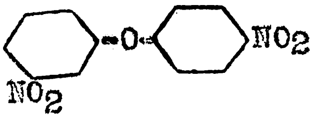
(2) Wt. of sample-----------------------------------.2180g.

Std. $AgNO_3$ sol'n. used ( 1cc. ≏ .0063465g. I)-14.63cc.

Wt. of iodine in sample---------------------------.0929g.

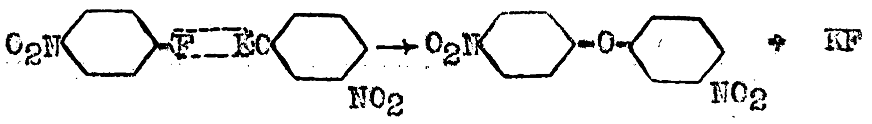
Percent iodine in sample----------------------42.6%

(4) 3-4'-Dinitrodiphenyl Ether.



A solution of 30g. of potassium hydroxide in 16cc. of hot water was added with stirring to 75g. of m-nitrophenol in 125cc. of absolute alcohol. By cooling in ice there was obtained 85g., or 89% of the theoretical, of the orange potassium salt of m-nitrophenol. Thirty grams of this potassium salt were added during 15 minutes, with stirring, to 28g. (4.1g. excess) of p-nitrofluorobenzene, heated in an oil bath at 135°. The orange color of the potassium salt soon faded and the mixture became brown in color, and freely fluid. After the addition was complete the temperature was maintained at 140-5° for fifteen minutes, then the mixture cooled and steam distilled, by which means 4.5g. of p-nitrofluorobenzene were recovered. After filtering and drying the crude crystalline product, which remained in the distilling flask, weighed 39 grams (89% of the theoretical). Recrystallization from 140cc. of boiling benzene, yielded colorless elongated prisms, melting at 123°.

Equation:



Analyses:

Calculated percent nitrogen (for $C_{12}H_8O_5N_2$; mol. wt. = 260.1) = 10.77%

Found: 10.91%, 10.90%

(1) Wt. of sample------------------------------------.1857g.

Std. $H_2SO_4$ sol'n used (1cc. ≏ .001422g.N) 14.24 cc.

Wt. of nitrogen in sample-------------------.02025g.

Percent nitrogen in sample-----------------10.91%

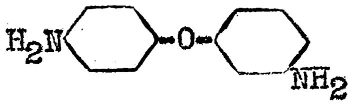
(2) Wt. of sample------------------------------------.2178g.

Std. $H_2SO_4$ Sol'n used (1cc. ≙ .001422g. N)--16.69cc.

Wt. of nitrogen in sample------------------------.02373g.

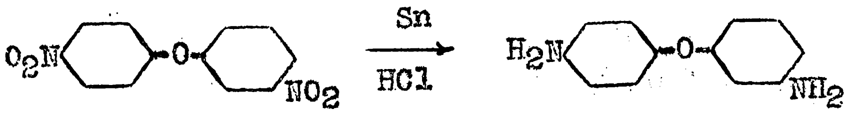
Percent nitrogen in sample--------------------10.90%

(5) <u>3,4'-Diaminodiphenyl Ether.</u>



To a gently refluxing mixture of 15g. of 3,4'-dinitrodiphenyl ether, 25 cc. of 95% ethyl alcohol, and 40g. of tim, were slowly added through the top of the condenser, 125cc. of concentrated hydrochloric acid (Sp. Gr. 1.2). The reaction was strongly exothermic, and heating was discontinued during the addition. The resulting solution was boiled gently for fifteen minutes after all the nitro compound had gone into solution, then most of the alcohol distilled off. After cooling, the solution was then diluted to approximately 400 cc., concentrated ammoniam hydroxide added until barely alkaline, then rendered just acid with hydrochloric acid, and excess hydrogen sulphide passed into the liquid. After filtering off the precipitate of tim sulphides, crushed ice and an excess ammonium hydroxide was added, and the solution allowed to stand in the ice box for an hour. The fine, cream colored, crystalline precipitate of the product, after filtering and drying weighed 9.8 grams (84% of the theoretical). The diamino ether was further purified by dissolving in dilute hydrochloric acid, boiling with charcoal, then reprecipitating from the cold acid solution by the addition of excess ammonium hydroxide, which yielded fine colorless glistening crystals, melting at 71-2°. The product was easily soluble in alcohol, and ether, but only slightly so in water or hot petroleum ether.

Equation:



Analyses:

Calculated percent nitrogen (for $C_{12}H_{12}ON_2$; mol. wt. = 200.1) = 14.00%

Found: 13.92%, 13.75%

(1) Wt. of sample--------------------------------.2107g.

Std. $H_2SO_4$ sol'n used (1cc.≙ .001453g N)-20.18cc.

Wt. of nitrogen in sample-------------------.02392g.

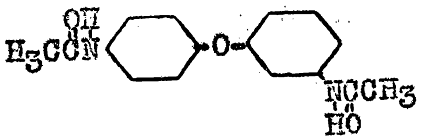
Percent nitrogen in sample----------------13.92%

(2) Wt of sample---------------------------------.2069g.

Std. $H_2SO_4$ soln used (1cc.≙ .001405g.N)--20.24 cc.

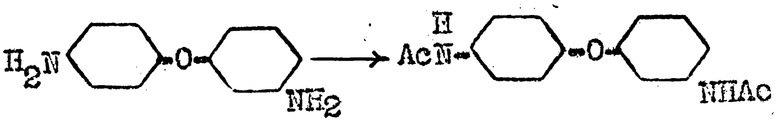
Wt. of nitrogen in sample----------------.02844g.
Percent nitrogen in sample---------------13.75%

### (6) 3,4'-Diacetaminodiphenyl Ether



Two grams of 3,4'-diaminodiphenyl ether were dissolved in 15cc. of glacial acetic acid, 15 cc. of acetic anhydride added, and the resulting solution boiled under reflux for 30 minutes, then poured into 300 cc. of ice water. After standing overnight in the ice box, the white solid precipitated was filtered off, washed (yield practically theoretical), and recrystallized from dilute ethyl alcohol, yielding a colorless crystalline product melting at 197-8°.

Equation:



Analyses:

Calculated percent nitrogen ( for $C_{16}H_{16}O_3N_2$; mol wt.= 284.15) = 9.86

Found: 9.89%, 9.84%

(1) Wt. of sample-----------------------------------------.1952g.

Std. $H_2SO_4$ sol'n used (1cc. ≑ .001422g. N)------13.56cc.

Wt. of nitrogen in sample---------------------------.01930g.

Percent nitrogen in sample------------------------9.89%

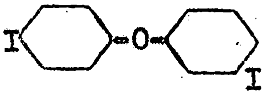
(2) Wt of sample-------------------------------------------.1194g.

Std. $H_2SO_4$ sol'n used (1cc ≑ .001405g N)---------8.36 cc.

Wt. of nitrogen in sample----------------------------.01174g.

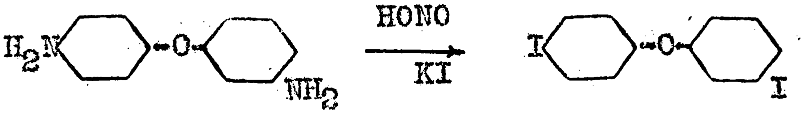
Percent nitrogen in sample-------------------------9.84%

### (7) 3,4'-Diiododiphenyl Ether.



To a cooled solution of 20cc. of concentrated sulfuric acid in 50cc. of water, were added 4.5g. of 3,4'-diaminodiphenyl ether and the mixture warmed and stirred until the amine had dissolved. The resulting solution was then cooled to 6° and diazotized by the addition, drop by drop, during twenty minutes, and with constant stirring, of an ice cold solution of 3.5g. of sodium nitrite in 15cc. of water. The sulphate salt separated to some extent on cooling, but dissolved during the addition of the sodium nitrite. After the addition was complete, the solutionwas allowed to stand for twenty minutes, then poured with rapid stirring into a solution of 10g. of potassium iodide in 25cc. of water containing about 25g. of crushed ice. Decomposition of the addition product, which partally occurred immediately, was completed by warming to 60 on the steam bath. When cold, an excess of dilute sodium sulfite solution was added to remove iodine present, then the solution containing the oily product extracted twice with ether. The combined ether extracts were theh dried over calcium chloride, the ether evaporated and the brown colored residual oil distilled under reduced pressure, using a special flask with a 2 cm column (See pages 26 and 27). With the exception of a small amount of residue left in the flask, the entire product distilled in the range 195-203° at 2 mm. pressure, with most of the diiodo ether boiling at 200-202°. The yield of the distilled product, a pale yellow oil, was 4.7g. or 50% of the theoretical. A small fraction which was again redistilled was collected from the middle of the distillation, for analysis, sp. gr., and index of refraction determinations. The index of refraction at 20°, using sodium light,was <u>1.694.</u>

Equation:



Specific gravity: (Using pyknometer bulb "A", calibrated page 77).

(1) Wt. of pyk. filled with 3,4'-diiododiphenyl ether @ 25°--2.6592g.

Wt. of pyk. empty---------------------------2.0002

Wt. of 3,4'-diiododiphenyl ether @25°-------.6590

Buoyancy correction-------------------------.0001

Corr. wt. of 3,4'-diiododiphenyl ether@25°-.6591

Calc. sp.gr. $\frac{25^\circ}{4^\circ}$ of " " See pg.77)--- 2.032

Analysis:

Calculated percent iodine (for $C_{12}H_8OI_2$; mol. wt.= 421.9) = 60.2%

Found: 60.2%

(1) Wt. of sample--------------------------------.2197g.

Std. $AgNO_3$ sol'n used (1cc≙.0063465gI)--20.83cc.

Wt. of iodine in sample---------------------.01322g.

Percent iodine in sample------------------60.2%

### (8) Iodination of 3-Iododiphenyl Ether.

To a cooled solution of 10g. of 3-iododiphenyl ether in 25cc. of glacial acetic acid were added slowly and with shaking, 6.0g. (0.5g. excess) of iodine monochloride, and the mixture warmed gently to the boiling point, where the reaction proceeded spontaneously for 2-3 minutes, with copious evplution of hydrogen chloride. After spontaneous boiling had subsided the solution was refluxed for fifteen minutes, cooled, and poured with stiring into 500 cc. of cold water, which precipitated the product as an oil. A small amount of chloroform was then added to dilute the oily product, the aqueöus portion decanted, and the oily layer shaken with dilute sodium sulfite solution until colorless. After separation, the chloroform solution was dried over calcium chloride, the chloroform removed by evaporation under reduced pressure, and the remaining oil distilled at a constant pressure of approximately 1.5mm., using a 15 cm. column, and collecting the following fractions:

(a) To 190o; boiling mostly at 150°; unchanged 3-iododiphenyl ether, 2.6g.

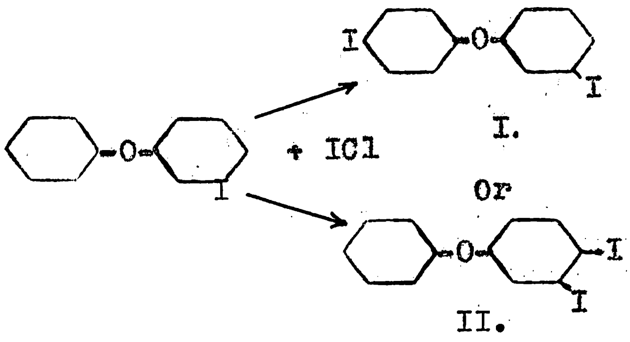
(b) 190-200°; 8.5g. of a pale yelöw oil boiling at 195°; the main product.

(c) 200-220o: 1.0 g.

(d) Above 220°: Small tarry residue of approximately 1g. left in flask.

A middle portion was also taken of fraction (b) the main product above, for analysis, specific gravity, and index determinations. Using sodium light, the index of refraction of this sample was <u>1.696</u> at 20°.

Equation:



Specific Gravity: (Using pyknometer bulb "A", calibrated page 77).

(1) Wt. of pyk. filled with the diiodo product @25° (See analysis below)----------2.6659g.

" " " empty-------------------------------<u>2.0002</u>

" " " diiodo product at 25°---------------.6657

Buoyancy correction--------------------------.0001

Corr. wt. of diiodo product-------------------.6658

Calculated sp. gr. $\frac{25^\circ}{4^\circ}$ od diiodo prod. (See page 77)----------------2.053

(2) Wt. of pyk. filled with the diiodo product (sample in (1) redistilled) @25°
-----------2.6654

" " " empty-----------------------------2.0002

" " diiodo product @ 25°-----------------.6652

Buoyancy correction-------------------------.0001

Corr. wt. of diiodo product-----------------.6653

Calc. specific gravity $\frac{25^\circ}{4^\circ}$ of diiodo product (see page 77)------2.051

Analysis:

Calculated percentage iodine (for $C_{12}H_8OI_2$; mol. wt.= 421.9) = 60.2%

Found: 60.1%

(1) Wt. of sample--------------------------------.2049g.

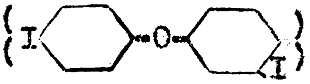
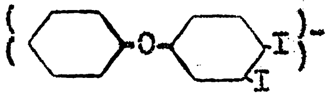
Std. $AgNO_3$ sol'n used (1cc. ≑ .0063465g.I)--19.42cc.

Wt. of iodine in sample----------------------.01233g.

Percent iodine in sample--------------------60.1%

Constitution of diiodo product from fraction (b):

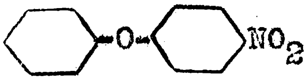
From other experience on substitution in diphenyl ether derivatives (See pages 48, 49 and 67) the product represented by I above (page 87) is the one to be expected. The constants of both I and II have been determined at other points in this investigation. These with those of the product here obtained (the latter designated by III) are listed below for comparison.

| | B.P. | Index(20°) | Sp.Gr.(25°) |
|---|---|---|---|
| I.  | 200-202@2mm. | 1.694 | 2.032 |
| II.  | 203-205@2mm. | 1.700 | 2.055 |
| III.(Prod. here obtained) | 195@1.5mm. | 1.696 | 2.051 |

The possible experimental error in the values obtained for indices of refraction is not greater than ± .0005; that for specific gravities not greater than about ± .003. The color of II was much deeper yellow than I or III. Boiling points are too close together to give any indicationof the constitution of the product here obtained. Considering the color, the facts already given regarding observed substitution in diphenyl ether nucleii, and that impurities which lower specific gravity of a sample likewise lower the index of refraction, it seems likely that I and III are the same substance. The discrepancies in indices of refraction between II and III are much greater than the possible experimental error; while it is quite possible that in the small quantity obtained of I, sufficient impurity was present to lower both index and specific gravity below that observed for III, which is probably the purer of the two samples. Whereas the values of indices of refraction and specific gravities given for I and III above, differ by 0.008 and 0.019 units respectively, this difference was slightly greater (about .003 and .026) for these samples of the two products before a previous redistillation of each, in which the first and last portions were discarded, showing further purification did tend to bring the values closer together. Quantities were insufficient, however, for further purification. A similar difference in these constants in found in the two samples of 2,4-diiododiphenyl ether which have been obtained by two different methods, (see pages 140and 142); the product obtained by Sandmeyer's reaction from the corresponding diamine being of lower purity as is observed here, which may be due to the greater formation of by-products in the diazotization of the two amino groups at once, some of which products are difficultly separable from the product of redistillation. Attempts to obtain solid nitration products of the above listed compounds for comparison were unsuccessful, resulting in further oils.

## GROUP C: SUBSTITUENTS IN POSITIONS 4 OR 4 AND 4'.

### (1) Preparation of 4-Nitrodiphenyl Ether.

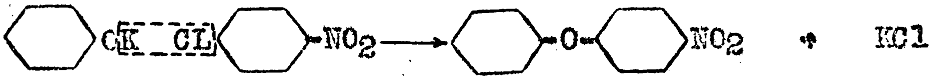


Most of the 4-nitrodiphenyl ether used in this investigation was prepared by the following method, which is a slight modification of that described by Haeussermann and Teichmann[12] (see page 10):

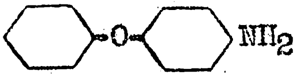
One hundred and eighty grams (3.2 mols) of potassium hydroxide were dissolved in 1000g (10.6 mols) of phenol by warming, 500g. (3.2 mols) of p-nitrochlorobenzene, and approximately 10g. of copper powder added, then the resulting mixture warmed gently to boiling (about 140°) over an air bath. After boiling under reflux at this temperature for 12 hours, the mixture was cooled, excess phenol washed out with dilute alkali, and the product steam distilled to remove unchanged p-nitrochlorobenzene. The crude 4-nitrodiphenyl ether remaining in the distilling flask (435 g. or 64% of the theoretical) was then separated and purified by distillation under reduced pressure, boiling at 220° at 30mm. The distilled product which weighed 385g., solidified immediately on cooling, and melted at 59-61°.

As has been described in the preparation of 2-nitrodiphenyl ether (page 53), higher yields of 4-nitrodiphenyl ether have also later been obtained by a much shorter method, using the same proportions of reactants and procedure as given for the preparation of the ortho isomer (page 53). The yield by this improved method was usually about 85%.

Equation:

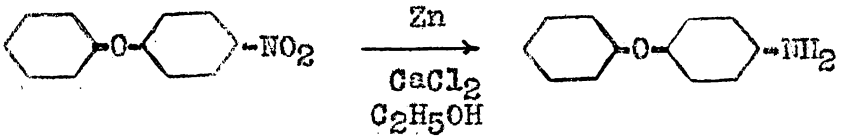


## (2) Preparation of 4-Aminodiphenyl Ether.

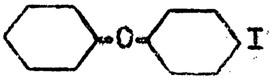


The first portions of this substance which were prepared, were obtained by reduction of 4-nitrodiphenyl ether with tin and hydrochloric acid, after the method of Haeussermann and Teichmann[12] (see page 18). Removal of tin salts and recovery of the product, which has rapidly darkened by atmospheric oxidation when in contact with alkaline solutions, made this method much less convenient than that given by Suter[3] (page 19). This latter method was therefore used for the preparation of the major portion of the 4-aminodiphenyl ether used, the yields of product being very nearly theoretical. On further purification of the product by distillation under reduced pressure, the boiling point was 175° at 4mm.

Equation:



(3) 4-Iododiphenyl Ether



This substance was obtained bybtwo different methods: (a) By direct iodination of diphenyl ether in glacial acetic acid, using iodine monochloride as iodinating agent; which method was found most convenient for preparation of large quantities. (b) By the Sandmeyer reaction, from 4-aminodiphenyl ether. Since the substance obtained by this method was identical with the mono-iodo product from (a), the constitution of the latter is therefore established. These methods are described as follows:

(a) In a 21. flask fitted with a dropping funnel, and reflux condenser attached to a hydrogen chloride absorption train, was placed a solution of 250g. of diphenyl ether in 400cc. of glacial acetic acid. Through the dropping funnel were added slowly in small portions, 250g. of iodine monochloride, shaking the flask after each addition. The reaction was exothermic and the temperature of the solution soon reached the boiling point, after which it was necessary to cool in a pan of cold water when boiling became too vigorous. After all the ICl had been added, the mixture was heated over the steam bath for two hours. Evolution of hydrogen chloride had almost ceased at the end of the first hour, and was only slight during the second hour of heating. After cooling, the contents of the flask were poured into 2l. of cold water, sufficient chloroform added to render the precipitated oily product freely liquid, then the oily layer separated and washed with water then with dilute sodium hydroxide until colorless. After drying the oily layer with sodium chloride, the mixture of products was distilled, using a 25 cm column, first removing the chloroform, then distilling the residual oil at 3mm. pressure, collecting the following fractions:

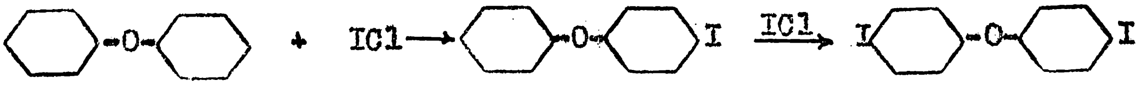
(i) 100-150°, mostly 105-110°C; 62 g., unchanged diphenyl ether which remained liquid on cooling.

(ii) 150-180°, mostly at 163oC; 256g (59% of the theoretical based on the diphenyl ether used) of 4-iododiphenyl ether which solidified on cooling, and which, when recrystallized from ethyl alcohol or heptane, yielded colorless irregular needles melting at 47°. That this product was 4-iododiphenyl ether, was shown by a mixed melting point with the known product page 96.

(iii) 180-240°, mostly 210-215°; 80g.; chiefly 4,4'-diiododiphenyl ether, as shown by comparison with the known sample page 121 . This represents 13% of the diphenyl ether used, converted into the diiodo product. This fraction solidified immediately on cooling, and when recrystallized from ethyl alcohol or heptane yielded colorless elongated plates melting at 139°.

(iv) Above 240°C; approximately 10g. of higher iodo derivatives of diphenyl ether.

Equation:



(b) To a cooled solution of 15 cc. of concentrated hydrochloric acid (sp. gr. 1.2) in 50 cc. of water, were added 9.2g. (0.05 mol.) of 4-aminodiphenyl ether, and the mixture stirred and warmed on the steam bath until the salt had formed. The resulting solution was then cooled to 0°

and diazotized by the addition drop by drop, during 10 minutes, and with constant stirring, of an ice cold solution of 3.5g. of sodium nitrite in 10cc. of water. After allowing to stand for 30 minutes, the diazo solution was poured with rapid stirring into a solution of 8.3 g. of potassium iodide in 10 cc. of water to which approximately 15g. of ice had been added. After allowing to warm to room temperature, the resulting mixture was heated to 60° on the steam bath to insure complete decomposition; then cooled and the oily product extracted from the solution with benzene, separated, the benzene layer washed with dilute alkali, and dried over calcium chloride. The benzene was then evaporated and the residual oil distilled under reduced pressure, boiling at 195° at 14 mm. The distilled product (approximately 75% yield) solidified immediately on cooling and melted at 46-48°. Mixed with the product from direct iodination of diphenyl ether from (a) page 95, the melting point was unchanged. Recrystallized from heptane or ethyl alcohol, the melting point was 47°.

This compound has been recently reported by Scarborough[31], who obtained it by this same method (b), and reports the melting point to be 48°, but does not give the yield obtained.

Equation:

Analyses:

Calculated percent iodine (for $C_{12}H_9OI$; mol. wt. = 296.0) = 42.9%

Found: 42.9%, 43.0%

(1) Wt of sample----------------------------------.2236g.

6
Std. $AgNO_3$ sol'n used (1cc. ≙ .006345g. I)-15.11 cc.

Wt. of iodine in sample--------------------.09590g.

Percent iodine in sample------------------42.9%

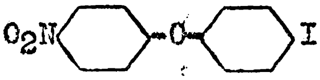
(2) Wt. of sample---------------------------------.3887g.

Std. $AgNO_3$ sol'n used (1cc. ≙ .012693 gI)---13.16 cc.

Wt. of iodine in sample-----------------------.01670 g.

Percent iodine in sample-------------------43.0%

### (4) 4-Iodo-4'-Nitrodiphenyl Ether.



This substance has been obtained by the following two separate methods: (a) By iodination of 4-nitrodiphenyl ether in glacial acetic acid, using iodine monochloride as iodinating agent. (b) By nitration of 4-iodo-diphenyl ether, in which reaction several peculiarities were observed, which are further described below. These methods are described as follows:

(a) To a cooled solution of 64.5g. (0.3 mol) of 4-nitrodiphenyl ether in 150 cc. of glacial acetic acid, were added 49.5g (0.9g. excess) of iodine monochloride, and the solution boiled under reflux (HCl absorption train) for one hour. The solution was then cooled and poured into 600cc. of cold water, which precipitated the oily product. After standing a short time the aqueous portion was decanted, the oil diluted slightly with ether, then shaken with dilute sodium sulphite solution until colorless. The oily layer was then separated, dried over calcium chloride, the ether evaporated, and the residual semi solid oily product distilled, collecting the following fractions at 3 mm. pressure:

(i) To 205°; approximately 10g. of unchanged 4-nitrodiphenyl ether.

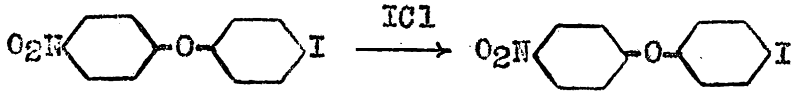
(ii) 205-215°, mostly 213°; 81g. (79% of the theoretical) of a pale yellow oil which solidified on cooling, and when recrystallized from alcohol or a mixture of heptane and ether, yielded nearly colorless plates melting at 69-70°.

(iii) Above 215°; small residue of approximately 2g. which remained in the distilling flask.

This product was shown to be 4-iodo-4'-nitrodiphenyl ether by its reduction and conversion through the Sandmeyer reaction into known 4,4'-diiododiphenyl ether. (See pages 104 and 122 ).

Scarborough[31] has recenly reported this product, having obtaining it by a method similar to that above, and records the melting point at 71°, but does not givs the yield obtained.

Equation:



Analysis:

Calculated percent iodine (for $C_{12}H_8O_3NI$; mol. wt. = 341.0) = 37.2%

Found: 37.3%

(1) Wt. of sample--------------------------------.2175g.

Std. $AgNO_3$ sol'n used (1 cc.≙ .0063465g.I)-12.79cc.

Wt. of iodine in sample------------------------.08117g.

Percent iodine in sample--------------------37.3%

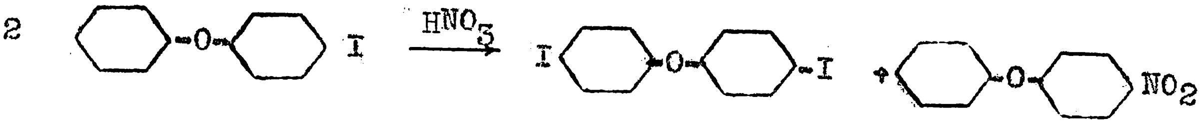
(b) After considerable experimentation, attempt-ing nitration of 4-iododiphenyl ether with various mixtures of nitric acids of specific gravities of 1.42 and 1.5, sulfuric acid, acetic acid and acetic anhydride, and at different temperatures, the following method was found to give maximum yields of a nitro product. In nearly all cases, one of the first products to be formed was a quantity of 4,4'-diiododiphenyl ether, showing the iodine atom had been removed from part of the 4-iododiphenyl ether and added to part of that remaining unchanged in solution. On continued nitration, one or both of the iodine atoms of the resulting 4,4'-diiododiphenyl ether were removed, being replaced by a nitro group, yielding a final product, 4,4'-dinitrodiphenyl ether.

To a cooled solution of 29.6g (0.1 mol) of 4-iododiphenyl ether in a mixture of 50 cc. of acetic anhydride and 50 cc. of glacial acetic acid, while stirring with a thermometer, were slowly added during 15 minutes, 7.0 cc. of fuming nitric acid (sp. gr. 1.5) in 7 cc of glacial acetic acid. The temperature was allowed to rise slowly to not above 55°, and maintained between 50-55° during the addition. After about two-thirds of the acid had been added, a crystalline precipitate of 4,4'-diiododiphenyl ether separated in sufficient abundance to give the solution a mushy consistency. This precipitate gradually dissolved, however, during the addition of the rest of the acid, and had completely disappeared in about 10 minutes; the solution becomming reddish in color. The temperature was maintained at the above value for 10 minutes longer, then the mixture allowed to stand at room temperature for ½ hour, by the end of which time the thermometer registered 35°. At this point the liquid was diluted with 500 cc. of cold water, and after standing for a short time, the precipitated oily product separated, diluted slightly with ether, washed with water then with dilute sodium sulfite solution. After drying over calcium chloride, and evaporation of the ether, the residual oily product was vacuum distilled at 3mm. pressure collecting the following fractions:

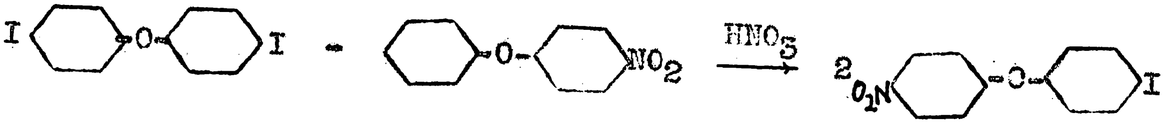
(i) To 205°; 4g.
(ii) 205-218°, mostly at 214°; 20.5g. of an oil which solidified on rubbing while cooling in ice.
(iii) 218-230°; 4g.

The product from (ii) was easily soluble in ether and acetic acid, but only slightly so in heptane or alcohol, and was precipitated as an oil by usual methods employed for recrystallization. A crystalline product was obtained, however, by allowing solutions of mixtures of ether and heptane or alcohol to evaporate, while cooling in an ice bath; or more conveniently by crystallization from mixtures of these solvents by strongly cooling in liquid ammonia, or in an ether-solid carbon dioxide mixture. After two such crystallizations approximately 11g. (32% of the theoretical) of faintly yellow plates melting at 68-9° remained; the remainder of the product was semi solid when strongly cooled but formed an oil on warming to room temperature. The crystalline product above was identical in appearance with the 4-iodo-4'-nitrophenol ether (of m.p. 79-80°) obtained from iodination of 4-nitrodiphenyl ether page 98, and when mixed with this latter substance the melting point was unchanged.

If the solution was filtered rapidly at the point in the above procedure at which a maximum of the 4,4'-diiododiphenyl had separated, the quantity of filtered off diiodo ether was always less than the theoretical amount, considering that half the molecules of the 4-iododiphenylether had given up their iodine atoms to the other half. The filtrate, when diluted, and the precipitated oil recovered as in the above procedure, then distilled, yielded as the first fraction, a small quantity of a pale yellow oil which crystallized after standing for several days, and was found by melting point and mixed melting point to be 4-nitrodiphenyl ether. The larger part of the recovered oil,however, proved to be the 4-iodo-4'-nitrodiphenyl ether obtained above. At least part of the 4-iododiphenyl ether, therefore, goes through the following reaction



Further reaction apparently takes place in the solution, after this, as follows:



To test this above reaction, the calculated amounts of 4,4'-diiododiphenyl ether (21.1g.) and 4-nitrodiphenyl ether (10.8g.) were mixed together, and nitrated exactly as in the above procedure. The diiododiphenyl ether dissolved gradually into the solution, which became reddish in color, as had occurred during the previous nitration. Recovery of products exactly as in the above procedure, yielded approximately the same quantity of 4-iodo-4'-nitrodiphenyl ether as was obtained using 4-iododiphenyl ether as the starting material, indicating that the course of part of the reaction, at least, had been as indicated in the above equation. No reaction occurred when equivalent quantities of 4,4'-diiododiphenyl ether and 4,4'-dinitrodiphenyl ether were fused together at 210° for an hour. Since considerable unidentified substances were obtained in these reactions, it is possible that other nitro isomers were also formed.

Analysis of product from nitration of 4-iododiphenyl ether:

Calculated percent iodine (for $C_{12}H_8O_3NI$; mol. wt. = 341.0) = 37.2%

Found: 37.3%

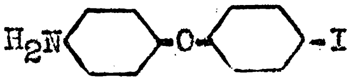
(1) Wt. of sample---------------------------------.2061g.

Std. $AgNO_3$ sol'n used (1cc.≏.0063465gI)--12.10cc.

Wt. of iodine in sample----------------------.0768g.

Percent iodine in sample------------------37.3%

### (5) 4-Iodo-4'-Aminodiphenyl Ether.

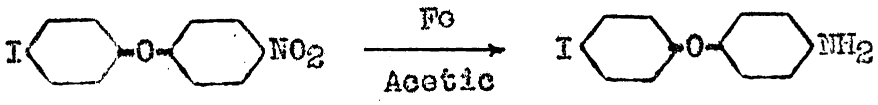


This compound has been obtained (a) by reduction of 4-iodo-4'-nitrodiphenyl ether; and (b) by hydrolysis of 4-iodo-4'-acetaminodiphenyl ether.

(a) To a gently boiling solution of 10g. of 4-iodo-4'-nitrodiphenyl ether in 70cc. of glacial acetic acid, contained in a 250cc. flask fitted with a reflux condenser and adapter, were added 10g. of iron powder, in small portions, shaking the flask meanwhile, and allowing the strongly exothermic reaction to subside after each addition. The mixture was kept hot for 5 minutes after the addition was complete, then rapidly filtered through a Buchner funnel, and the unchanged iron and iron salts washed with a small amount of acetic acid. The filtrate was then diluted to 600cc. with ice water, and most, but not all, of the acetic acid neutralized with concentrated ammonium hydroxide; the appearance of green $Fe(OH)_2$ indicating the quantity necessary. This latter procedure decreased the solubility of the amine in the solution. After standing for two hours in the ice box, the product had separated from the cloudy solution as a fine flocculent precipitate. This was filtered off, washed, and dried; then purified by two extractions with a 200cc. portion of boiling petroleum ether (heptane b.p. approx. 95°), from which on cooling in ice , a total of 7.8g. (86% of the theoretical) of nearly colorless, elongated plates melting at 91-2° were obtained.

The constitution of this compound was established by its conversion by the Sandmeyer reaction, to known 4,4'-diiododiphenyl ether. Scarborough has recently reported this substance, having obtained it by methods similar to those here described in (a), and (b); with the exception that a stannous chloride-hydrogen chloride solution was used in the reduction above. The product was reported to melt at 91°, but no yields were given.

Equation:



Analyses:

Calculated percent iodine (for $C_{12}H_{10}ONI$; mol. wt.= 311.0) = 40.8%

Found: 40.6%, 40.7%

(1) Wt. of sample--------------------------------0.2000g.
Std. $AgNO_3$ sol'n used (1cc= .0063465gI)12.80cc.
Wt. of iodine in sample-------------------.08124g.
Percent iodine in sample----------------40.6%

(2) Wt. of sample---------------------------------.2040g.
Std. $AgNO_3$ sol'n used (1cc= .0063465gI)13.09cc.
Wt. of iodine in sample-------------------.08308g.
Percent iodine in sample----------------40.7%

(b) A solution of 10g. of 4-Iodo-4'-acetaminodiphenyl ether (see page 108) in mixture of 50cc. of 95% ethyl alcohol and 50cc. of concentrated hydrochloric acid (sp.gr. 1.2), was refluxed over the water bath for 2½ hours, then cooled diluted somewhat with water. When cold 7g. (80% of the theoretical) of the sparingly soluble hydrochloride salt of 4-iodo-4'-aminodiphenyl ether were filtered off. Recrystallized from boiling water with charcoal, this salt formed silvery white crystals which melted at approximately 250°. Four grams of the finely powdered hydrochloride, when ground in a mortar with 5-7 cc. of concentrated ammonium hydroxide, filtered, washed and dried, gave 3.5g. (98% of the theoretical) of 4-iodo-4'-aminodiphenyl ether, which melted at 90°. Recrystallized from boiling heptane with charcoal the melting point of the iodo-amine was 91-2°, and undepressed by mixing with a sample of the product from (a) above.

Equation:

Analysis of hydrochloride salt:

Calculated percent HCl (for $C_{12}H_{10}ONI \cdot HCl$; mol. wt.= 347.5) = 10.50%

Found: 10.74%

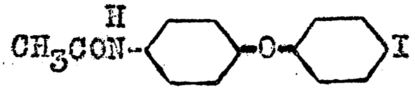
(1) Wt. of sample-----------------------------------.2275g.

Std. NaOH sol'n used (.0995N)-----------6.73cc.

Wt. of HCl in sample-------------------------.02444g.

Percent HCl in sample--------------------10.74%

### (6) 4-Iodo-4'-Acetaminodiphenyl Ether.

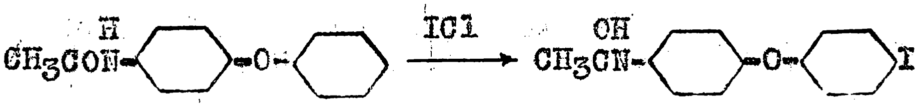


This substance was obtained by (a) iodination of 4-acetaminodiphenyl ether; and (b) by acetylation of 4-iodo-4'-aminodiphenyl ether:

(a) Fifty grams of 4-aminodiphenyl ether were acetylated by boiling in a mixture of 100cc. of glacial acetic acid and 75 cc. of acetic anhydride for an hour; then the resulting solution poured into cold water. The precipitated product, filtered and dried, weighed 55g. (90% of the theoretical), and after recrystallization from alcohol, then benzene, melted at 129-30°. (Reported 127°)[12].

To a solution of 22.7g. (0.1 mol) of 4-acetaminodiphenyl ether in 100 cc. of glacial acetic acid were added 20g. (3.8g. excess) of iodine monochloride, and the resulting solution boiled under reflux for two hours. Evolution of hydrogen chloride was very rapid at first, but only slight after 30 minutes of heating. When cool, the solution was poured into cold water, the precipitate collected on a filter, then recrystallized from 95% alcohol using charcoal. The product (white crystals melting at 169°) was shown to be identical with product below (b) by mixed melting point tests.

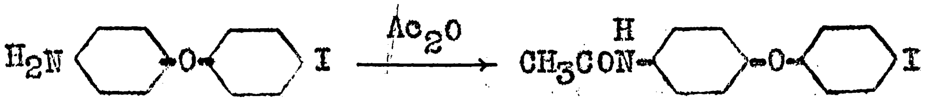
Equation:



(b) Four gramsof 4-iodo-4'-aminodiphenyl ether were acetyated by refluxing in a mixture of 40 cc. of glacial acetic acid and fifteen cc. of acetic anhydride for 30 minutes. When cool the resuting solution was poured into cold water and the white solid precipitate formed (4.2 g. or 93% of the theoretical) collected on a filter. Recrystallized from boiling 95% ethyl alcohol, the melting point was 172-3°.

This product has recently been reported by Scarborough[31], who obtained it by methods similar to those above, and recorded a melting point of 174°, but no yields.

Equation:



Analysis:

Calculated percent iodine (for $C_{14}H_{12}O_2NI$; mol. wt.= 353.0) = 36.0%

Found: 35.9%

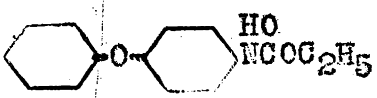
(1) Wt. of sample----------------------------------.2059g.

Std. $AgNO_3$ sol'n used (1cc.≏ .0063465gI)---11.66cc.

Wt. of iodine in sample------------------------.0740g.

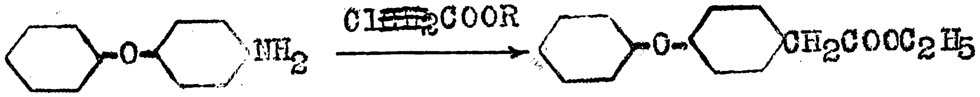
Percent iodine in sample--------------------35.90%

(7) 4-Phenoxy-Phenyl Urethane.-



A solution of 18.5g. (0.1 mol) of 4-amino diphenyl ether in 100 cc. of benzene was turbinated with 15g.(0.18 mols) of sodium bicarbonate in 100 cc. of water, and 20g. (o.18 mols) of ethyl chlorocarbonate slowly added. When the reaction was completethe benzene layer was evaporated to dryness over the steam bath, and the residue (25g) recrystallized from petroleum ether (heptane), using decolorizing charcoal. The purified product (colorless needles melting at 62-3° weighed 16g. (62% of the theoretical), and was readily soluble in alcohol, benzene, and ether, but insoluble in water.

Equation:



Analysis:

Calculated percent nitrogen (for $C_{15}H_{15}O_3N$; mol. wt.= 257.1) = 5.45%

Found: 5.40%, 5.38%.

(1) Wt. of sample-----------------------------------.2012g.

Std. $H_2SO_4$ used(1cc≙.001453g.N)-----------7.47cc.

Wt. of nitrogen in sample--------------------.01085g.

Percent nitrogen in sample------------------5.40%

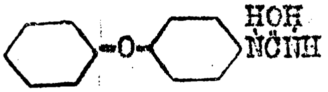
(2) Wt. of sample-----------------------------------.2024g.

Std. $H_2SO_4$ used (1cc≙.001453gN)------------7.49cc.

Wt. of nitrogen in sample--------------------.01088g.

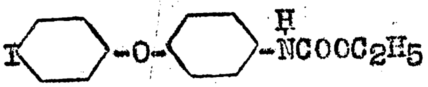
Percent nitrogen in sample------------------5.38%

### (8) 4-Phenoxy-Mono-Phenyl Urea



A suspension of 9.25g. (0.05 mol) of 4-aminodiphenyl ether in a solution of 5 cc. of concentrated hydrochloric acid and 30 cc. of water was warmed, then cooled in cold water to obtain the hydrochloride salt in a finely divided condition. To this was added drop by drop, with stirring, a solution of 5g. (0.9g. excess) of potassium cyanate in 20 cc. of water. When the addition was almost complete, the separation of the urea began, and the mass became nearly solid soon after all was added. The product was then filtered off, washed with water, and when dry weighed 9.5g. (crude yield 84%). Recrystallization from hot 50% ethyl alcohol yielded 5g. of colorless, elongated rectangular plates melting at 177°. (reported melting point 178° corr.)[45].

### (9) 4-(4-Iodophenoxy)-Phenyl Urethane.

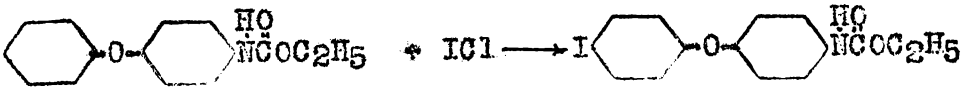


This compound has been obtained (a) by direct iodination of 4-phenoxyphenyl urethane; and (b) by treatment of 4-iodo-4'-aminodiphenyl ether with ethyl chlorocarbonate. Since the products were identical in both, cases, the constitution of the iodination product from (a) is established by the synthesis in (b).

(a) To a solution of 13.6g. (.06 mol) of 4-phenoxy-phenyl urethane in 75 cc of glacial acetic acid were added 12g. (.074 mols) of iodine monochloride and the mixture refluxed gently for two hours. Evolution of hydrogen chloride was rapid during the first 15 minutes, but gradually diminished thereafter. The resulting solution was then poured into water, decolorized with silute sodium sulfite, and the precipitated product collected on a filter.

Recrystallization from alcohol, then petroleum ether, yielded nearly colorless (slight pink tinge) elongated plates melting at 125-6°.

Equation:



Analyses:

Calculated percent iodine (for $C_{15}H_{14}O_3NI$; mol. wt. = 383.1) = 33.1%

Found: 33.0%, 33.1%

(1) Wt. of sample--------------------------------.2580g.

Std. $AgNO_3$ sol'n used (1cc=.006326gI)---13.48cc.

Wt. of iodine in sample--------------------.08527g

Percent iodine in sample-----------------33.0%

(2) Wt. of sample---------------------------------.2106g.

Std. $AgNO_3$ sol'n used (1cc.= .0063465gI)-10.98 cc.

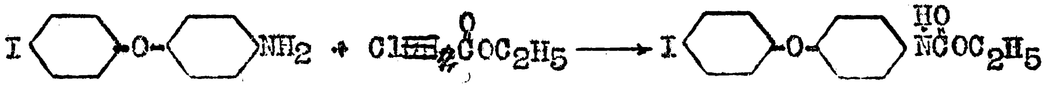
Wt. of iodine in sample---------------------.06969g.

Percent iodine in sample--------------------.33.1%

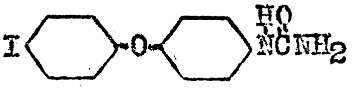
(b) To a solution of 5 g. 4-iodo-4'-aminodiphenyl ether and 2cc. of pyridine in 30cc. of acetone, was added with shaking, while cooling in an ice bath, 1.7 cc. (0.2cc. excess) of ethyl chlorocarbonate. After

5 minutes the resulting solution was diluted with cold water, and the (pink colored) crystalline precipitate collected on a filter. The crude yield (m.p. 120-2°) was practically theoretical. Recrystallization from hot 90% ethyl alcohol, then petroleum ether (heptane b.p.95°) yielded slightly pinkish ellngated plates, melting at 125-126°, identical in appearance with the product from (a), and with melting point undrepresed by mixture with the latter:

Equation:



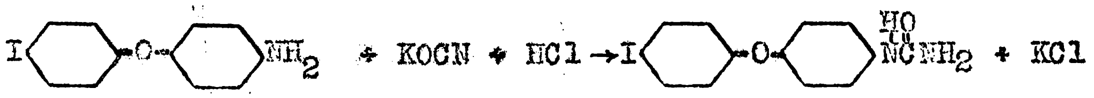
### (10) 4-(4-Iodophenoxy)-Mono-Phenyl-Urea.



This substance was obtained successfully from 4-iodo-4'-aminodiphenyl ether, with potassium cyanate in acid solution. Several attempts were made to iodinate 4-phenoxy-mono-phenyl urea, using the same method as given above for iodination of 4-phenoxy-phenyl-urethane, and other variations in which sodium acetate was added, and in which the reaction mixture was heated for a longer time (8 hours) at a lower temperature (steam bath). The product obtained in these cases, consisted of a mixture of substances from which a pure sample of the desired iodo-substituted urea was not successfully separated. With no sodium acetate present the main product was the hydrochloride of 4-iodo-4'-aminodiphenyl ether. When sodium acetate was used, appreciable quantities of 4-acetaminodiphenyl ether were obtained, indicating some hydrolysis of the urea and acetylation of the resulting 4-aminodiphenyl ether had occurred. The successfyl method for the preparation of the desired substance was the following:

A suspension of 5g. of finely powdered 4-iodo-4'-aminodiphenyl ether, in 100 cc. of water containing 15 cc. of concentrated hydrochloric acid (sp.gr.1.2), was warmed with stirring to obtain the hydrochloride salt, then cooled to room temperature and a solution of 5g. of crude potassium cyanate in 25cc. of water added slowly with stirring. Stirring was continued for an hour, then the solution neutralized with sodium carbonate solution (to convert any excess hydrochloride back to the amine), warmed slightly, then cooled, filtered and washed with a small amount of hot heptane. The crude product weighed 4.9g. (86% of the theoretical) and on recrystallizing from slightly diluted ethyl alcohol, separated as flat irregular plates melting at 200-1°.

Equation:



Analysis:

Calculated percent iodine (for $C_{13}H_{11}O_2N_2I$; mol. wt.= 354.0) =35.9%

Found: 36.1%

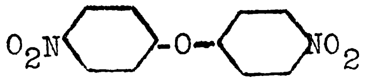
(1) Wt. of sample---------------------------------.2120g.

Std. $AgNO_3$ sol'n used (1cc=.0063465G.I)-12.05cc.

Wt. of iodine in sample--------------------.07648g.

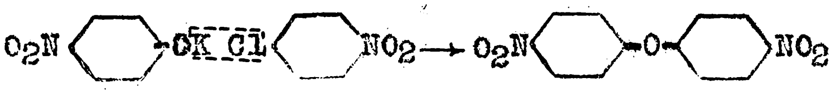
Percent iodine in sample-----------------36.1%

## (11) Preparation of 4,4'-Dinitrodiphenyl Ether.



This substance was obtained according to the method described by Haeussermann and Teichmann[12], which has been given on page 13. The potassium salt of p-nitrophenol was obtained by adding slowly with stirring, a solution of 11.2g. (0.2 mol) of potassium hydroxide in 6 cc. of water, to 27.8g. (0.2 mol) of p-nitrophenol in 50 cc. of absolute alcohol, while cooling the latter in an ice bath. When the resulting mixture was thoroughly cooled, the yellow salt was filtered off and dried in a vacuum dessicator. The yield was 34g. or 96% of the theoretical. Using 50g. of p-nitrochlorobenzene, 12.5g. of the potassium salt of p-nitrophenol and heating for one hour (see page 13 for procedure) there was obtained, after recrystallization of the crude product from 100cc. of benzene, 5.5g. (30% of the theoretical) of the 4,4'-dinitrodiphenyl ether, melting at 142-5° as recorded by Haeussermann and Teichmann. This substance was used in identifying the 4,4'-dinitrodiphenyl ether obtained in attempted nitrations of 4-iodo-diphenyl ether (see page 100).

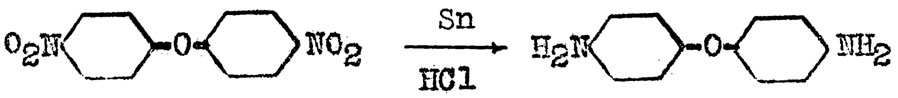
Equation:



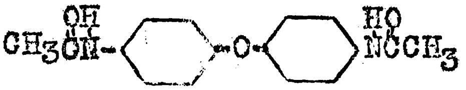
## (12) Preparation of 4,4'-Diaminodiphenyl Ether.

This compound was obtained by reduction of 4,4'-dinitrodiphenyl ether in alcohol solution, using tin and hydrochloric acid employing proportions of reactants and following a procedure exactly as has been given for the preparation of 3,4'-diaminodiphenyl ether on page 8. The crude amine (yield approx. 85%) was obtained as colorless glistening crystals melting at 184-6°. (reported 186-7° by Haeussermann and Teichmann[12]) and was used in other experiments without further purification.

Equation:

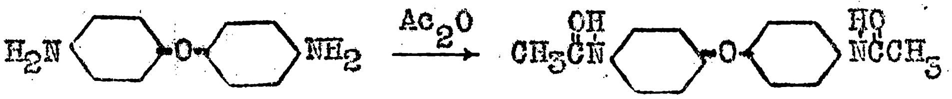


## (13) 4,4'-Diacetaminodiphenyl Ether.



Two grams of 4,4'-diaminodiphenyl ether were dissolved in 15 cc of glacial acetic acid, 15 cc of acetic anhydride added, and the resulting solution boiled under reflux for ½ hour, then poured into 300 cc. of ice water. After meutralizing most, but not all of the acetic acid with ammonium hydroxide, and allowing to stand for a short time in the ice box, the white solid was filtered off (yield practically theoretical) and recrystallized from dilute ethyl alcohol. The collrless crystalline product melted at 225°.

Equation:



Analyses:

Calculated percent nitrogen (for $C_{16}H_{16}O_3N_2$; mol. wt.= 284.15) = 9.86%

Found: 9.63%, 9.81%

(1) Wt. of sample------------------------------------.1538g

Std. $H_2SO_4$ sol'n used (1cc.≏.001420gN)---10.41cc.

Wt. of nitrogen in sample--------------------.01481g

Percent nitrogen in sample------------------9.63%

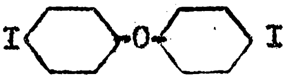
(2) Wt. of sample------------------------------------.2045g.

Std. $H_2SO_4$ son'n used (1cc≏.001453gN)-----13.8cc.

Wt. of nitrogen in sample----------------------.02005g

Percent of nitrogen in sample----------------9.81%

### (14) 4,4'-Diiododiphenyl Ether.



This substance has been obtained, as described page 95, as a by-product in the preparation of 4-iododiphenyl ether by direct iodination of diphenyl ether, using glacial acetic acid as a solvent and iodine monochloride asiodinating agent. Three further methods used in the synthesis of this compound are as follows: (a) From 4,4'-diaminodiphenyl ether by the Sandmeyer reaction; hence establishing the constitution of samples of this substance obtained by other methods. (b) From 4-iodo-4'-aminodiphenyl ether by the Sandmeyer reaction, which establishes the constitution of this amine and its parent nitro compound, obtained as described on pages 98 and 104 respectively. (c) By further iodination of 4-iododiphenyl ether, using iodine monochloride in glacial acetic acid solution. The procedure in each of these cases is described as follows:

(a) To a cooled solution of 4.0 cc. of concentrated sulfuric acid in 15 cc. of water, was added a solution of 1.5g. of 4,4'-diaminodiphenyl ether in 15 cc. of glacial acetic acid. The resulting mixture was then cooled to 0° and diazotized by the addition, drop by drop, during 10 minutes, and with constant stirring, of an ice cold solution of 1.4g. of sodium nitrite in 10cc. of water. On cooling the salt of the diamine separated to some extent, but this gradually dissolved during the diazotization. After standing at 0° for 30 minutes, the cold diazonium solution was poured with rapid stirring into a solution of 4g. of potassium iodide in 20 cc. of water, to which approx. 25g. of ice had been added. The bright red addition product which formed was then decomposed by heating the mixture to 70° on the water bath, After cooling, a small amount of dilute sodium sulfite solution was added to remove excess iodine, then the precipitate filtered off and recrystallized from boiling 95% ethyl alcohol, using charcoal. The recrystallized product, colorless plates melting at 139°, weighed 2 grams.

This compound has been recently reported by Scarborough[31], who obtained it by the Sandmeyer reaction from 4-iodo-4'-aminodiphenyl ether, or by allowing excess iodine monochloride to react with diphenyl ether in glacial acetic acid. This investigator recorded a melting point of 139°, but no yields were stated.

Equation:

Analysis:

Calculated percent iodine(for $C_{12}H_8OI_2$; mol. wt.= 421.9) = 60;2%

Found: 60.1%

(1) (Bomb heated 2o minutes after ignition)

Wt. of sample----------------------------.2067g.

Std. $AgNO_3$ sol'n used (1cc.= .0063465gI)-19.56 cc.

Wt. of iodine in sample------------------------.1241g.

Percent iodine in sample------------------60.1%

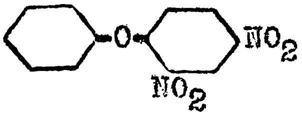
(b) A suspension of 3.5g. (approx..01 mol) of the finely powdered hydrochloride salt of 4-iodo-4'-amino diphenyl ether in 30 cc. of water, to which had been added 5 cc. of concentrated hydrochloric acid and 10 cc. of glacial acetic acid, was cooled to 0° and diazotized by the addition drop by drop, with constant stirring, of an ice cold solution of 0.7g. of sodium nitrite in 5cc. of water. After standing for an hour at 0° to insure complete diazotization, stirring frequently, the diazonium solution was poured with rapid stirring into a solution of 2.0g. of potassium iodide in 10cc. of water, to which a small quantity of crushed ice had been added. When the solutions were well mixed, the orange colored addition product was decomposed by warming to 65° on the water bath. After cooling, the yellowish solid product was filtered off and recrystallized from hot 95% ethyl alcohol using charcoal. The colorless plates obtained(3.2g. or 75% of the theoretical) melted at 139°, undepressed by mixture with the product from (a) above.

(c) To a solution of 14.8g. (0.05 mol) of 4-iodo-diphenyl ether in 50cc. of glacial acetic acid, were added

8.5g. (0.4g. excess) of iodine monochloride, and the mixture boiled under reflux for fifteen minutes. The immediate copious evolution of hydrogen chloride greatly diminished after the first few minutes of heating, and was only slight at the end of this time. The mixture was then cooled, diluted with water, decolorized with a small amount of sodium sulfite solution, and the pinkish solid collected on a filter. The crude product weighed 19.5g. (92% of the theoretical) and after recrystallization from 250 cc. of boiling petroleum ether (heptane b.p. approx. 95°) melted at 139°, undepressed by mixture with the product from (a) page 121.

## GROUP D: SUBSTITUENTS IN POSITIONS 2 AND 4.

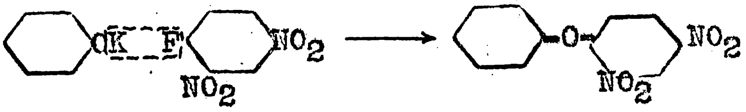
### (1) Preparation of 2,4-Dinitrodiphenyl Ether.



The first portions of this substance used were obtained by allowing 2,4-dinitrofluorobenzene to react with potassium phenate, in an excess of phenol. However, since the reaction using 2,4-dinitrochlorobenzene occurred easily on warming, and this latter compound was much more readily available than the fluoro compound, the major portions of the dinitroether were synthesized using the dinitrochlorobenzene. Both methods of synthesis are given below, since these involve the preparation of different starting materials.

(a) Fluorobenzene was first nitrated to p-nitrofluorobenzene by adding 25g. of this compound, slowly with stirring to a mixture of nitric acid sp. gr. 1.42 (30 cc.), nitric acid sp. gr. 1.5 (15cc.), and concentrated sulfuric acid (40 cc.), keeping the temperature from rising above 25° during the addition, by cooling in ice water. The stirring was continued for an hour, maintaining the temperature at the above value, or slightly below, then the mixture diluted with water, the oily layer separated, washed with dilute sodium carbonate solution, dried over calcium chloride and distilled. The product (80-90%yield) boiled at 205° and was shown by its use in synthesis of diphenyl ether derivatives to be practically pure p-nitrofluorobenzene. Further nitration to 2,4-nitrofluorobenzene was carried out according to the method of Holleman and Beekman (Ref. 15 p 253), by heating 15g. of p-nitrofluorobenzene in a mixture of 15 cc. of fuming nitric (d. 1.5), 30 cc. of concentrated nitric acid (d.1.42) and 30 cc. of concentrated sulfuric acids, for two hours on the water bath. The oily product was obtained by dilution of the nitrating acids, and after washing well with water, was separated and used in later experiments without further purification. The yield was 16g. (81% of the theoretical).

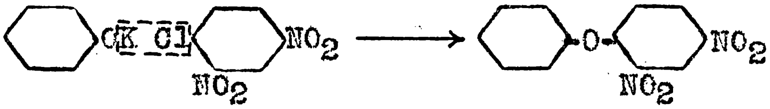
To a warm solution, 7g. of potassium hydroxide in 25g. of phenol were added slowly in small portions, 15g. of 2,4-dinitrofluorobenzene. The reaction was exothermic and the temperature of the solution rose rapidly to the boiling point. When the addition was complete, the temperature was kept at this point for 5 minutes, then the resulting dark green mixture poured into cold water. The precipitated oil, which soon became solid, was collected on a filter and washed several times with water, containing a small quantity of alkali. The melting point of the crude product (21g. or the theoretical yield) was 67°. Recrystallization from boiling heptane yielded faintly yellow needles melting at 70-1°. (Reported 71°; see page 14.)



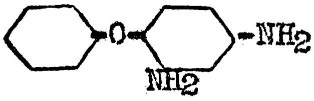
(b) For the preparation of 2,4-dinitrochlorobenzene the following method, a slight variation of that described by Hoffman and Dame[48], was used: One hundred and fifty grams of chlorobenzene were gradually added over a period of two hours to a stirred mixture of 250g. of fuming nitric acid (sp. gr. 1.5) 250g. of concentrated sulfuric acid, and 250g. of fuming sulfuric acid, the temperatute rising to approx. 50-60$^{\circ}$ during the addition. After all the chlorobenzene had been added the mixture was heated over the steam bath for two hours, then poured into water, the yellow solid washed several times by decantation, then steam distilled to remove any unchanged chlorobenzene or mononitrochlorobenzenes. The yellow oil remaining in the distilling flask was separated while hot, and solidified immediately on cooling. The yield was 256g. or 94% of the theoretical. The recovered product (m.p. 48-9$^{\circ}$) was very nearly pure 2,4-niditrochlorobenzene, as described by Hoffman and Dame. (m.p. when pure 50$^{\circ}$).

Fifty grams of potassium hydroxide were melted in 140g. of phenol by warming in a 1 liter flask fitted with an air reflux condenser. While still hot 140g. of molten 2,4-dinitrochlorobenzene, prepared as above were added slowly in small portions, through the top of the condenser; Heat was evolved and the mixture, soon becoming brown, rose rapidly to the boiling point, so that some cooling was necessary before the addition was complete. After all the dinitrochlorobenzene had been added, the mixture was boiled gently over a luminous flame for five minutes, shaking meanwhile, then poured out with stirring into cold water containing excess alkali. The precipitated oil soon solidified, and after filtering, washing, and drying, weighed 175g. (97% of the theoretical), and melted at 64-67°. A sample recrystallized from boiling heptane melted at 71°. Most of the product, however, was used later in reactions without further purification.

Equation:

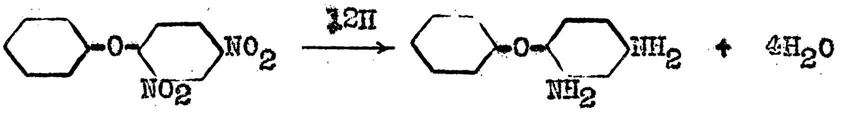


### (2) 2,4-Diaminodiphenyl Ether.

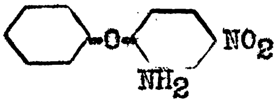


Good yields of this compound were obtained by reducing 2,4-dinitrodiphenylether with such reducing agents as iron in acetic acid, or stannous chloride-hydrogen chloride in ether or alcohol. The following method, however, was found most convenient:

Twenty-six grams (0.1mol) of 2,4-dinitrodiphenyl ether were dissolved in 125 cc. of 95% ethyl alcohol, by warming, and the resulting solution shaken with gaseous hydrogen under 40 pounds pressure, using finely divided paatinum as a catalyst. (See ref. 17 for details of apparatus and preparation of catalyst). Absorption of the theoretical quantity of hydrogen took place in about ½ hour; after which the platinum was filtered from the solution and the latter diluted to 600cc. with water and crushed ice. The light colored gum which was immediately precipitated, soon became crystalline, and after allowing most of the ice to melt, was filtered off. The yield was practically theoretical of fine, nearly colorless plates melting at 65-7° (Reported melting point 67°)[21], and was used in later experiments without further purification.



### (3) 2-Amino-4-Nitrodiphenyl Ether.

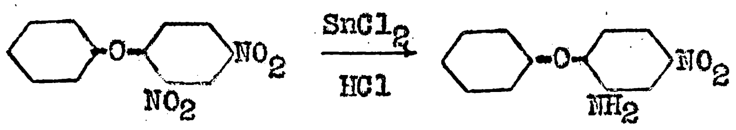


This substance has been obtained by Bogert and Evans[21], but was erroneously supposed by them to be 2-nitro-4-aminodiphenyl ether, as has been shown by experiments in this investigation (see pages 23-25 and 130).

The following procedure is the samexas that described by the above investigators, except for the recovery of product and the minor point mentioned below in connection with the addition of the reducing agent.

A solution of 104g. (o.4 mol) of 2,4-dinitrodiphenyl ether in 300 cc. of 95% ethyl alcohol was placed in a 1 liter flask fitted with an air reflux condenser and a thermometer, then warmed to approx. 50°. Through the top of the condenser were then added, in small portions, 270.8g. (1.2 mols) of crystallized stannous chloride and 120cc. of concentrated hydrochloric acid (sp. gr. 1.2), shaking the flask after each addition, and cooling in cold water to keep the temperature at 60-70°. After keeping the mixture hot for an hour, mostvof the alcohol was removed by distillation under reduced pressure. The remaining mixture was then filtered, the precipitate (a) saved for later extractions, and the filtrate (b) cooled. To the latter cold excess 40% NaOH was added, until the tin hydroxides had completely dissolved, then the dark orange product (c) recovered by filtering through glass wool. The precipitate (a) above was extracted twice with 150cc. portions of 35% hydrochloric acid, recovering further portions of the product by adding ammonium hydroxide to the extracts when cold. The combined precipitates of the product, when recrystallized from hot 95% alcohol yielded approximately 30g. of glistening garnet red plates melting 106-7°(uncorr.) This is about the same yield as reported by Bogert and Evans, who describe their product as garnet red prisms or orange redplates melting at 107-8° corr." In the procedure as given by Bogert and Evans, the stannous chloride was added in a solution of 250cc. of concentrated hydrochloric acid, then the whole neutralized with ammonia after the reaction. In the experiment described above, 20 cc. of hydrochloric acid was first added, then in small portions, most of the stannous chloride before further additon of the acid. The reaction continued although this was insufficient HCl for the formation of stannic chloride. A separate trial showed 2,4-dinitrodiphenyl ether to be easily reduced in alcohol solution by adding cryst. stannous chloride, without addition of hydrochloric acid, the product being the same as in the above experiment.

Equation:

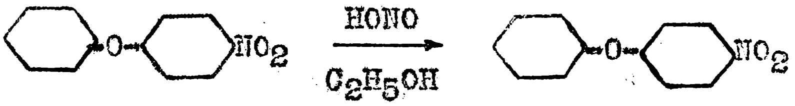


(4) Proof of Constitution of 2-Amino-4-Nitro-Diphenyl Ether by Deamination.

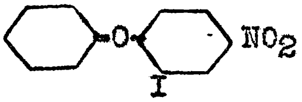
To a solution of 3.5g. of 2-amino-4-nitrodiphenyl ether in 25cc. of 95% ethyl alcohol were added 5 cc. of concentrated sulfuric acid. This solution was then cooled to 0° and an ice cold solution of 1.2g. of sodium nitrite in 3cc. of water added with stirring. After standing in ice for 15 minutes the resulting deep red solution was warmed gently under reflux. Near the boiling point, the deep red color changed to brown, with much frothing, and the odor of acetaldehyde was easily distinguishable at the top of the condenser. After boiling for 15 minutes the resulting mixture was cooled and poured with stirring into ice water. The precipitated oily product was separated after standing for an hour, washed, then extracted with 75cc. boiling heptane, which dissolved all but a small residue of tarry material. After strong cooling in an ice-salt bath had failed to induce crystallization in the yellowish viscous oil which separated from the heptane solution, the latter was evaporated and the residual oil (2.5g.) distilled at 2mm pressure. The distilled product (1.9g.) a pale yellow oil, boiled in the range 155-65°, mostly at 160°, and solidified immediately on cooling. After washing once with a small quantity of cold heptane, the melting point was 57-9°; mixed with known 4-nitrodiphenyl ether (of m.p. 60-61°), the melting point was 58-60°, thus proving the original compound to be 2-amino-4-nitrodiphenyl ether rather than

2-nitro-4-aminodiphenyl ether.

Equation:

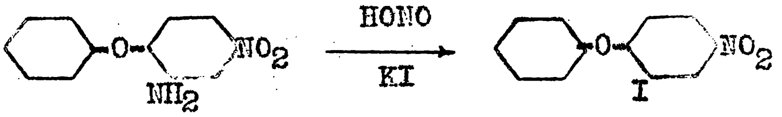


## (5) 2-Iodo-4-Nitrodiphenyl Ether.



To a solution of 11.5g. (.05 mol) of 2-amino@4-nitrodiphenyl ether in 50 cc. of glacial acetic acid was added with stirring a cooled solution of 30 cc. of concentrated sulfuric acid in 50 cc. of water. The resulting mixture was then cooled to 0° and diazotized by the addition, drop by drop with stirring, during 10 minutes, of an ice cold solution of 3.5g. of sodium nitrite in 15cc. of water. After standing for 5 minutes the diazonium solution was poured rapidly with stirring into a solution of 8.33g. of potassium iodide in 25cc. of water, to which 50g. of ice had been added. Decomposition of the orange addition product which was immediately formed, occurred mostly at 5-10° on warming. The temperature was raised to 60° to insure complete decomposition, then the mixture cooled, the oily product separated, washed, diluted with a small quantity of ether, and shaken with dilute sodium sulfite to remove a trace of iodine. After drying over calcium chloride, the ether was evaporated and the residual oil distilled at 2.mm. pressure, collecting the portion boiling in the range 200-6°, mostly at 205°. The distilled product a pale yellow oil, weighed 11.6g. (68% of the theoretical), a small residue (approx. 2.5g.) of higher boiling material remaining in the flask. On cooling and rubbing the oil solidified easily and melted at 58-60°. Recrystallization from 95% ethyl alcohol yielded fine, colorless rectangular plates, melting at 61°.

Equation:



Analysis:

Calculated percent iodine (for $C_{12}H_8O_3NI$; mol wt. = 341.0) = 37.2%

Found: 37.3%

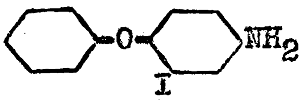
(1) Wt. of sample------------------------------.2108g

Std. $AgNO_3$ sol'n used (1cc ≏ .006326gI)--12.43 cc.

Wt. of iodine in sample-------------------.7863g.

Percent of iodine in sample-------------37.3%

### (6) 2-Iodo-4-Aminodiphenyl Ether.

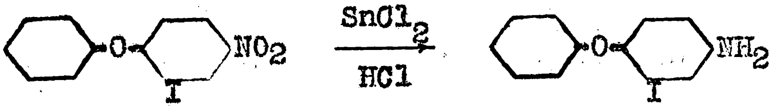


Reduction of 2-iodo-4-nitrodiphenyl ether with hydrogen, using platinum catalyst, apparently removed part of the iodine. The water solution obtained after precipitation of the product from the alcohol used in reduction, gave an abundant flocculent precipitate when acidified with nitric acid and silver nitrate solution was added. The oily product from this reduction did not give a pure acetyl derivative, and distilled over a wide range. The desired iodo-amine was obtained satisfactorily by the following method, however:

A solution of 8.0g. 2-iodo-4-nitrodiphenyl ether in 75cc. of 95% ethyl alcohol was added slowly to a warm solution of 22g. of cryst. stannous chloride in 35cc. of concentrated hydrochloric acid, then the resulting mixture refluxed for 15 minutes or until the ether was all in solution. Excess alcohol was removed by distillation over the steam bath, the remaining liquid, from which a small amount of tim double salt had crystallized, cooled well in ice, 100g. of crushed ice added, then cold 40% sodium hydroxide stired slowly into the solution until the flocculent tin hydrocides first produced had dissapeared.

The resulting milky solution was then extracted with ether, the ether layer washed with a small quantity of cold water, then the ether evaporated, removing last traces by heating over the steam bath. The reddish oily product (colored by atmospheric oxidation), when thoroughly drym weighed 7.1g. (97% of the theoretical). Distillation under reduced pressure gave a clear colorless oil boiling at 200° at 2 mm., which became very viscous at -10° but did not solidify. The hydrochloride salt of this amine was found to be only slightly soluble in water (cold), and recrystallized from boiling water in glistening colorless plates which darkened and melted at 245°. Alkaline solutions of the product were reddened easily by atmospheric oxidation. The index of refraction at 20° was 1.677, using sodium light.

Equation:



Specific Gravity:

Calibration of pyknometer bulb: "B"

Wt. of pyk. filled with $H_2O$ @ 25°-------------1.8124g.

Wt. of pyk. empty @ 25o---------------------1.6389

Observed weight of $H_2O$ @ 25°----------------0.1735g.

Buoyancy correction (see page 27)-----------0.0001

Corrected wt. of water at 25°---------------0.1736g.

Vol. of pyk. (Sp.gr. $H_2O$ $\frac{25^\circ}{4^\circ}$=.99707)--------0.1741ml.

(1) Wt. of pyk. filled with 2-iodo-4-amino
diphenyl ether @ 25°--------1.9291g.

Wt. of pyk. empty---------------------------1.6389

Wt. of 2-iodo-4-aminodipmenyl ether @25°-- .2902

Buoyancy corrections------------------------ .0001

Corr. wt. of 2-iodo-4-am.diphenyl ether@25°.2903

Calc. sp. gr. $\frac{25^\circ}{4^\circ}$ of " " " ----1.667

Analysis:

Calculated percent iodine (for $C_{12}H_{10}ONI$; mol. wt.= 311.0) = 40.8%

Found: 40.8%

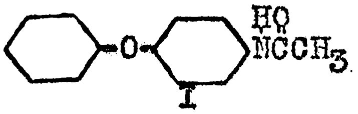
(1) Wt. of sample-----------------------------------.2520g.

Std.$AgNO_3$ sol'n used (1 cc.= .006326g.I)-16.25 cc.

Wt. of iodine in sample----------------------.1028g.

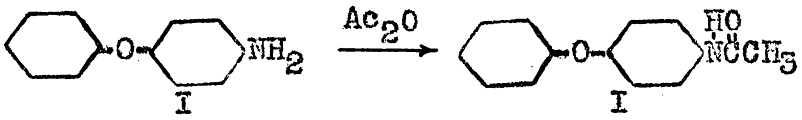
Percent iodine in sample------------------40.8%

### (7) 2-Iodo-4-Acetaminodiphenyl Ether.



A solution of 1.6g. 2-iodo-4-aminodiphenyl ether in a mixture of 15cc. of glacial acetic acid and 10 cc. of acetic anhydride was refluxed gently for 30 minutes, then diluted with cold water. The yield of the white solid obtained, after drying, was practically theoretical. Recrystallization from dilute alcohol, then from hot heptane (only slightly soluble in the latter) yielded pearly plates, with a slight pink tinge, which melted at 119-20°.

Equation:



Analysis:

Calculated percent ionine (for $C_{14}H_{12}O_2NI$; mol. wt.= 353.0) = 36.0%

Found: 36.1%

(1) Wt. of sample--------------------------------.2049g.

Std. $AgNO_3$ sol'n used (1cc ≏ .006326gI)-11.71 cc.

Wt. of iodine in sample--------------------.7402g.

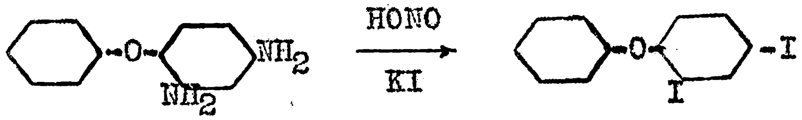
Percent iodine in sample------------------36.1%

### (8) 2,4-Diiododiphenyl Ether.

This substance has been synthesized by the Sandmeyer reaction from both 2,4-diaminodiphenyl ether and 2-iodo-4-aminodiphenyl ether. Higher yields with less by-products were obtained from the latter compound. The procedures were as follows:

(a) To a solution of 4.3g. of 2,4-diaminodiphenyl ether in 25 cc. of glacial acetic acid, was added a cooled solution of 15cc. of concentrated sulfuric acid in 25 cc. of water, and the resulting mixture cooled to 0°. To this was added drop by drop, with stirring, an ice cold solution of 3.0 g. of sodium nitrite in 10cc. of water, then the resulting orange solution allowed to stand in ice for 30 minutes. If no acetic acid was used in this experiment, considerable tarry material, which gave a strong odor of phenol, separated during the diazotization. The above diazo solution was then poured with rapid stirring into a solution of 7.2g. of potassium iodide in 30cc. of water, to which approximately 75g. of ice had been added. A pinch of copper powder was then added and the orange addition product decomposed by warming on the steam bath. Nitrogen was first evolved at approximately 10°, producing a dark gum, the solution keeping an orange color, however, until a temperatur of approx. 60° was reacher, where further evolution of nitrogen occurred. After keeping at 70° for 20 minutes, thw mixture was cooled well, the aqueous portion decanted, and the dark oil remaining subjected to steam distillation until no more white solid came over. Decolorization of the well cooled distillate with dilute sodium sulfite solution, then filtration yielded approx. 1g. of crystalline material of m.p. 71-2° identified 2,4-diiodophenol. This substance (analyzed below) corresponded to the following description of 2,4-diiodophenol in Beilstein: m.p.=72°, sublimes easily at 100°, easily soluble in alcohol, ether, and dilute alkali. (see also Neumann, Ann. 241, 71 76.) After cooling, the water was decanted from tarry material remaining in the distilling flask, then the latter extracted by boiling for 15 minutes with 100cc. of heptane, which dissolved, all except a small amount of carboneous material. The heptane solution, decolorized with charcoal and evaporated, yielded 4.0g. of a pale yellow oil, of which 3.5g. (38% of the theoretical boiled in the range 190-205°, mostly at 198° at 2 mm. pressure. The index of refraction of the product was <u>1.698</u> at 20°, using sodium light.

Equation:



Specific gravity: (Using pyk. bulb "A" calibrated p. 77)

(1) Wt. of pyk filled with 2,4-diiodo-
diphenyl ether @ 25°--------------2.6555g.
Wt. of pyk. empty-----------------2.0002
Obs.wt. of 2,4-diiododiphenyl ether@25°-- .6553
Buoyancy correction------------------- .0001
Corr. wt. of 2,4-diiododiphenyl ether@25° .6554
Calc. sp. gr. $\frac{25^\circ}{4^\circ}$ " " -----2.021

Analyses:

(1) 2,4-diiodophenol: Calculated percent iodine (for $C_6H_4OI_2$; mol. wt.= 345.9) = 73.4%
Found: 73.0%
Wt. of sample-----------------------------.2098g.
Std. $AgNO_3$ sol'n used (1cc.= .006326g.I)24.21cc.
Wt. of iodine in sample------------------.1532g.
Percent iodine in sample----------------73.0%

(2) 2,4-Dioododiphenyl ether: Calculated percent iodine (for $C_{12}H_8OI_2$; mol. wt. = 421.9) = 60.2%
Found: 60.0%
Wt. of sample-----------------------------.2040g.
Std. $AgNO_3$ sol'n used (1cc = .0063465gI)--19.30 cc.
Wt. of iodine in sample------------------.1225g.
Percent iodine in sample-----------------60.0%

(b) To a solution of 2.8g. of 2-iodo-4-aminodiphenyl ether in 20cc. of glacial acetic acid, was added a cooled solution of 10cc. of concentrated sulfuric acid, in 10cc. of water, and the resulting mixture cooled to 0°. The sulfate salt of the amine separated out somewhat, but dissolved during the addition drop by drop, with stirring, of an ice cold solution of 0.7g. of sodium nitrite in 5cc. of water. The resuting diazo solution was reddish brown in color. After standing for five minutes this cold solution was poured with rapid stiring into a solution of 1.7g. of potassium iodide in 15 cc. of water, to which about 25g. of ice had been added. On warming, the resulting orange addition product decomposed mostly at approximately 35°, but was heated further to 60° to insure complete decomposition. After cooling, the oily product (no tar) was separated from the aqueous suspension, taken up in 50cc. of hot heptane, the resulting solution shaken with warm dilute sodium sulfite solution to remove a trace of iodine, boiled with a small amount of charcoal, then evaporated. Steam distillation of the resulting pale yellow oil (3.1g.) gave no 2,4-diiodophenol as was obtained in the preceeding experiment, (page 139). Distillation under reduced pressure gave 2.9g. (76% of the theoretical) of a clear pale yellow oil boiling at 193-200°, mostly at 198°; and whose index of refraction at 20° was <u>1.700</u> for sodium light.

Equation:

Specific Gravity: (Using pyk. bulb "A" calibrated page 77)

(1) Wt. of pyk. filled with 2,4-diiododiphenyl
ether @ $25^{\circ}$----------2.6669g.
" " " empty-------------------------------2.0002g.
Obs. wt. of 2,4-diiododiphenyl ether@$25^{\circ}$--- .6667g.
Buoyancy correction------------------------- .0001g.
Corr. wt. of 2,4-diiododiphenyl ether @$25^{\circ}$- .6668g.
Calc. sp. Gr. $\frac{25^{\circ}}{4^{\circ}}$ of " " --------2.056

Analysis:

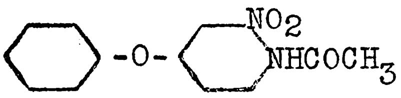
Calculated percent iodine (for $C_{12}H_8OI_2$; mol. wt. = 421.9) = 60.2%

Found: 60.1%

(1) Wt. of sample-----------------------------------.2118g.
Std. $AgNO_3$ sol'n used (1cc.≏.006326gI)---20.13cc.
Wt. of iodine in sample----------------------.1274g.
Percent iodine in sample-------------------60.1%

## GROUP E: SUBSTITUENTS IN POSITIONS 3 AND 4.

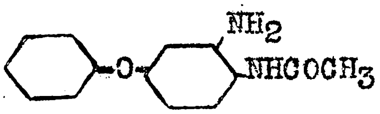
### (1) 3-Nitro-4-Acetaminodiphenyl Ether.



To a well cooled solution of 50g. of 4-acetaminodiphenyl ether (see page 108) dissolved in 200 cc. of glacial acetic acid, was added with stirring, during the course of 5 minutes, a mixture of 70cc. of concentrated nitric acid (sp. gr. 1.42) in 100 cc. of glacial acetic acid. Heat was evolved during the addition, and the mixture was cooled in a pan of cold water to keep the temperature below 45°. Gradual dilution with cold water, after standing for 20 minutes, precipitated the product in deep yellow needles, in practically quantitative yield. The crude dry product melted at 101-2°, and after recrystallization from 95% alcohol or heptane, melted at 103-4°. (Reported 100° (31); 104° (32)).

Synthesis of this compound and its proof of constitution by other investigators have been previously discussed pages 15-17. No yields have been reported in the literature.

### (2) 3-Amino-4-Acetaminodiphenyl Ether.

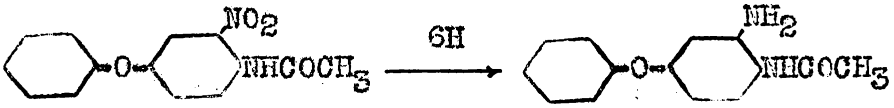


This substance was obtained in good yields, by reduction of 3-nitro-4-acetaminodiphenyl ether using iron powder in acetic acid, or by Suter's method of reduction given page 19. More convenient, however, was the following method using hydrogen with platinum catalyst:

A warm solution of 27.2g. (o.1 mol) of 3-nitro-4-acetaminodiphenyl ether was reduced by shaking with hydrogen under 40 pounds pressure, in the presence of 0.2g of finely divided platinum as catalyst. (See Ref. 17 for details of method). Absorption of the calculated volume of hydrogen (0.3 mols) was complete in approximately $\frac{1}{2}$ hour. The alcohol solution was then filtered free of platinum, and most of the alcohol evaporated under reduced pressure. A small quantity remaining with the precipitated oily product was diluted with ice water then decanted, leaving 23.9g. (98.5% of the theoretical) of a light colored gum which soon crystallized on rubbing, and melted at 124-5°, Recrystallization of the product from slightly diluted ethyl alcohol, by strong cooling in an ice-salt bath, yielded glistening ivory plates of an alcohol addition product, which lost alcohol at approx. 80° on heating, and when thoroughly dry, melted at 125-126°. The product from other reductions was easily purified by precipitation from cold, very dilute solutions of hydrochloric acid, but was not sufficiently soluble in hot heptane to crystallize in quantity from this liquid.

Oesterlin[32], who obtained a very small quantity of this compound, as described page 17, reported the melting point to be 124°.

Equation:



Analyses:

Calculated percent nitrogen (for $C_{14}H_{14}O_2N_2$; mol. wt.= 242.0) = 11.58%

Found: 11.43%, 11.68%

(1) Wt. of sample------------------------------.2069g.

Std. $H_2SO_4$ sol'n used (1cc.=.001453gN)-16.28 cc.

Wt. of nitrogen in sample------------------.02366g.

Percent nitrogen in sample---------------11.43%

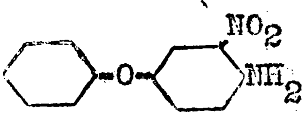
(2) Wt. of sample------------------------------.2167g.

Std. $H_2SO_4$ sol'n used (1cc.=.001453gN)-17.42 cc.

Wt. nitrogen in sample ---------------------.02531g.

Percent nitrogen in sample---------------11.68%

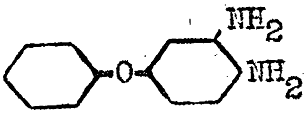
### (3) 3-Nitro-4-Aminodiphenyl Ether.



Hydrolysis of 3-nitro-4-acetaminodiphenyl ether using alcoholic-hydrogen chloride was extremely slow, requiring several hours of boiling, even in solutions of equal quantities of concentrated hydrochloric acid (sp. gr. 1.2) and 95% alcohol. The hydrolysis was more rapid however, being complete in anhour if carried out in an autoclave at a temperature of 120° (pressure = 9 atm.). The product is a very weak base and does not readily form a salt with mineral acids in aqueous solutions. The following method recently used by Oesterlin[32], who gave only meager details and no yields, was found much more convenient:

To a solution of 54.4g. (0.2 mol.) of 3-nitro-4-acetaminodiphenyl ether in 250 cc. of 50% alcohol, were added 50g. of cryst. barium hydroxide, and the mixture refluxed for one hour. After cooling, the dark orange solution was poured out into a large quantity of ice water which precipitated the product as an oil, soon becoming crystalline. The yield was practically theoretical, the crude product melting at 80-82°. Recrystallization from slightly diluted ethyl alcohol removed a trace (less than 1g.) of barium carbonate, and yielded a deep reddish orange prisms melting at 82°. (Reported: 47-8° and 81° [32]; 82° [31]) No crystalline form melting at 47-8° was observed in this investigation.

### (4) 3,4-Diaminodiphenyl Ether.



This compound was easily obtained (a) by reduction of 3-nitro-4-aminodiphenyl ether using hydrogen with platinum catalyst; or (b) by combined hydrolysis and reduction of 3-nitro-4-acetaminodiphenyl ether using zinc dust in alkaline solution. In one attempt to obtain this substance by hydrolysis of 3-amino-4-acetaminodiphenyl ether, using barium hydroxide in 50% alcohol, as described by Oesterlin[32], the product was accidentally lost, and on a second trial boiling for ½ hour was found to give only incomplete hydrolysis.

(a). Ten grams of 3-nitro-4-aminodiphenyl ether in 100cc. of warm 95% alcohol were reduced by shaking with hydrogen under 3 atm. pressure, using 0.2g. of platinic oxide as catalyst. The reddish orange color of the nitro compound disappeared in about 1 hr., indicating completion of the reaction. Evaporation of most of the alcohol undrer reduced pressure, after filtering off the platinum black, and dilution of the last portions, yielded 8.3g. (97% of the theoretical) of a slightly darkened oil which soon solidified on rubbing, and melted at 66-7°. The diamine was easily soluble in ether and alcohol, somewhat so in benzene and carbon tetrachloride, but only slightly soluble in heptane and water. A small quantity of the product recrystallized from warm heptane, on strong cooling, in the form of colorless hexagonal plates, which melted at 68-9°, and did not darken on standing. The diamine hydrochloride did not melt at 240°. The melting point of the diamino ether has recently been reported as being 66° by Oesterlin[32] (see page 17).

Equation:

Analyses:

Calculated percent nitrogen (for $C_{12}H_{12}ON_2$; mol wt.= 200.1 ) ≐ 14%

Found: 14.00%, 14.02%.

(1) Wt. of sample------------------------------------.1036g.

Std. $H_2S^{O}{}_4$ sol'n used (1cc≐.001453gN)--9.96cc.

Wt. of nitrogen in sample--------------------.01447g.

Percent nitrogen in sample------------------14.00%

(2) Wt. of sample--------------------------------------.2132g.

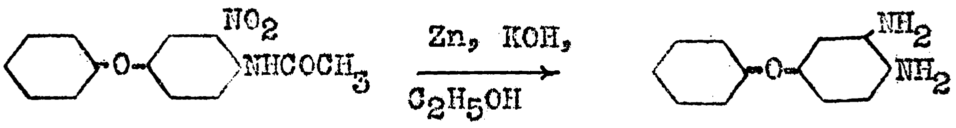
Std. $H_2SO_4$ sol'n used (1cc≐.001453gN)---20.57 cc.

Wt. of nitrogen in sample---------------------.02989g.

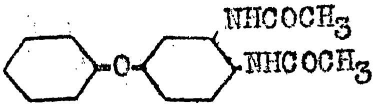
Percent nitrogen in sample------------------14.02%

(b)A solution of 5g. of potassium hydroxide in 10cc. of water was added to 5.5g. of 3-nitro-4-acetaminodiphenyl ether in 50cc. of 95% ethyl alcohol and the mixture warmed to boiling under reflux. Through an adapter were added 12g. of zinc dust, in small portions, allowing the exothermic reaction to subside after each addition, and keeping the mixture well stirred. The deep orange color of the solution disappeared after most of the zinc had been added. The mixture was boiled gently for 5 minutes after the addition was complete, then filtered, and most of the alcohol removed from the filtrate by distillation under reduced pressure. The mixture remaining was then diluted with a small quantity of cold water, and extracted with ether. On evaporation of the ether extract, removing last traces over the steam bath, there remained 3.4g. (84% of the theoretical) of an oil which, when cool, after short rubbing solidified to a gray crystalline mass. The crude product melted at 65-7°, unchanged when mixed with a sample of the diamine from (a) above.

Equation:



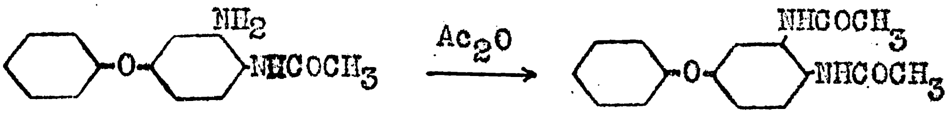
### (5) 3,4-Diacetaminodiphenyl Ether.



This compound was obtained by acetylation of either (a) 3-amino-4-acetaminodiphenyl ether, or (b) 3,4-diaminodiphenyl ether.

(a) A solution of 2g. of 3-amino-4-acetaminodiphenyl ether in a mixture of 10cc. of glacial acetic acid and 5cc. of acetic anhydride was refluxed gently for ½ hour, then cooled and poured into ice water. A white solid separated on standing, but only in small quantity, due to the solvent action of the acetic acid present. The solution was then made just neutral to litmus by the cautious addition of ammonium hydroxide (became cloudy); and after standing several hours in the ice box, the precipitate filtered off. The crude yield was 1.9g. (81% of the theoretical). Recrystallization from hot water gave colorless crystals melting at 187-188°.

Equation:



Analyses:

Calculated percent nitrogen(for $C_{16}H_{16}O_3N_2$; mol. wt. = 284.2) = 9.86%

Found: 9.96%, 9.89%

(1) Wt. of sample------------------------------------.1293g.

Std. $H_2SO_4$ sol'n used (1cc.≏.001453gN)-----8.86cc.

Wt. of nitrogen in sample--------------------.01287g.

Percent nitrogen in sample------------------9.96%

(2) Wt. of sample------------------------------------.1786g.

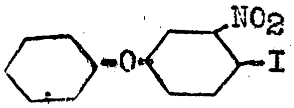
Std. $H_2SO_4$ sol'n used (1cc≏.001453gN)----12.16 cc.

Wt. of nitrogen in sample--------------------.01767g.

Percent nitrogen in sample------------------9.89%

(b) 2 g. of 3,4-diaminodiphenyl ether were acetylated by boiling with acetyl chloride in acetic acid for 20 minutes; then the product recovered as in the immediately preceding experiment. The yield was practically the same as described above, and the melting point and mixed melting point with the product above were identical. (187-8°).

### (6) 3-Nitro-4-Iododiphenyl Ether.



To a solution 34.5g. (.15 mol) of 3-nitro-4-aminodiphenyl ether dissolved in 125cc. of glacial acetic acid by warming, was added a cooled mixture of 40 cc. of concentrated sulfuric acid in 30 cc. of water, and the resulting deep red solution cooled to 0°. To this, was added drop by drop, with stirring, during 15 minutes, an ice cold solution of 10.5g. of sodium nitrite in 30cc. of water, during which addition the deep red color changed to orange. After standing in ice for 30 minutes, the diazonium solution was poured with rapid stirring into a solution of 25g. of potassium iodide in 50cc. of water to which 50g. of crushhd ice had been added. Most of the resulting orange addition product decomposed to a dark oil immediately. After heating to 60° over the steam bath to insure complete decomposition, the mixture was cooled, diluted with 800cc. of cold water, and the aqueous pprtion separated from the oily product. The oil was then diluted slightly with chloroform, a trace of iodine removed by washing with dilute sodium sulfite solution, the oily layer dried over calcium chloride, then transferred to a distilling flask where the chloroform was removed, and the residual oil distilled under reduced pressure. The product 36g. (70% of the theoretical) of a clear, deep yellow oil, was collected in the intevral 185-98° at $1\frac{1}{2}$ mm. pressure, boiling mostly at

190-1°. A heavy residue of approx. 6g. remained undistilled in the flask. A small fraction was collected from the middle of the distillation for analysis, specific gravity, and index of refraction determinations. At 20°, the index of refraction was 1.657 using sodium light.

Equation:

Specific Gravity: (Using pyk. bulb "A", calibrated page 77)

(1) Wt. of pyk. filled with 3-nitro-4-iododiphenyl ether @ 25°-------------2.5586g.

Wt. of pyk. empty----------------------------2.0002g.

Obs. wt. of 3-nitro-4-iododiphenyl ether@ 25°----------------.5584

Buoyancy correction---------------------------.0002

Corr. wt. of 3-nitro-4-iododiphenyl ether @ 25°-----------------.5586

Calc. sp. gr. $\frac{25^{\circ}}{4^{\circ}}$ ---" "---------------1.722

Analysis:

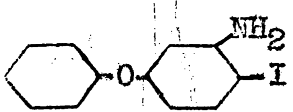
Calculated percent iodine (for $C_{12}H_8O_3NI$; mol. wt.= 340.1) = 37.2%

**Found:** 37.2%

(1) Wt. of sample--------------------------------.2558g.

Std. $AgNO_3$ sol'n used (1cc≏.0063465gI)--15.01cc.
Wt. of iodine in sample--------------------.09527g.
Percent iodine in sample------------------37.2%

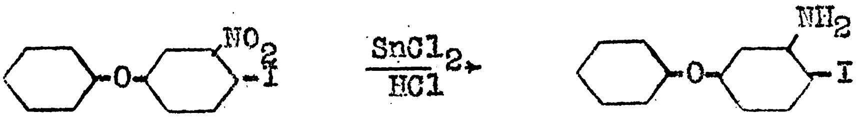
### (7) 3-Amino-4-Iododiphenyl Ether



An attempt was made to reduce 3-nitro-4-iododiphenyl ether using a slight excess of stannous chloride in alcohol solution, and following a procedure exactly as has been described for the preparation of 2-iodo-4-aminodiphenyl ether (page 134), but the iodine was removed in the process giving a good yield of 3-aminodiphenyl ether. Using exactly the calculated amount of the reducing agent in ether solution, however, the reduction was successful. The procedure was as follows:

To a cooled solution of 17.1g. (05 mol) of 3-nitro-4-iododiphenyl ether in 200 cc. of dry ether were added 28.6g. of anhydrous stannous chloride (cryst. dehydrated by heating), and the resulting mixtureshaken and cooled in an ice bath while a rapid stream of dry hydrogen chloride was passed in. The stannous chloride gradually dissolved, and an about ½ hour the tin double salt began to separate. When the solution was thoroughly saturated and precipitation had ceased, (after about 1 hour) the double salt was filtered from the cold ether solution; then the amine recovered by mixing the salt with crushed ice, adding cold 40% sodium hydroxide until the tin hydroxides had dissolved, and extracting the resulting milky suspension with ether. After washing the ether extract with a small amount of water, then removing the ether by evaporation over the steam bath, 12g. (77% of the theoretical) of the oily product remained. On distillation under reduced pressure, practically all of the product distilled at 183-4° at 1½mm. pressure. The index of refraction was 1.676 at 20°, using sodium light.

Equation:



Specific gravity: (Using pyk. bulb "A", calibrated page 77).

(1) Wt. of pyk. filled with 3-amino-4-iododiphenyl ethera @ 25°------------2.5397g.

Wt. of pyk. empty--------------------------2.0002

Obs. wt. of 3-amino-4-iododiphenyl ether @25°--------------.5395

Buoyancy correction------------------------.0002

Corr. wt. of 3-nitro-4-iododiphenyl ether
@ 25°---------.5397

Calc. sp. gr. $\frac{25°}{4°}$ of " " "-----1.664

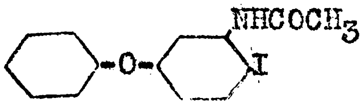
Analysis:

Calculated percent iodine (for $C_{12}H_{10}ONI$; mol. wt.= 311.0) = 40.8%

Found: 40.9%

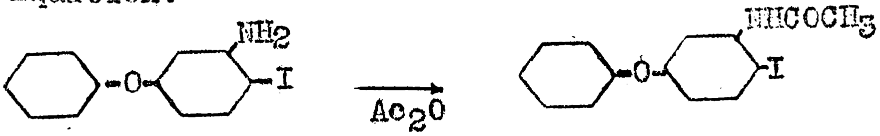
(1) Wt. of sample---------------------------------.2577g.
St.d $AgNO_3$ sol'n used (1cc≐.0063465gI)--16.61 cc.
Wt. of iodine in sample--------------------.1054g.
Percent iodine in sample-----------------40.9%

(2) <u>3-Acetamino-4-Iododiphenyl Ether.</u>



Two grams of 3-amino-4-iododiphenyl ether were acetylated by boiling with 10cc of glacial acetic acid and 10cc. of acetic anhydride for 30 minutes, then the mixture diluted with ice water. A white solid separated from the resulting milky solution after short standing (yield nearly theoretical) which, when filtered and dried, melted at 137-40°. Two crystallizations from dilute ethyl alcohol yielded colorless rectangular prisms, melting at 143-4°.

Equation:



Analysis:

Calculated percentage iodine (for $C_{14}H_{12}O_2NI$;mol. wt.= 353.0) = 36.0%

Found: 35.7%, 36.0%

(1) Wt. of sample--------------------------------.2044g.

Std. $AgNO_3$ sol'n used (1cc.≙ .0063465gI)11.50cc.

Wt. of iodine in sample----------------------.07299g.

Percent iodine in sample-------------------35.7%

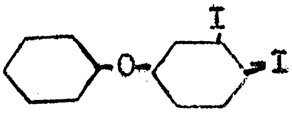
(2) Wt. of sample---------------------------------.2367g.

Std. $AgNO_3$ sol'n used (1cc.≙ .0063465gI)-13.41 cc.

Wt. of iodine in sample----------------------.08511g.

Percent iodine in sample-------------------36.0%

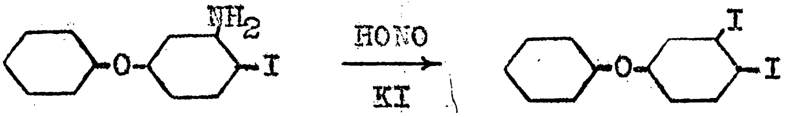
(9) 3,4-Diiododiphenyl ether.



This substance was synthesized by the Sandmeyer reaction quite easily from 3-amino-4-iodo-diphenyl ether, but no pure sample was obtained by the same reaction from 3,4-diaminodiphenyl ether. The results of the latter experiment are also briefly described below, since it ispossible that small quantities may have been formed.

(a) To a solution of 3.0g. of 3-amino-4-iodo-diphenyl ether in 15cc. of glacial acetic acid, was added a cooled solution of 10cc. of sulfuric acid in 15cc. of water; then the resulting mixture cooled to 0$^{o}$, and diazotized by the addition, drop by drop, with stirring, of an ice cold solution of 0.68g. of sodium nitrite in 5 cc. of water. After standing for 10 minutes the resulting orange solution was poured with rapid stirring into a solution of 1.7g. of potassium iodide in 25cc. of water to which 25g. of crushed ice had been added. Decomposition of the orange addition product, which mostly occurred immediately, was completed by warming the mixture to 60o on the steam bath. After cooling, the dark oily product was diluted slightly with chloroform, the oily layer separated, washed with dilute sodium sulfite solution to remove a trace of iodine, and dried over calcium chloride. The chloroform was then evaporated, and the residual oil distilled under reduced pressure, using a small fractionating flask (see pages 26-7). The main portion boiled in the interval 195-208°, mostly at 203-5°, at 2 mm. pressure, with a small residue remaining in the flask. The distilled product (2.5g. or 62% of the theoretical) was a deep yellow oil, for which the index of refraction was <u>1.700</u> at 20°, using sodium light.

Equation:



Specific Gravity: (Using pyk. bulb "A", calibrated page 77).

(1) Wt. of pyk. filled with 3,4-diiododiphenyl ether @ 25°-----------2.6667g.

Wt. of pyk. empty----------------------------2.0002

Obs. wt. of 3,4-diiododiphenyl ether @ 25°----------.6665

Buoyancy correction--------------------------.0001

Corr. wt. of 3,4-diiododiphenyl ether@25°.6666

Calc. Sp. Gr. $\frac{25^\circ}{4^\circ}$ of " "------2.055

Analysis:

Calculated percent iodine (for $C_{12}H_8OI_2$; mol. wt.= 421.9) = 60.2%

Found: 60.3%

(1) Wt. of sample--------------------------------.2325g.

Std. $AgNO_3$ sol'n used (1cc.≈ .0063465gI)-22.12 cc.

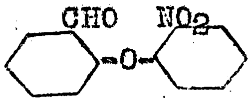
Wt. of iodine in sample-------------------------.1404g.
Percent iodine in sample-------------------60.3%

(b) When 3,4-diaminodiphenyl ether, was diazotized in a manner similar to that above, using two equivalents of sodium nitrite, considerable dark gum formed in the diazonium solution; and much iodine was liberated on additionto the potassium iodide solution, indicating that not all of the sodium nitrite had been used. Only traces of oil were present in the black heavy product. In another trial in which the temperature was maintained at -5 to -10° during the diazotization, less dark gummy material formed in the diazo solution, and an orange-brown addition product was formed on addition to the potassium iodide solution. Decomposition gave a thick black gum, which on distillation and refractionation of the product gave a small quantity of a deep yellow, iodine containing oil, boiling indefinitely at 150-225° at 2mm. becoming very viscous (more so than 3,4-diiododiphenyl ether) on cooling to room temperature, and whose index of refraction was 1.649 at 20° for D of sodium.(Compare 1.700 for 3,4-diiododiphenyl ether.)This product was undoubtedly a mixture of substances but may have contained some 3,4-diiododiphenyl ether.

## SERIES II CARBOXYLIC DIPHENYL ETHERS.

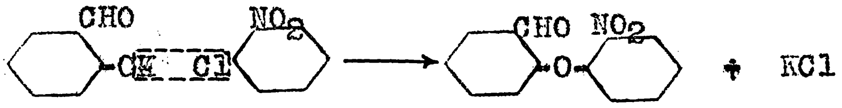
### A. DERIVATIVES OF 2-PHENOXY-BENZOIC ACID.

### (1). 2-(2-Nitrophenoxy)-Benzaldehyde.



To 215g. (1.37 mol) of o-nitrochlorobenzene kept at 165-70°, was added with stiring during 45 minutes, 100g. (0.62 mol) of the potassium salt of salicylaldehyde (prepared as described on page 27 of the Master's thesis[47]) The temperature was then raised to 190-200°, where it was maintained for 6 hours; then the mixture cooled and steam distilled for 8 hours to remove excess o-nitrochlorobenzene. Water was then decanted from the dark oily residue remaining in the distilling flask, and this residue extracted several times with a 500 cc. portion of boiling 95% ethyl alcohol, each time decolorizing the latter with charcoal before cooling to induce crystallization. The product (105g. or 70% of the theoretical) was yellow to yellowish brown in appearance and after recrystallization from heptane using charcoal, was obtained as bright yellow needles melting at 76-7°.

Equation:



Analyses:

Calculated percent nitrogen (for $C_{13}H_9O_4N$; mol. wt.= 243.1) = 5.76%

Found: 5.66%, 5.88%

(1) Wt. of sample------------------------------------.2825g.

Std. $H_2SO_4$ sol'n used (1cc.≏ .001453gN)---11.00 cc.

Wt. of nitrogen in sample---------------------.01598g.

Percent nitrogen in sample------------------5.66%

(2) Wt. of sample------------------------------------.2257g.

Std. $H_2SO_4$ sol'n used ( 1cc.≏ .001453gN)--9.14cc.

Wt. of nitrogen in sample---------------------.01328g.

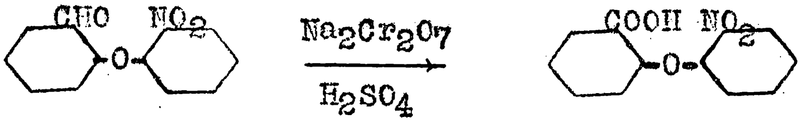
Percent nitrogen in sample-----------------5.88%

(2) <u>2</u>-(<u>2</u>-Nitrophenoxy)-Benzoic acid.

To a solution of 24.5 g. of sodium dichromate in 25cc. of water were added 20g. of 2-(2-nitrophenoxy)-

benzaldehyde, and the mixture warmed until the aldehyde melted; then a cooled solution of 18cc. of concentrated sulfuric acid in 20cc. of water added slowly to the stirred mixture during ½ hour. Stirring(mechanical) was continued and the mixture kept just below the boiling point for an hour, then cooled, diluted with water, and the precipitate extracted several times with hot dilute sodium hydroxide solution. When cooled and acidified the combined extract gave 16g. (75% of the theoretical) of the acid, which on recrystallization from 180cc. of hot benzene using charcoal, yielded a colorless crystalline product melting at 152-3°.

Equation:



Analyses:

Calculated percent nitrogen (for $C_{13}H_9O_5N$; mol. wt.= 259.1) = 5.41%

Found: 5.31%, 5.25%

(1) Wt. of sample------------------------------.2110g

Std. $H_2SO_4$ sol'n used (1cc.≏ .001405g.N) 8.00cc.

Wt. of nitrogen in sample------------------.01124g.

Percent nitrogen in sample----------------5.31%

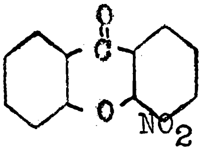
(2) Wt. of sample------------------------------.2084g.

Std. $H_2So_4$ sol'n used (1cc≏.001405gN)-7.79 cc.

Wt. of nitrogen in sample---------------.01095g.

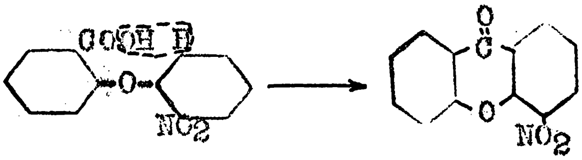
Percent nitrogen in sample-------------5.25%

### (3) 4-Nitroxanthone.



A solution of 5g. of 2-(2-nitrophenoxy)-benzoic acid in 25cc. of concentrated sulfuric acid was heated in boiling water for 30 minutes, then diluted with cold water and the precipitated white solid collected on a filter. The yield of crude product was practically theoretical. After washing and treating with warm dilute sodium hydroxide to remove any unchanged acid present, and again filtering and washing, the nitroxanthone was recrystallized from boiling glacial acetic acid, from which it separated in fine colorless needles mleting at 190°. The product was not sufficiently soluble in alcohol, ether, or water to be easily recrystallized from these solvents. The melting point of this substance has been reported[39] at 127°, which is far from agreement with the above. (see page 41).

Equation:



Analyses:

Calculated percent nitrogen (for $C_{13}H_7O_4N$; mol. wt.= 241.1) = 5.80%

Found: 5.67%, 5.65%

(1) Wt. of sample------------------------------0.2167g.

Std. $H_2SO_4$ sol'n used (1cc.$\approx$.001453gN)--8.46 cc.

Wt. of nitrogen in sample-----------------.01229g.

Percent nitrogen in sample---------------5.67%

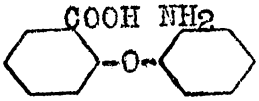
(2) Wt. of sample-------------------------------.2134g.

Std. $H_2SO_4$ sol'n used (1cc$\approx$.001453gN)--8.29 cc.

Wt. of nitrogen in sample-----------------.01205g.

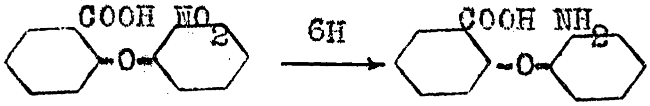
Percent nitrogen in sample---------------5.65%

### (4) 2-(2-Aminophenoxy)-Benzoic Acid.



Eighteen grams of 2-(2-nitrophenoxy)-benzoic acid dissolved in 150cc. of warm 95% ethyl alcohol were reduced by shaking with gaseous hydrogen under pressure of 3 atm., in the presence of 0.2g. of platinum catalyst. (See ref. 17 for construction of apparatus and preparation of catalyst.) After apporximately ½ hour absorption ceased, when the calculated quantity (.208 mols) of hydrogen had been used. The alcohol solution was then warmed to dissolve some of the amine which had separated, filtered free from platinum, then cooled to 0° in ice. Filtration gave 8.0g. of colorless meedles melting at 153°, to which another 6.1g. was added by addition of 250g. of crushed ice to the filtrate, then filtering when most of the ice had melted. Total recovered yield: 14.1g. or 89% of the theoretical.

Equation:



Analyses:

Calculated percent nitrogen (for $C_{13}H_{11}O_3N$; mol. wt. = 229.1) = 6.11%

Found: 6.12%, 6.10%

(1) Wt of sample---------------------------------.2121g.

Std. $H_2SO_4$ sol'n used (1cc≏.001453gN)-8.93cc

Wt. of nitrogen in sample-----------------.01298g.

Percent nitrogen in sample--------------6.12%

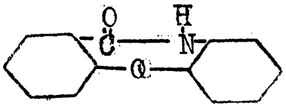
(2) Wt. of sample------------------------------.2401g.

Std. $H_2SO_4$ sol'n used (1cc≏.001453gN)-10.09cc.

Wt. of nitrogen in sample-----------------.1466g.

Percent nitrogen in sample--------------6.10%

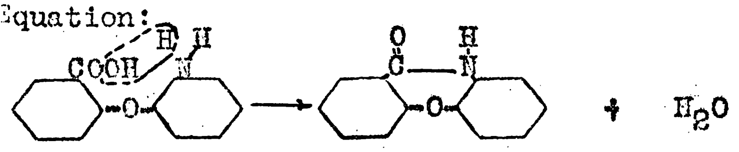
(5) 2-(2-Aminophenoxy)-Benzoic acid Lactam.



This substance was obtained by heating either (a) 2-(2-Aminophenoxy)-benzoic acid or (b) its acetyl derivative (2-(2-acetaminophenoxy)-benzoic acid) above their melting points for a short time.

(a) Two grams of 2-(2-aminophenoxy)-benzoic acid contained in a test tube were heated in a sulfuric acid bath at 210-5° for 5 minutes. Water was evolved and collected on the sides of the tube. On cooling the liquid, which crystallized immediately, was powdered, washed first with dilute ammonium hydroxide, then with dilute hydrochloric acid to remove any unchanged amino-acid, and when dry melted at 210-11°. The yield was practically theoretical. Recrystallization from dilute ethyl alcohol yielded colorless crystals with melting point still at 210-11°.

Equation:



Analyses:

Calculated percent nitrogen (for $C_{13}H_9O_2N$; mol. wt. = 211.1) = 6.64%

Found: 6.67%, 6.64%

(1) Wt. of sample--------------------------------.1544g.

Std. $H_2SO_4$ sol'n used (1cc. ≏ .001378gN)7.48cc.

Wt. of nitrogen in sample----------------.01031g.

Percent nitrogen in sample---------------6.67%

(2) Wt. of sample---------------------------------.1532g.

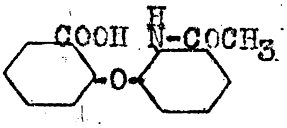
Std. $H_2SO_4$ sol'n used (1cc ≏ .001378gN)--7.38cc.

Wt. of nitrogen in sample----------------.01017g.

Percent nitrogen in sample---------------6.64%

(b) One gram of 2-(2-acetaminophenoxy)-benzoic acid (page 169), when heated in a test tube at 250°, as in the above experiment for five minutes, eliminated acetic acid; detected by condensation on the walls of the test-tube, by wet litmus, by odor, and by giving a cloud with ammonia after the tube had cooled. After washing the powdered product with dilute ammonia, and drying, the melting point was 205-7°; mixed with the product from (a) above (of m.p. 210-11°), the melting point was 207-9°, showing the two substances to be identical. This substance was also found to be formed to some extent when 2-(2-aminophenoxy)-benzoic acid was acetylated by boiling ½ hour in a mixture of acetic acid and acetic anhydride. (See the following described experiment).

### (6) 2-(2-Acetaminophenoxy)-Benzoic acid.

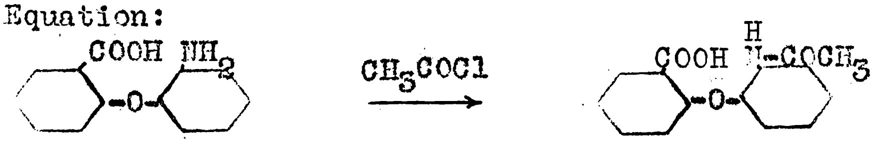


This substance was obtained, mixed with the lactam of 2-(2-aminophenoxy)-benzoic acid, when 2-(2-aminophenoxy)-benzoic acid was boiled in a mixture of glacial acetic acid and acetic anhydride for ½ hour. The pure acetyl derivative was obtained, however, when acetyl chloride was used as acetlyating agent instead of acetic anhydride.

A solution of 1.5g. of 2-(2-aminophenoxy)-benzoic acid in a mixture of 5cc. of glacial acetic acid and 5 cc of acetyl chloride, was boiled under reflux for 10 minutes, then diluted with ice water. An abundant white precipitate was formed in practically quantitative yield, which after recrystallization from dilute ethyl alcohol yielded colorless elongated plates melting at 178-9°.

The acetyl derivative was readily soluble in dilute ammonia, forming the salt, but on acidifying this alkaline solution with acetic acid only a faint cloudiness appeared, without separation of the acid. The addition of a strong acid such as hydrochloric acid, however, produced immediate precipitation, showing the 2-(2-acetaminophenoxy)-benzoic acid to be comparable in strength with acetic acid.

Equation:



Analyses:

Calculated percent nitrogen (for $C_{15}H_{13}O_4N$; mol.wt.= 271.1) = 5.17%

Found: 5.27%, 5.11%

(1) Wt. of sample--------------------------.2034g.

Std. $H_2SO_4$ sol'n used (1cc≏.001378gN)-7.78cc.

Wt. of nitrogen in sample---------------.01072g.

Percent nitrogen in sample--------------5.27%

(2) Wt. of sample-----------------------------.2100g.

Std. $H_2SO_4$ sol'n used (1cc≏.001378gN)-7.78 cc.

Wt. of Nitrogen in sample---------------.01072g.

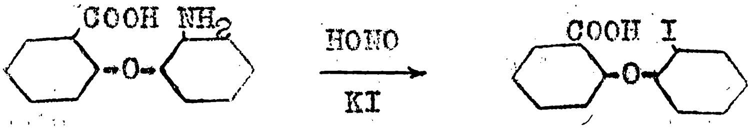
Percent nitrogen in sample--------------5.11%

### (7) 2-(2-Iodophenoxy)-Benzoic Acid.

To a solution of 5.0g of 2-(2-aminophenoxy)-benzoic acid in 25cc. of glacial acetic acid were added a cooled solution of 10cc. of concentrated sulfuric acid in 15cc. of water; then the resulting solution cooled to 0°C, and diazotized by the addition, drop by drop, with stirring, of an ice cold solution of 1.6g. of sodium nitrite in 10cc. of water. After standing in ice for 10 minutes, the resulting clear orange solution was poured rapidly with stiring into a solution of 3.7g. of potassium iodide in 20 cc. of water, to which approximately 50g. of crushed ice had been added. Partial decomposition of the orange addition product, which occurred immediately, was completed by warming the mixture to 70° on the water bath. After cooling well, and dilution to approximately 400 cc., the aqueous portion was decanted from the dark oily semi-solid material. Solution of the latter in dilute alkali and reprecipitation from the ice cold solution with hydrochloric acid, yielded a cream colored solid (8g.) which became gummy on warming to room temperature. By three extractions of this product with a 200cc. portion of boling petroleum ether (heptane b.p. approx. 95°)

cooling well in ice each time to recover the product, there was obtained a total of 5.0g. (67% of the theoretical) of pale yellow irregular prisms, which after further recrystallization from dilute alcohol, then heptane, melted at 132-3°. The product was easily soluble in alcohol, hot benzene, ether and acetic acid, but insoluble in water.

Equation:



Analyses:

Calculated percent iodine (for $C_{13}H_9O_3I$; mol. wt.= 340.1) = 37.3%

Found: 37.1%, 37.0%

(1) Wt. of sample--------------------------------.2677g.

Std. $AgNO_3$ sol'n used(1cc≏.0063465gI)-15.66 cc.

Wtof iodine in sample-----------------------.09939g.

Percent iodine in sample----------------37.1%

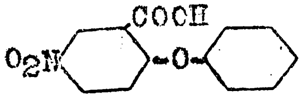
(2) Wt. of sample--------------------------------.2223g.

Std. $AgNO_3$ sol'n used(1cc.≏ .0063465gI)-12.96 cc.

Wt. of iodine in sample--------------------.08225g.

Percent iodine in sample----------------37.0%

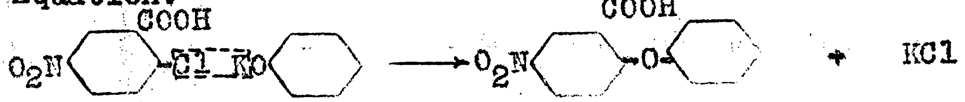
## (8) Preparation of 2-Phenoxy-5-Nitro-Benzoic Acid.



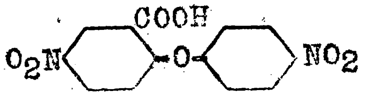
The following procedure has been found to give higher yields of 2-phenoxy-5-nitro-benzoic acid, than that previously described on pages 17-20 of the Master's Thesis[47].

Forty grams of potassium hydroxide were dissolved, by warming, in 125g. of phenol, and excess water formed eliminated by boiling under air reflux until the temperature of the mix. was 165°. After cooling to 120°, 50g. of 2-chloro-5-nitro-benzoic acid(obtained as described page 18 of Master's thesis), and 0.5g. of copper powder were added, and the mixture heated in air bath, boiling gently for 2 hours. The temperature rose gradually as water was eliminated, from 140° at the beginning to 175° at the end of the first hour, where it remained constant during the remaining period of heating. When cool the mixture was poured into ice water acidified with hydrochloric acid, and the precipitated greyish-brown product filtered and washed free of phenol with ice water, containing a small amount of hydrochloric acid. When dry, the crude product weighed 56.5g. (88% of the theoretical) and melted at 165-7°. For most experiments, further purification was unnecessary. A pure product was best obtained by crystallization of the sodium or potassium salts from concentrated alkaline solutions, as described in the master's thesis.

Equation:



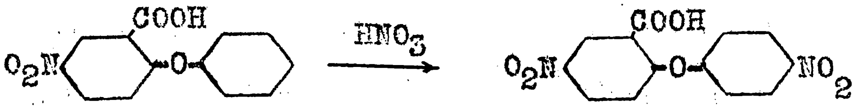
### (9) 2-(4-Nitrophenoxy)-5-Nitro-Benzoic Acid.



This substance was obtained by nitration of either (a) 2-phenoxy-5-nitro-benzoic acid, or (b) 2-(4-nitro-phenoxy)-benzoic acid. Since the product was identical in both cases, it could be no other than 2(4-nitro-phenoxy)-5-nitro-benzoic acid.

(a) Fifteen grams of 2-phenoxy-5-nitro-benzoic acid were added slowly, with stirring, to 100 cc. of concentrated nitric acid (sp. gr. 1.42), and the mixture warmed slightly and kept at 40-5° for ½ hour, cooling if necessary as the reaction proceeded. After this time, the solution, was allowed to stand overnight at room temperature to complete the reaction, then cooled thoroughly in an ice salt mixture. The brown crystalline precipitate, after filtering (using glass wool), washing, and drying, weighed 10g. (57% of the theoretical) and melted at approx. 160°. The product was purified by dissolving in dilute alkali and precipitating as its barium salt using 10g. of $BaCl_2$ in water, recovering the salt, and acidifying in cold water suspension. Further crystallization from dilute acetic acid gave nearly colorless, elongated prisms which showed a transition point at 158°, and melted finally at 170-1°, but on slow heating, partial melting occurred at 158o, and the liquid was soon seen to become entirely crystalline and melt sharply at 170-1°. A separate experiment showed no water vapor or gaseous products were evolved during this transition or melting. Further the sodium salt of the dinitroacid was found to be only very slightly soluble in aqueous solutions in the presence of a small excess of sodium hydroxide, hence could be filtered off and the crude product purified in this manner. (Compare also the slight solubility of the sodium and ammonium salts of certain sulfonic acids of diphenyl ether)[4]. Acidification of the sodium salt dissolved in water, gave a white gum which soon became solid and melted at 170-1°, without showing the transition at 158o, but after recrystallization from dilute acetic acid showed the transition point. Dilution of the nitric acid filtrate from which the crude product was separated, gave a gummy mass of decomposition products which on purification yielded only a fraction of a gram of additional dinitro acid. Arbenz[36] has reported this compound to be formed by nitration of 2-phenoxy-benzoic acid at 0° with fuming nitric acid, and reports a melting point of 153°. (See also page 43).

Equation:



Analysis:

Calculated percent nitrogen(for $C_{12}H_8O_7N_2$; mol. wt.= 304.1) = 9.21%

Found: 9.17%

(1) Wt. of sample------------------------------.2063g.

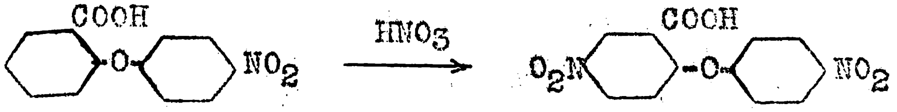
Std. $H_2SO_4$ sol'n used (1cc=.001378gN)-13.72 cc.

Wt. of nitrogen in sample-----------------.01891g.

Percent nitrogen in sample--------------9.17%

(b) To 40 g, of fuming nitric acid cooled in an ice bath, were added slowly with stirring, and in small portions, 8.7g. of 2-(4-nitrophenoxy)-benzoic acid, keeping the temperature below 5°. Solution was immediate and heat was evolved after each addition. After standing for ½ hour, the mixture was diluted with cold water, the aqueous portion decanted from the gummy precipitate, and the latter washed by decantation. On stirring for a few minutes with warm benzene the product became solid. When filtered from the benzene, and dried the solid yellowish powder weighed 9.2g. and melted indefinitely at approx. 140°. This product was purified by dissolving in warm, very dilute sodium hydroxide, filtering, adding an excess of sodium hydroxide to make the solution about 5%, then cooling well in ice, filtering off the sodium salt, and recovering the dinitro acid by acidification of the latter in cold water suspension. Further purification by recrystallization from dilute acetic acid gave approximately 6g. (59% of the theoretical) of elongated prisms showing the transition at 158° and melting at 170-1°, exactly as the product from the experiment described in (a). A mixed melting point of the two products behaved exactly in the same manner.

Equation:



Analyses:

Calculated percent nitrogen (for $C_{13}H_8O_7N_2$; mol. wt. 304.1) = 9.21%

Found: 9.31%

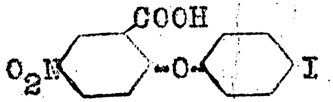
(1) Wt. of sample-----------------------------------.1393g.

Std. $H_2SO_4$ sol'n used (1cc.= .001378gN)----9.41 cc.

Wt. of nitrogen in sample--------------------.01297g.

Percent nitrogen in sample------------------9.31%

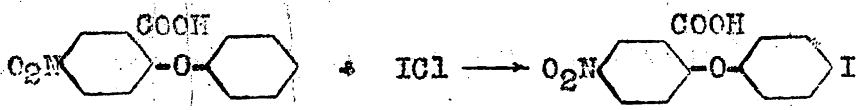
### (10) 2-(4-Iodophenoxy)-5-Nitro-Benzoic Acid.



To a solution of 11.4 (0.044 mols) of 2-phenoxy-5-nitrobenzoic acid in 25cc. of glacial acetic acid were added 9.0g. (.055 mols) of iodine monochloride, and the resulting solution heated over the steam bath for 10 hours, at the end of which time evolution of hydrogen chloride was only slight. The mixture was then poured out into ice water, decolorized with a small amount of sodium sulfite solution, and the precipitate recovered on a filter. Purification by dissolving in dilute alkali and reprecipitation with acid, then recrystallization from 200 cc. of 50% ethyl alcohol, discarding the first .5g of the product crystallizing in the latter (higher iododerivative), yielded 11g. (65% of the theoretical), of a light tan crystalline product melting at 176-7°. Another recrystallization from dilute ethyl alcohol gave colorless irregular prisms melting at 177-8°.

The constitution of this product was established by its conversion, by reduction and the Sandmeyer reaction, to 2-(4-iodophenoxy)-5-iodo-benzoic acid. (See page 181).

Equation:



Analysis:

Calculated percent iodine (for $C_{13}H_8O_5NI$; mol. wt.= 385.0) = 33.0%

Found: 33.2%, 33.3%

(1) Wt. of sample--------------------------------.2307g.

Std. $AgNO_3$ sol'n used (1cc≈.0063465gI)-12.05 cc.

Wt. of iodine in sample-------------------0.07648g.

Percent iodine in sample-----------------33.2%

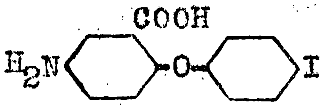
(2) Wt. of sample----------------------------------.2000g.

Std. $AgNO_3$ sol'n used(1cc≈.0063465gI)----10.48cc.

Wt. of iodine in sample---------------------.06651g.

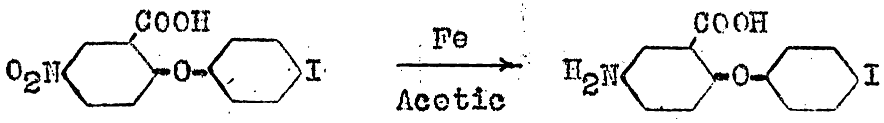
Percent iodine in sample-----------------33.3%

(11) <u>2-(4-Iodophenoxy)-5-Amino-Benzoic acid.</u>

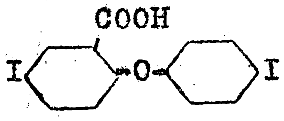


To a warm solution of 5.0g. of 2-(4-iodophenoxy)-5-nitrobenzoic acid in 25 cc. of glacial acetic acid were added in small portions, 7.0g. of iron powder and the mixture gently refluxed for 5 minutes after the first exothermic reaction had subsided. While hot the mixture was rapidly filtered through a Buchner funnel, and the precipitate of unchanged iron and iron acetates washed with a small amount of acetic acid. Dilution of the filtrate with ice water gave a milky solution which soon became clear with the separation of the colorless crystalline product in nearly quantitative yield. When dry the product melted at 180-2°; mixed with the product obtained from the iodination of 2-phenoxy-5-acetaminobenzoic acid (of melting point 184-5° ; see Master's Thesis page 45, also this thesis page 44) the melting point was 180-3°, showing the two compounds to be the same.

Equation:



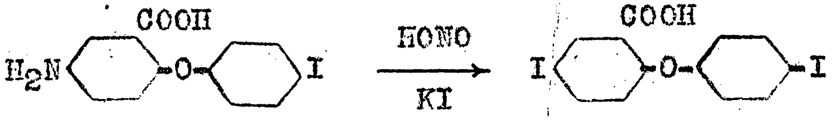
## (12) 2-(4-Iodophenoxy)-5-Iodo-Benzoic Acid.



This substance was obtained (a) from 2-(4-iodophenoxy)-5-amino-benzoic acid by the Sandmeyer reaction; (b) from 2-(4-nitrophenoxy)-5-nitro-benzoic acid by reduction followed by the Sandmeyer reaction; and (c) from direct iodination of 2-phenoxy-5-iodobenzoic acid which had been obtained as described in the Master's Thesis page 38. The preparation by method (b) establishes the constitution of the product obtained by the other two methods; hence also the constitution of 2-(4-iodophenoxy)-5-nitro-benzoic acid, and 2-(4-iodophenoxy)-5-amino-benzoic acid, as obtained as described on pages 178 and 179, respectively.

(a) Two and one half grams of 2-(4-iodophenoxy)-5-amino-benzoic acid were dissolved in a slightly warmed mixture of 25 cc. of glacial acetic acid, 10 cc. concentrated sulfuric acid and 10 cc. of water, then the resultingmixture cooled to 0$^{o}$ and diazotized by the addition, drop by drop, with stirring, of an ice cold solution of 0.7g. of sodium nitrite in 5cc. of water. After standing for10 minutes the diazonium solution was poured with rapid stirring into solution of 8.0g. of potassium iodide in 20 cc. of water to which a small quantity of crushed ice had been added. The resulting orange addition product was decomposed by warming to 70° over the steam bath, then the solution cooled well and diluted to 250cc. with cold water containing a small amount of sodium sulfite to remove excess of iodine. The solid product was then filtered off and recrystallized from dilute ethyl alcohol, then from petroleum ether (heptane b.p. approx. 95°), yielding approximately 75% of the theoretical of fine, pale yellow elongated prisms melting at 175-6°.

Equation:



Analyses:

Calculated percent iodine (for $C_{13}H_8O_3I_2$; mol. wt. 465.9) = 54.5%

Found: 54.5%; 54.3%

(1) Wt. of sample------------------------------.2257g.

Std. $AgNO_3$ sol'n used (1cc.= .006326gI)19.45 cc.

Wt. of iodine in sample-------------------.1230g.

Percent iodine in sample----------------54.5%

(2) Wt. of sample----------------------------.2015g.

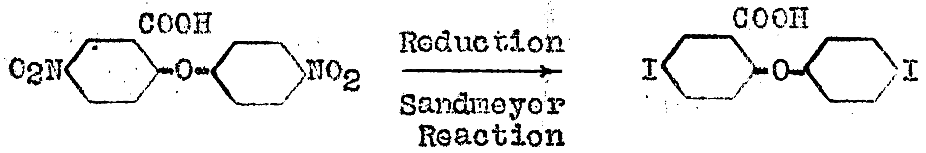
Std. $AgNO_3$ sol'n used (1cc=.006326gI)17.29 cc.

Wt. of iodine in sample------------------.1094g.

Percent iodine in sample---------------54.3%

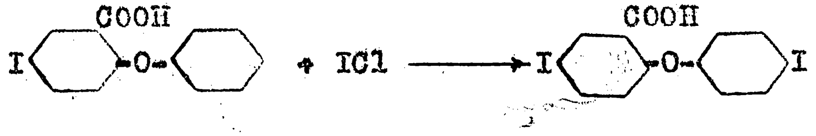
(b) A rapid stream of dry hydrogen chloride was passed into a cooled (ice bath) mixture of 5g. of 2-(4-nitrophenoxy)-5-nitro-benzoic acid and 25g. of cryst. stannous chloride in 70cc. of ether, contained in a 250cc. flask, for approximately ½ hour, or until reduction was complete and the solution was well saturated with hydrogen chloride. Approximately 150cc. of warm water was then added and the ether evaporated over the steam bath. While hot, the tin was precipitated by passing in hydrogen sulfide, then the sulfides removed by filtration and washed. After boiling to expel excess hydrogen sulfide, there was added to the resulting clear solution, 10cc. of concentrated hydrochloric acid and 30cc. of acetic acid, then the mixture cooled to 0$^{\circ}$, and diazotized by the addition drop by drop, with stirring, of an ice cold solution of 4.0g. of sodium nitrite in 20 cc. of water. After standing in ice for 20 minutes, the resulting solution was poured with rapid stirring into a solution of 12g of potassium iodide in 50 cc. of water to which 50 g. of crushed ice had been added. The resulting orange precipitate was decomposed by heating to 65° on the water bath, and after cooling well, the dark semi-solid product filtered, dissolved in cold dilute alkali, and reprecipitated with acid. By several extractions of the resulting light colored precipitate using a 150cc. portion of boiling heptane, cooling well in ice after each extraction, there was obtained approximately 4.5g., of pale yellow elongated prisms, which after recrystallization from diluteethyl alcohol using charcoal, then again from heptane, melted at 174-6°, undepressed by mixture with, and identical in appearance with the product from (a).

Equation:



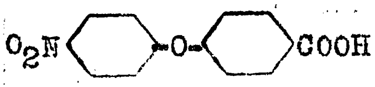
(c) A solution of 3.7g. of 2-phenoxy-5-iodo-benzoic acid in 10cc. of glacial acetic acid, to which 2. 0g. of iodine monochloride had been added, was heated over the steam bath for ten hours, then diluted with water containing a small amount of sodium sulfite to discharge excess iodine. After reprecipitation of the product from alkali, with hydrochloric acid, then two recrystallizations from alcohol using charcoal, and finally from heptane, there was obtained a small quantity (about 1.5g.) of pale yellow crystalline material melting at approx. 170°, which when mixed with the pure products from (a) and (b) gave melting points only 2-3 degrees lower than those for the pure samples alone. The product was difficult to purify due to presence of some of the original 2-phenoxy-5-iodo-benzoic acid, which was not of greatly different solubility in recrystallizing solvents.

Equation:



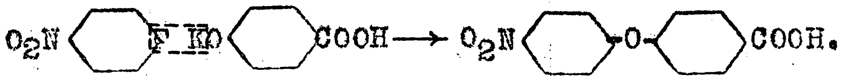
B. DERIVATIVES OF 4-PHENOXY BENZOIC ACID.

(1) Preparation of 4-(Nitrophenoxy)-Benzoic Acid.

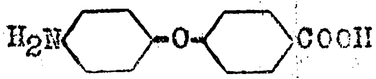


Forty-three grams (0.2 mol) of the dry potassium salt of p-hydroxy-benzoic acid (prepared by stirring the equivalent quantity of potassium hydroxide in water, into a water suspension of p-hydroxy-benzoic acid, then evaporating to dryness) were heated with 65g. (37g. excess) of p-nitrofluorobenzene at 190-200° for one hour. When cool the excess of p-nitrofluorobenzene was removed by steam distillation (recovered 40g.). After filtering off a small residue (2g.) of a by-product, 4,4'-dinitrophenyl ether, the solution memaining in the distillation flasky was acidified and the white precipitate washed well with water yielding 37g. (71% ofvthe theoretical) of the crude acid, which after recrystallization from dilute acetic acid melted at 235-6°. (Reported 235-6° [40]; 236-7° [49]).

Equation:

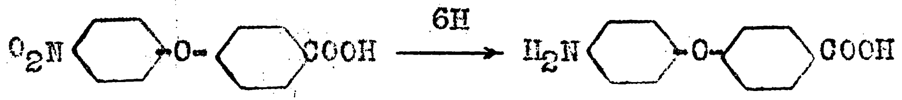


## (2) 4-(4-Aminophenoxy)-Benzoic Acid.

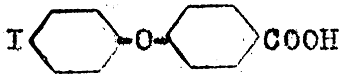


Nineteen grams of 4-(4-nitrophenoxy)-benzoic acid in 175 cc. of warm 95% ethyl alcohol were reduced by shaking with hydrogen ubder 3 atm. pressure, in the presence of 0.2g. of platinum catalyst, and the amine recovered in a manner exactly as has been described for 2-(2-aminophenoxy)-Benzoic acid page 165. The colorless crystalline product obtained (16.3g. or 97% of the theoretical) melted at 193-4°, as reported by Haussermann and Bauer[49]. (See also page 45).

Equation:



(3) 4-(4-Iodophenoxy)-Benzoic Acid.



To a solution of 10.0g. of 4-(4-aminophenoxy)-benzoic acid in 40 cc. of glacial acetic acid was added a cooled solution of 20cc. of concentrated sulfuric acid in 100cc. of water, and the resulting mixture cooled to 0°. The sulfate salt of the amino acid separated out considerably. While stirring rapidly, there was added drop by drop, an ice cold solution of 3.1g. of sodium nitrite in 15 cc. of water. The nitrous acid formed was used up immediately, with very little evolution of oxides of nitrogen, but the appearance and mushy consistency of the solution changed only slightly. No clear orange diazonium solution as it is usually obtained, was formed. After standing for 10 minutes, stirred frequently, the mixture was poured with rapid stirring into a solution of 7.3g. of potassium iodide in 50 cc. of water to which 100g. of ice had been added. A deep brick red addition product formed immediately. The mixture was then diluted to 500 cc., then warmed slowly to 95°. The red color gradually changed to light brown during heating, but very little decomposition occurred until approximately 80° had been reached, when the precipitate rose to the surface in the form of froth. After keeping at 95° for a few minutes to complete the decomposition, the mixture was well cooled, and the cream colored product (14g.) filtered off. An attempt to dissolve the latter in dilute sodium hydroxide precipitated the salt in practically quantitative yield when only a very slight excess of alkali had been added. This, filtered off and acidified gave 12.1g. (81% of the theoretical) of the crude iodo acid, which, by recrystallization from ethyl alcohol, was obtained as fine nearly colorless crystals, melting at 216-7°. The product was soluble in ether, hot benzene or acetic acid, but insoluble in water.

Equation:

Analyses:

Calculated percent iodine (for $C_{13}H_9O_3I$; mol. wt.= 340.1 ) = 37.3%

Found: 37.1%; 37.2%.

(1) Wt. of sample---------------------------.2142g.

Std. $AgNO_3$ sol'n used (1cc=.0063465gI)-12.51 cc.

Wt. of iodine in sample-------------------------.07940g.

Percent iodine in sample---------------------37.1%

(2) Wt. of sample------------------------------------.1881g.

Std. $AgNO_3$ sol'n used (1cc.≏.0063465gI)----11.02cc.

Wt. of iodine in sample------------------------.06995.

Percent iodine in sample---------------------37.2%

## SUMMARY

1. The three mono iodo derivatives of diphenyl ether have been synthesized. Two of these, the 2-(ortho) and 4-(para) isomers, have been nitrated and the constitution of the products obtained established. All three mono iodo isomers have been iodinated further to diiodo diphenyl ethers, and the constitution of the products obtained established, with the possible exception of that obtained from iodination of the 3-(meta) isomer.
2. Five isomeric diiodo derivatives of diphenyl ether have been synthesized; each by more than one method, with the exception of 3,4-diiododiphenyl ether.
3. Diphenyl ether has been iodinated directly in large quantity, and the constitution of the products obtained established.
4. The 2- and 4-nitrodiphenyl ethers have both been iodinated and the constitution of the products obtained established.
5. A large number of di-substituted diphenyl ethers have been obtained. These include mixed derivatives containing two of the following groups: nitro, amino, acetamino, benzoylamino, iodo, urea, or urethane.
6. The acetyl and urethane derivatives of 4-aminodiphenyl ether have both been iodinated and the con-

stitution of the products obtained established by syntheses by other methods. The acetyl derivative has also been nitrated and the product used in further syntheses.

7. The compound previously recorded in the literature as 2-nitro-4-aminodiphenyl ether has been shown to be 2-amino-4-nitrodiphenyl ether.

8. The advantageous use of 4-nitrofluorobenzene and 2,4-dinitrofluorobenzene in synthesis of substituted diphenyl ethers has been demonstrated.

9. In addition to boiling points, specific gravities, and indices of refraction have been determined for a number of the synthesized compounds which were found to be oils.

10. Studies made on certain iodo and other derivatives of 2-phenoxy-benzoic acid(Master's thesis) have been extended. Among the compounds synthesized are also certain previously unobtained disubstituted derivatives with the substituent groups: nitro, amino, and iodo. 4-Nitro-xanthone, and a lactam with a seven membered ring are included in these syntheses.

11. A mono iodo derivative of 4-phenoxy-benzoic acid has been synthesized for comparison with obtained iodo derivatives of 2-phenoxy-benzoic acid.

12. The relative directive influences of the iodine atom and carboxyl group, as compared with certain other substituents in diphenyl ether nucleii, have been determined.

## BIBLIOGRAPHY

1. Mailhe and Murat, C. r. 154, 715 (1912).

2. Ryan and Drumm, Sci. Roy. Dublin Soc. 17, 313 (1924).

3. Suter, J. A. C. S. 51, 2581 (1929).

4. Suter, J. A. C. S. 53, 1112 (1931).

5. Mailhe and Murat, C. R. 154, 601 (1912).

6. Buchan and McCombie, J. C. S. 137, (1931).

7. Ullmann et. al., Ber. 29, 1881 (1896); Ber. 37, 854 (1904); Ber. 38, 2113 (1905); Ann. 350, 83, 117 (1906); Ann. 355, 362 (1907).

8. Haeussermann et al., Ber. 29, 1446 and 2084 (1896); Ber. 30, 738-40 (1897).

9. Jones and Cook, J. A. C. 38, 1537 (1916).

10. Raiford and Colbert, J. A. C. S. 48, 2660 (1926).

11. Harington and Barger, Biochem. JOurnal 21, 169-83 (1927).

12. Haeussermann and Teichmann, Ber. 29, 1448 (1896).

13. F. Ullmann, Ber. 29, 1881 (1896).

14. Wallach and Heusler, Ann. 243, 242 (1888).

15. Holleman and Beekman, Rec. des Trav. chim. 23, page 235 et seq. (1904).

16. Rarick, Brewster, and Dains, J. A. C. S. 55, 1289 (1933).

17. Adams, Vorhees, and Shriner-"Organic Syntheses", John Wiley and Sons Inc., New York, (1928) Vol. VIII, page 10 and 92.

18. Willgerodt and Wiegand, Ber. 42, 3764 (1909).

19. McCombie, Macimillan and Scarborough, J. C. S., 134, 529 (1931).

20. Cain, "Chemistry and Technology of Diazo Compounds", 2nd. edition, Edward Arnold and Co., London (1920).

21. Bogert and Evans, J. Ind. Eng. Chem. 18, 299-302 (1926).

22. Vignon, C.r., 142, 159 (1906).

23. Cook, J. A. C. S. 32, 1291, (1910).

24. Anschutz and Heusler, Ber. 19, 2161 (1886).

25. Noyes and Skinner, J. A. C. S. 39, 2718 (1917).

26. Haeussermann and Bauer, Ber. 30, 738-40 (1897).

27. Ullmann and Sponagel, Ann, 350, 83-107 (1906).

28. Miss Henley, J. C. S., 1223 (1930).

29. Hoffmeister, Ann. 159, 208, (1871).

30. Willgerodt, Ber. 12, 767 (1879).

31. Scarborough, J.C.S., (1929), pages 2361-7.

32. Oesterlin, Monatsch. 57, 31-44 (1931).

33. Seyewetz, et. al, Bull. soc. chim. IV, vol. 3,p.497, (1908) and preceding articles.

34. Fox and Turner, J. C. S. (1930), p. 1853-67.

35. C. Graebe, Ber. 21, 501 (1888).

36. Arbenz, Annalen 257, 82-77 (1890).

37. Ullmann and Wagner, Annalen 355, 362 (1907).

38. Purgotti, Gazz. chim. Ital. 44(I), 642 (1914).

39. Dhar, J. C. S. 117, 1057-65 (1920).

40. Suter and Oberg, J. A. C. S. 53, 1566 (1931).

41. Lea and Robinson, J. C. S. 129, 376-83 and 411-13. (1926).

42. Henley and Turner, J. C. S., 928 and 1115 (1930).

43. Thorpe and Whitley, "Students Manual of Organic Chemical Analyses". Reference; Jodlbauer, Chem. Soc. Abstr., (1886) 834; and Dyer (Chem. Soc. Trans.) (1898) 814.

44. Clarkson and Gomberg, F. A. C. S. 52, 2885 (1930)

45. Lange and Reed, J. A. C. S. 48, 1072 (1926).

46. Lesslie and Turner, J. C. S. 281-5 (1932).

47. Strain, "Certain Iodine and Other Derivatives of 2-Phenoxy-Benzoic Acid", K. U. Thesis 1931.

48. Hoffman and Dame, J. A. C. S. 41, 1016 (1919).

49. Haeussermann and Bauer, Ber. 29, 2084 (1896).

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