IODINATED DERIVATIVES OF DIPHENYL ETHER

by

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INTRODUCTION AND HISTORICAL

The object of this investigation is to prepare and study various mono- and di-iodo derivatives of substituted diphenyl ethers and their intermediate compounds. Positions 4 and 4' have been studied chiefly, especially with reference to the difference in solubility which is found upon changing the groups in position 4. The different substances studied are: phenoxy acetophenone; phenoxy benzoic acid; phenoxy phenoxy acetic acid; phenoxy phenyl glycine; and phenoxy phenyl acetic acid.

The study of iodo derivatives of diphenyl ether has been recently greatly stimulated by the work of Harrington and Barger[1], who proved quite conclusively that thyroxine was a tetra-iodo derivative of a substituted diphenyl ether. Thyroxine, a normal constituent of the thyroid gland, has been the subject of much controversy in the last twenty years. The work of Harrington and Barger, however, has settled the question as to the constitution of thyroxine, although much is being done toward studying its physiological activity.

Thyroxine is classified as a hormone, a name given to the compounds or secretions of certain glands. Bayliss and Starling[2] named substances of this kind, which were secreted into the blood and aroused other organs to activity, hormones from the Greek word, <u>hormao</u>, meaning I arouse. Several of these hormones have been isolated and their chemical structure determined. Isolating these hormones made possible the synthesis of them.

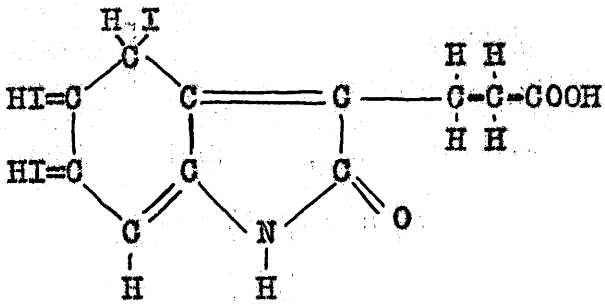
The main difficulty in isolating and determining the chemical constitution of these hormones, is due to the minuteness of the quantity present in the gland. Thyroxine is a fine example of this difficulty in as much as Harrington and Barger[1] obtained yields of only 0.027 percent thyroxine from thyroid glands.

Kocher[3] in 1882 recognized that the operative removal of the thyroid goiter produced symptoms similiar to those of myxoedema, which was attributed to thyroid deficiency. Murray[4] found that to inject an extract of thyroxine and later give it orally was quite effective in myoxedema and also in cretinism, which is a permanent infantile condition due to the defective development of the thyroid.

The favorable effect of iodine therapy in thyroid diseases led Kocher to believe that this active principle was associated with iodine. Later Baumann[5] showed that iodine was a normal constituent of the thyroid gland. Baumann used ten percent sulfuric acid to hydrolyze the gland and from it obtained a brownish substance which contained four to ten percent iodine and possessed some physiological properties. This substance, however, was regarded as impure thyroxine. Later it was shown that his results were due to the strong hydrolyzing agent which he had used.

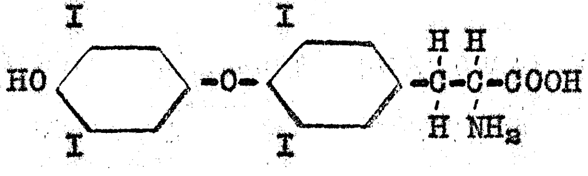
Kendall[6] at the Mayo Clinic was the first to isolate thyroxine in a pure condition, which he did by using a milder hydrolyzing agent than that of Baumann. Kendall used five percent sodium hydroxide solution and then continued the hydrolysis with baryta. This hydrolysis and that fact that the sodium salt of thyroxine was soluble in water made possible his success. Kendall gave the name Thyroxine to this product as he was of the opinion that the compound was an oxindole derivative. The crystalline compound which he isolated contained sixty five percent iodine and was very physiologically active. However, the method by which he obtained this product was very costly and the yields very small, only 0.0011 percent. He obtained only thirty three grams of thyroxine from three tons of fresh glands. Because of the great possibilities of benefiting humanity, Kendall's method of procedure was taken up commercially by Squibb's and Sons.

Kendall[7] at this time proceeded to study the chemical activity and constitution of thyroxine. In 1919 he published a paper wherein he gave the empirical formula for thyroxine as $C_{11}H_{10}O_3NI_3$. He also assigned to it the following structural formula:



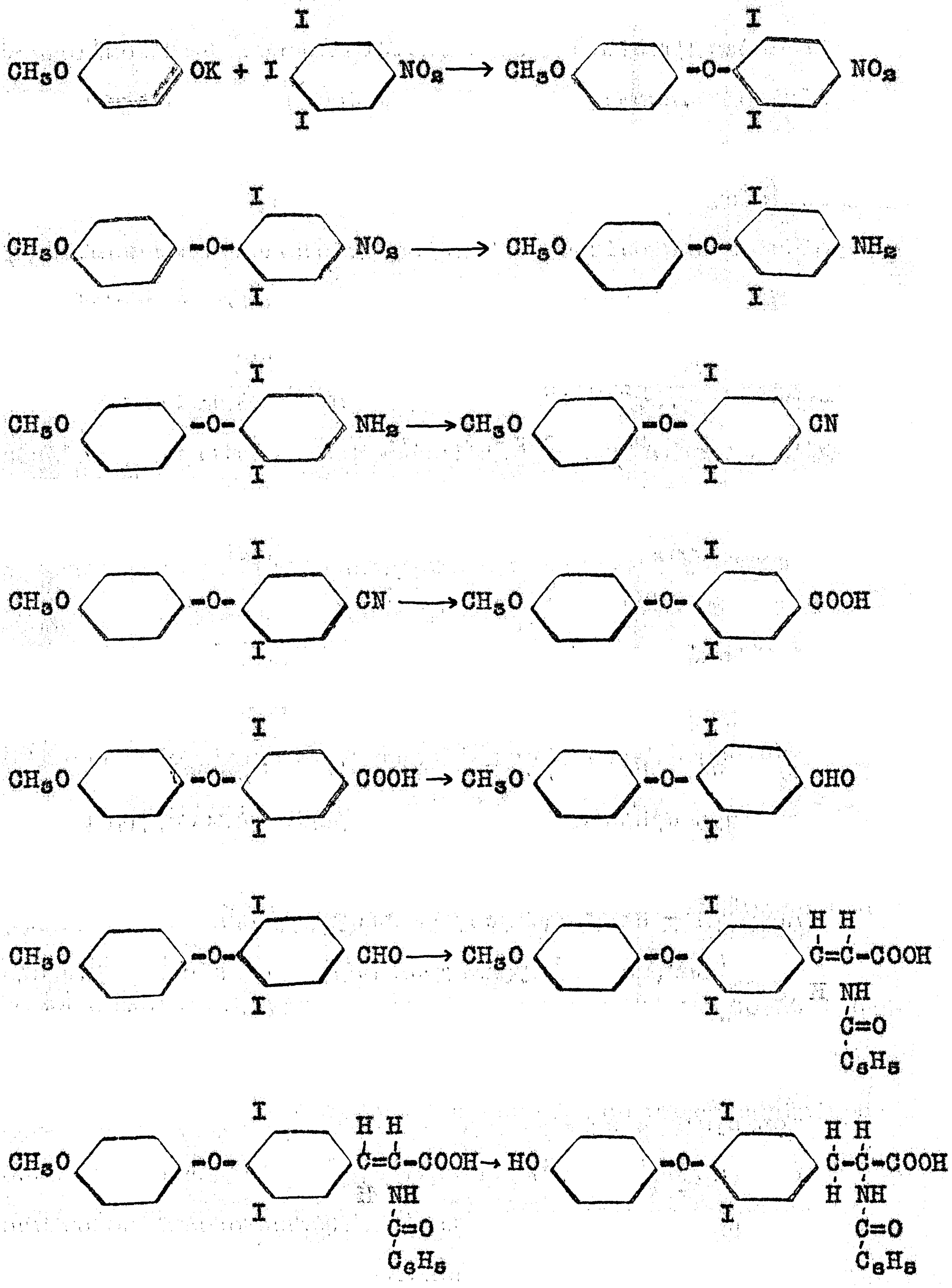
Osterberg[8] at this time claimed to have synthesized the aforementioned compound. His synthesis, according to Kendall, proved that the structural formula which he assigned to thyroxine was correct. However, no experimental evidence was ever offered to substantiate Osterberg's claims; so, as a result of the work which Harrington and Barger did, Kendall later withdrew his claims. If one compares Kendall's formula with the corrected formula for thyroxine he will notice that it is four carbon atoms, one hydrogen atom, one oxygen atom and one iodine atom short of the accepted formula.

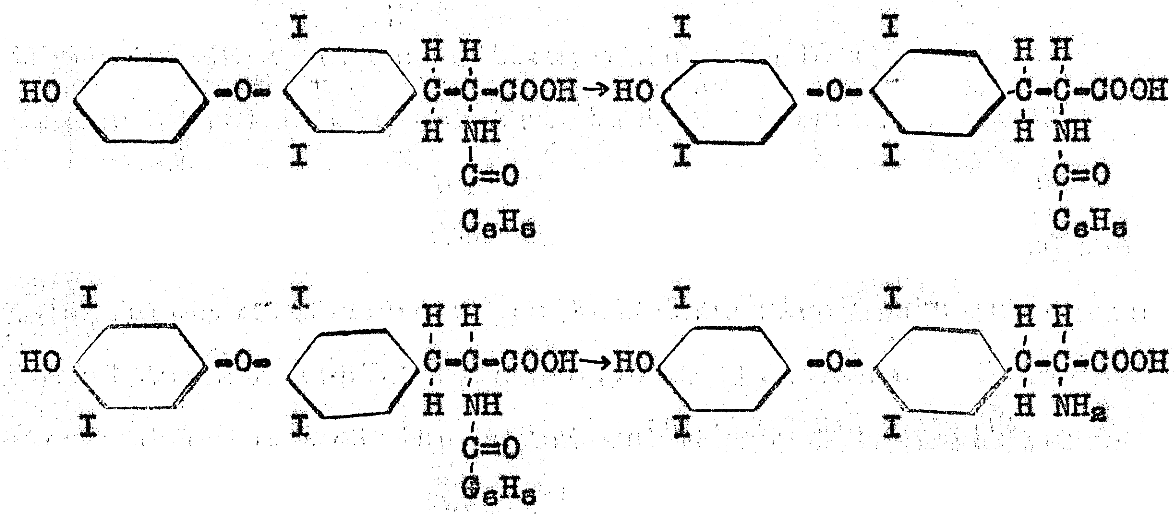
In 1924, two English Biochemists, Harrington and Barger[1], undertook the task of determining the structure of thyroxine. In 1927 they published the results of their work in the Biochemical Journal[1]. There can be no question as to the accuracy of their results since they determined the structure of thyroxine both by degradation and by synthesis. The following formula was submitted:



As may be seen, the above compound is a tetra-iodo derivative of a substituted diphenyl ether.

A brief schema for the preparation of thyroxine is given as follows:





The object of this investigation was not to synthesize thyroxine, but rather to prepare derivatives of the 4-(3',5'-di-iodo, 4'-hydroxy phenoxy) phenyl radical.

Concerning the iodo derivative of diphenyl ether, there were only a few known until the work of Brewster and Strain[9] was published in 1934. They prepared three of the mono- and five of the di-iodo derivatives, but they did not have any of the iodines in the 3-5- positions. The positions emphasized by them were the 2, 2-4-, 4-4'-, and 2-4'-. In Brewster and Strain's work the positions occupied other than by the iodine were chiefly 2- and 4-. They used nitro and amino groups in these positions. In this investigation the only positions occupied other than by iodine were 4- and 4'-. The groups in position 4- were: $-COOH$; $-COCH_3$; $-CH_2-COOH$; $-OCH_2-COOH$; and $-NHCH_2COOH$. In position 4' there was either nitro, amino, acetamino, hydroxyl or methoxy groups.

Diphenyl ether has been known for nearly a century.

It was first prepared in 1845 by Ettling and Stenhouse[10] by destructive distillation of copper benzoate. Ten years later List and Lampricht[11] isolated a substance from the destructive distillation of copper benzoate which they named phenyl oxide. The properties of diphenyl ether were first studied in detail in 1870 by Hoffmeister[12], who prepared it by the action of benzene diazo sulfate on phenol. Since then one of the successful methods of preparing diphenyl ether is the treating of sodium phenolate with chloro benzene. This was first accomplished by Maikpar[13] in 1873. Many derivatives of diphenyl ether have been prepared, both from direct substitution on phenol and from fusion of substituted phenols and halogen derivatives of benzene. Ullman[14] was the first to use copper catalyst in this type reaction. He reports that in the preparation of diphenyl ether from phenol and bromo benzene, the yield increased from 0.9 percent to eighty seven percent when copper was used.

Cook and his coworkers[15] prepared many diphenyl ether derivatives, including nitro-methyl phenyl ethers, tolyl and bromotolyl ethers, and mono-nitro phenyl ethers. Maihle[16], Sabatier[17], and other French chemists made a study of the nitration products of diphenyl ether. Their work included the reducing of the nitro group to the amino group and the subsequent formation of dyes by azo coupling. In England, Scarborough and his coworkers[18] have prepared many nitro derivatives of diphenyl ether as well as some methoxy and methyl derivatives. In America, Raiford and

Colbert[19] have worked on amino derivatives of diphenyl ether as intermediates for dyes. Clarkson and Gomberg[20] have also prepared some iodo diphenyl ethers. Suter[21] and his associates have carried on considerable work on phenoxy sulfonic acids and other derivatives of diphenyl ether. Reference to his work will be made later.

At the present time diphenyl ether and diphenyl ether derivatives are beeing studied in England, Germany, and America. The use of diphenyl ether as a heat transfer agent is being investigated. Some derivatives of diphenyl ether have been patented for use as bactericides and as internal disinfectants[22]. Suter[22] has studied the anaesthetic properties of diphenyl ether derivatives.

Several physiological tests of the iodo compounds made in this investigation have been performed. Both the results and the procedure used in making these tests are discussed on pages 43 and 147.

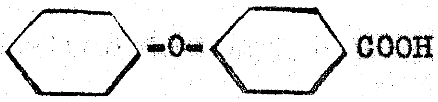
The compounds synthesized in this work are divided into five groups or series. They are:

1) 4-Phenoxy Benzoic Acid Series. Position 4- is occupied by a carboxyl group.
2) 4-Phenoxy Acetophenone Series. Position 4- is occupied by an aceto group.
3) 4-Phenoxy Phenoxy Acetic Acid Series. Position 4- is occupied by an oxyacetic acid group.
4) 4-Phenoxy Phenyl Acetic Acid Series. Position 4- is occupied by an acetic acid group.
5) 4-Phenoxy Phenyl Glycine Series. Position 4- is occupied by a $-NHCH_2COOH$ group.

Each of these series will be discussed separately and the compounds synthesized will be listed as above.

Preceding each discussion is given a graphic representation of the reactions for each series.

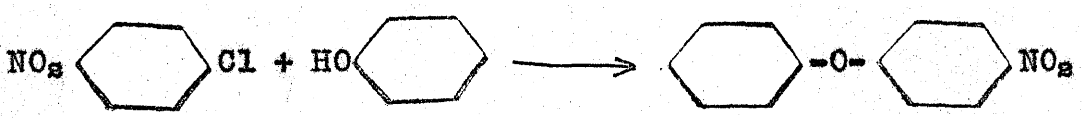
4-PHENOXY BENZOIC ACID SERIES



4-Hydroxy benzoic acid is found in nature in unripe catalpa plants along with protocatechuic acid[51]. It is also found in pollen and petal of the Gundilla Vobusta nut.[52] Small quantities of 4-hydroxy benzoic acid are found in the urine of horses[53] and dogs[54,55]. It is interesting to note that many esters of 4-hydroxy benzoic acid have been patented for use as antiseptics and for their germicidal properties.

Reimer and Tierman[57] were among the first to report the synthesis of 4-hydroxy benzoic acid. They used carbon tetrachloride with phenol and potassium hydroxide, obtaining a mixture of the 2-hydroxy benzoic acid and the 4-hydroxy benzoic acid. In this reaction more of the 4- compound is formed. Korner[58] synthesized 4-hydroxy benzoic acid by melting 4-iodo benzoic acid with potassium hydroxide. Baumann[60] and Barth[59] treated tyrosine with potassium hydroxide and obtained 4-hydroxy benzoic acid along with many other products. Harrington and Barger[1] found 4-hydroxy benzoic acid to be one of the degradation products of thyroxine. Treating vetexin, homovetexin[64], scietellarin[64], and carthamin[65] with an alkali solution gave 4-hydroxy benzoic acid as one of the products.

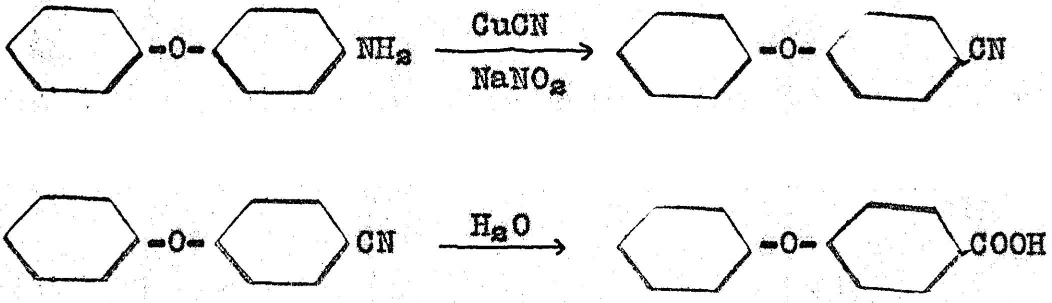
The original plan was to start with 4-nitro chlorobenzene and couple this with phenol, thus preparing 4-nitro diphenyl ether.



The 4-nitro diphenyl ether was then reduced to the amino diphenyl ether. This reduction was accomplished in two ways. Both methods gave good yields and are applicable to large quantities. However, by the use of catalytic hydrogen, results were obtained that averaged between 90 and 100 percent yields, giving a product which required only a little purification. 4-Nitro diphenyl ether reduces very easily and quickly in large quantities.

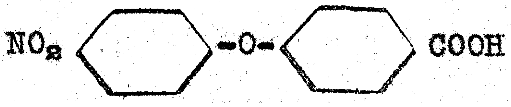
It is interesting to note at this time that when a carboxy grouping is placed in the 4- position of the other benzene ring, that the compound did not reduce so easily. There can be no question that the influence of the -COOH grouping is very apparent in retarding this reduction.

The 4-amino diphenyl ether was then diazotized and a nitrile formed. The yield on this was not very high, being around 35 to 40 percent, although the hydrolysis of this nitrile gave very satisfactory results. This diazotization was accomplished by Sandmeyer's reaction using cuprous chloride.

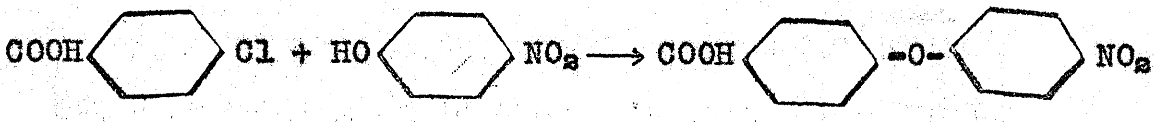


The nitration of the 4-carboxy diphenyl ether was accomplished by methods which differ from the customary nitration methods as shown on page 54. The yields however, are small and the product required a great deal of purification. That the $-NO_2$ grouping goes to the 4'- position is proven by the synthesis of 4-(4'-nitro phenoxy) benzoic acid, using other methods.

Haussermann and Bauer[37] reported that the compound:



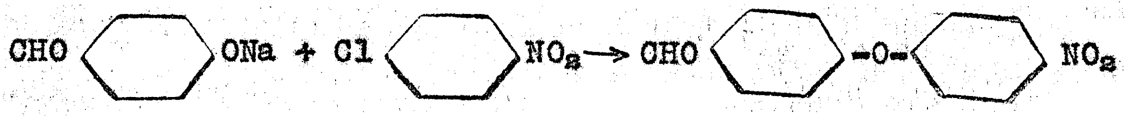
could be prepared in a much simpler manner by the following reaction:



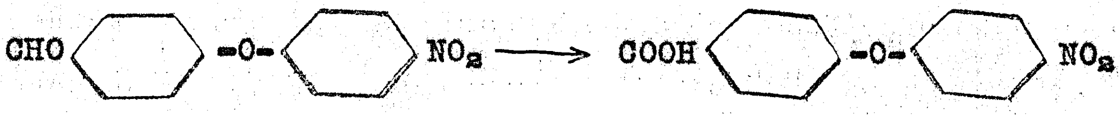
This procedure was tried many times, using different proportions as well as many different catalysts, however, no satisfactory results were obtained.

To obtain 4-(4'-nitro phenoxy) benzoic acid which was the starting compound of the further synthesis, two successful methods were used and the above synthesis was discarded.

Suter and Oberg's method[22] of preparing 4-(4'-nitro phenoxy) benzoic acid was accomplished by using 4-hydroxy benzaldehyde and 4-nitro chlor benzene:

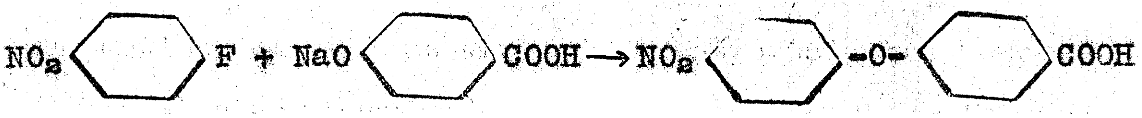


This aldehyde was then oxidized to the acid:



This procedure gave a fair yield of the desired product. However, it was not as efficient as other methods and was discarded in favor of the method of Brewster, Rarick and Dains.[6]

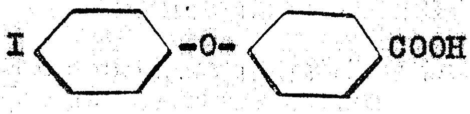
The use of 4-nitro fluorobenzene[6] and 4-hydroxy benzoic acid gave the product in one step, giving a very high yield and a product requiring very little purification.

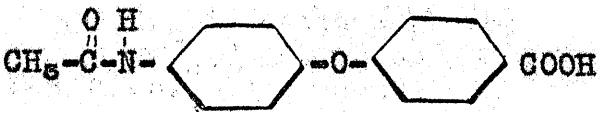


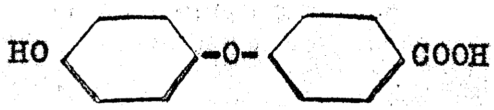
The above reaction made possible the preparation of a larger amount of 4-(4'-nitro phenoxy) benzoic acid, which was then converted into the amine.

The reduction of the nitro to the amine grouping was accomplished by the use of catalytic hydrogen. However, this reduction was the most difficult of all the reductions attempted. It was absolutely necessary that the 4-(4'-nitro phenoxy) benzoic acid be of the very highest purity. This product also being only slightly soluble in alcohol made it necessary to keep the solution warmed at all times during the reduction. The amine will also separate out from the alcohol solution upon cooling.

From the 4-(4'-amino phenoxy) benzoic acid three products were made:

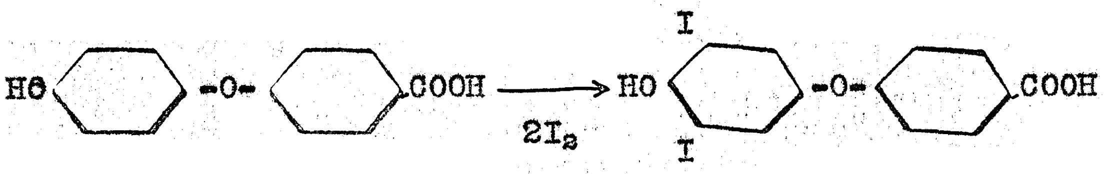




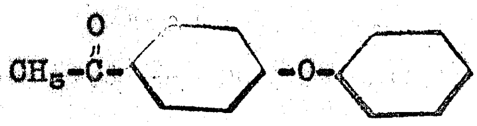


4-(4'-Hydroxy phenoxy) benzoic acid can be purified from heptane or hot water. It is a white crystalline product melting at 193°C.

From the 4-(4'-hydroxy phenoxy) benzoic acid it was necessary to prepare 4-(3',5'-di-iodo-4'-phenoxy) benzoic acid which was accomplished by the iodination with iodine, potassium iodide and ammonium hydroxide. This di-iodo compound is a white crystalline substance which melts with decomposition at 222 to 225°C.



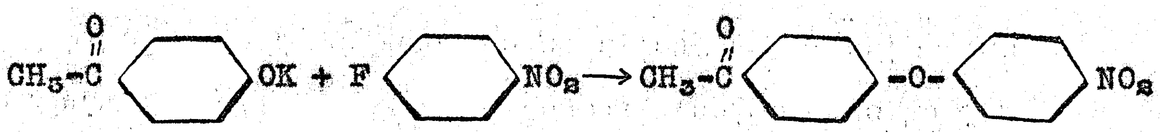
4-PHENOXY ACETOPHENONE SERIES



The starting compound in this series is 4-hydroxy acetophenone, also called 4-acetophenol, 4-acetyl phenol and methyl-4-hydroxy phenyl ketone. It occurs in nature in Apiin, a substance which is found in leaves, stems and seeds of parsley. It was first isolated by Lindenhorn[28] but was not identified until A.G. Perkins[29] decomposed the glucoside, Apiin, and obtained among many other products phloroglucinol and 4-hydroxy acetophenone. 4-Hydroxy acetophenone has also been prepared by Perkins[34] who obtained it by heating vitexin with alcoholic potassium hydroxide. Tauret[30] by the hydrolysis of picein, obtained a small quantity of 4-hydroxy acetophenone. Klingel[31] prepared this compound by the diazotization of 4-amino acetophenone. Nenchi and Stoeber[32] used phenol, acetyl and ferric chloride in carbon disulfide solution to prepare 4-hydroxy acetophenone. Henrard[33] substituted zinc chloride for the ferric chloride in the above reaction and obtained 4-hydroxy acetophenone, while Michal and Palmer[35] used acetic acid in place of acetyl chloride.

4-Hydroxy acetophenone was chosen for several reasons. The original plan was to have the acetyl group as a starting point, so that the hydrogen cyanide could be added and by subsequent hydrolysis produce a carboxyl group. The presence of a carboxyl group would have made possible an aqueous solution of the compound by making its sodium salt. The addition of hydrogen cyanide would have given a method for the synthesis of an hydroxy acid, containing an assymetrical carbon atom. However, all attempts to add hydrocyanic acid to the ketone were unsuccessful.

The first step in this series was the synthesis of 4-(4'-nitro phenoxy) acetophenone, which had been prepared previously in 1927 by Dilthey, Back, Grutering and Hansdorfer[36], and also by Suter and Oberg[28]. Suter used 4-nitro diphenyl ether, aluminum chloride and acetyl chloride. Briefly their procedure is as follows: To a solution of 10.8 grams of 4-nitro diphenyl ether (0.05 moles) and 13.3 grams (0.1 mole) of anhydrous aluminum chloride in one hundred cc. of carbon disulfide was added during the ten minutes, five grams (0.06 mole) of acetyl chloride. After refluxing for fifteen minutes, the solvent was removed by distillation and the residue heated for half hour longer on the steam bath. Water was added and the product crystallized from ninety five percent ethyl alcohol. The yield was seven grams, fifty five percent of the theoretical of a colorless product melting at 80°C. Rarick, Brewster, and Dains[26] prepared this compound by the use of 4-hydroxy acetophenone and 4-nitro fluorobenzene. Their procedure gave a high yield of 4-(4'-nitro phenoxy) acetophenone which requires very little pruification. 4-Hydroxy acetophenone and 4-nitro fluorobenzene were heated together for two hours at 160°C. The solution is steam distilled to remove the excess 4-nitro fluorobenzene. It was then filtered while hot and the 4-(4'-nitro phenoxy) acetophenone separates out as a white mass. After purifying from ninety five percent ethyl alcohol, the compound melts at 81°C. The yield was ninetynto ninety five percent of the theoretical. Quantities up to five tenths of a mole may be used with the same success.



Attempts to add hydrogen cyanide to this compound failed to give any addition compounds. It is also of interest to note that 4-(4'-nitro phenoxy) acetophenone would not iodinate. Direct iodination with iodine monochloride in acetic acid failed to give a product which showed a positive test for iodine with concentrated sulfuric acid.

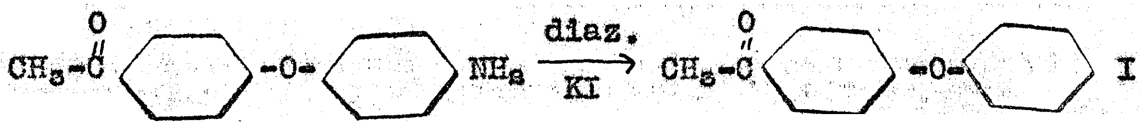
The 4-(4'-nitro phenoxy) acetophenone was then reduced to 4-(4'-amino phenoxy) acetophenone. This amino derivative had been prepared by Dilthey[38], by the use of zinc chloride and hydrochloric acid on the nitro compound. The reduction proceeds rapidly under these conditions, but as the amine hydrochloride salt is very soluble, the solution must be neutralized to remove the free amine. It is then recrystallized from a mixture of benzene and petroleum ether and gives a melting point of 123°C. Dilthey does not state what percentage yield he obtained.

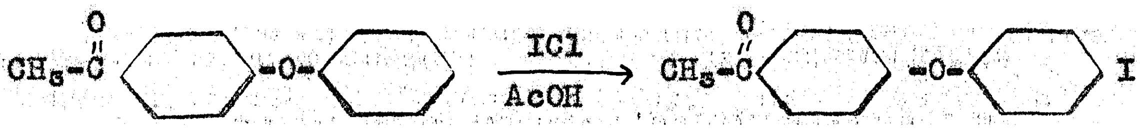
Reduction of the 4-(4'-nitro phenoxy) acetophenone by the use of catalytic hydrogenation gave excellent results. The yield was bery nearly theoretical. The procedure is to dissolve the nitro compound in ethyl alcohol, add 0.2 grams of platinum oxide[57] and place in a shaker under pressure of thirty five pounds of hydrogen. The reaction is complete in a few minutes. The compound is recrystallized from ethyl alcohol and gave a mleting point of 123°C.

From 4-(4'-amino phenoxy) acetophenone four different compounds were prepared. Namely, replacing the amino group with iodine and an hydroxyl group and formation of the acetyl and benzoyl derivatives.

4-(4'-Iodo phenoxy) acetophenone was synthesized by making the sulfuric acid salt of the amine and then diazotizing the salt with a solution of sodium nitrite. This solution was poured slowly into a cold solution of potassium iodide and gave a tarry mass from which yellow crystals were obtained by extracting with heptane. The iodine could go into only one position, that occupied by the amino group. Direct iodination of 4-phenoxy acetophenone was accomplished by using glacial acetic acid and iodine monochloride. The compound formed by direct iodination gave the same melting point as that prepared from the amino product, indicating therefore that the two compounds are identical. The mixed melting points gave no depression.

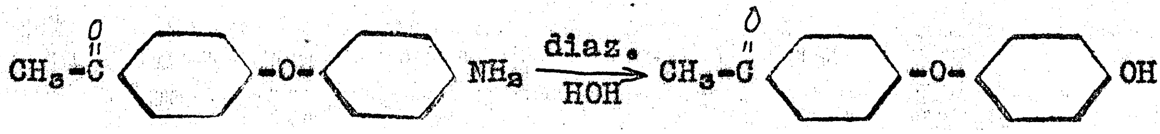
also showing that the two compounds are identical. It was shown therefore that iodine goes into the 4'- position upon direct iodination. The melting point of the compound was 96.5°C.



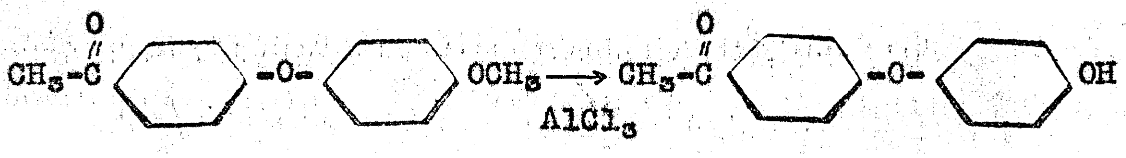


The acetyl and benzoyl derivatives were prepared in the ordinary way. However, the acetyl group required heating of several hours in acetic anhydride.

To replace an amino group with a hydroxyl group is usually a source of much trouble. No difficulty was encountered here, however, the yields were only fifty percent of the theoretical. The hydroxy compound is purified from heptane giving white crystals which melt at 153°C. The sodium salt of 4-(4'-hydroxy phenoxy) acetophenone was not very soluble in water.

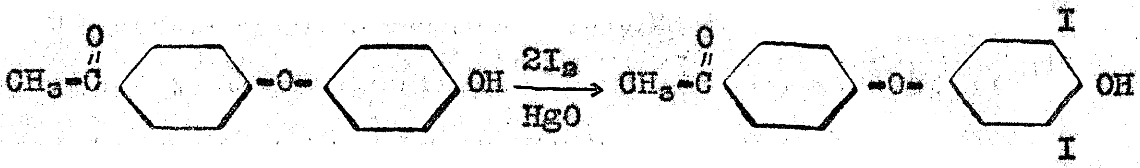


4-(4'-Hydroxy phenoxy) acetophenone was prepared by another method. 4-Hydroxy acetophenone was reacted with 4-bromo anisole, forming 4-(4'-methoxy phenoxy) acetophenone. The methoxy compound was then converted to the hydroxy compound derivative by treatment with aluminum chloride. The 4-(4'-hydroxy phenoxy) acetophenone prepared from the methoxy derivative proved to be identical with that prepared by the diazotization of 4-(4'-amino phenoxy) acetophenone.



To prepare 4-(3',5'-di-iodo-4'-hydroxy phenoxy) acetophenone from the hydroxy compound necessitated a change in the method of iodination. The use of iodine and potassium iodide with ammonia and water was not satisfactory, due to the reaction of nitrogen iodide on the ketone grouping. The iodine compound which is formed has a distinct odor of iodoform. Chattaway[38] in 1913 obtained iodoform by the treatment of acetophenone with nitrogen iodide. He found that iodoform is formed as a product of the systematic action of nitrogen iodide on ketones. Datta and Prosad[39] confirmed Chattaway's work and also obtained iodoform from methyl ethyl ketone when they treated it with nitrogen iodide. This was also the case with diethyl ketone. Datta and Prosad[39] report that if concentrated solutions of ketones are used and the reaction carried out at low temperatures, that small yields of iodo ketones may be obtained. It was necessary to abandon this procedure in this investigation and iodinate 4-(4'-hydroxy phenoxy) acetophenone by another method.

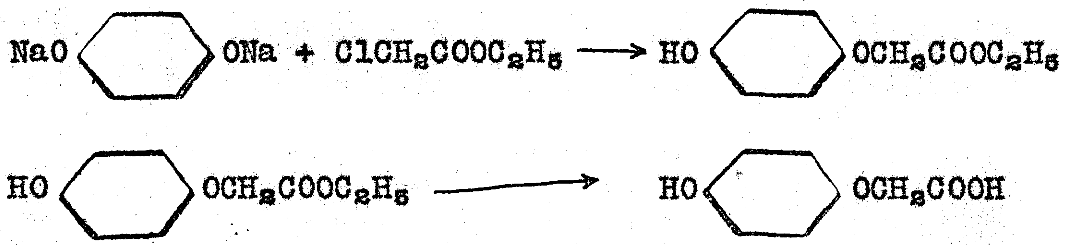
The method used in iodinating 4-(4'-hydroxy phenoxy) acetophenone is as follows: The hydroxy compound is dissolved in ethyl alcohol, and treated with mercuric oxide and iodine. This gave the di-iodo compound, the sodium salt of which is only slightly soluble. The compound had no physiological action on tadpoles.



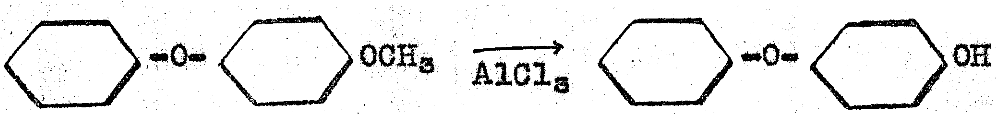
4-PHENOXY PHENOXY ACETIC ACID SERIES

In the synthesis of this series, different type reactions were employed. It was the original plan to start with 4-hydroxy phenoxy acetic acid and couple this with nitro fluorobenzene. This was not successful as the preparation of 4-hydroxy phenoxy acetic acid from hydroquinone did not give sufficient yields to merit the use of this product.

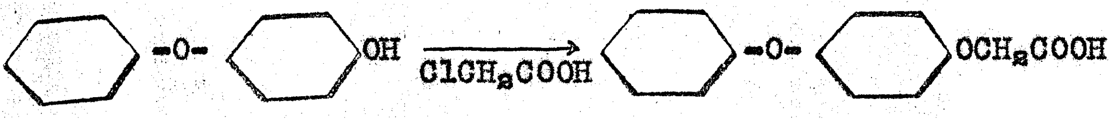
4-Hydroxy phenoxy acetic acid had been prepared from hydroquinone by Carter and Lawrence[81]. The sodium salt of hydroquinone was prepared by reaction with metallic sodium in alcohol (absolute). To this was added one mole of bromo ethyl acetate and the solution boiled on a water bath. The mono derivative was separated from the di-derivative by treatment with dilute sodium hydroxide, which keeps the mono derivative in solution. The ester was hydrolyzed and the 4-hydroxy phenoxy acetic acid was formed and melted at 152°C.



Since the use of 4-hydroxy phenoxy acetic acid was abandoned the next step taken was to prepare 4-phenoxy phenoxy acetic acid. This was done by fusing phenol with brom anisole using a copper catalyst, and obtaining 4-phenoxy anisole. Very good yields were obtained in this reaction. The methyl group was split off with aluminum chloride, giving 4-phenoxy phenol.



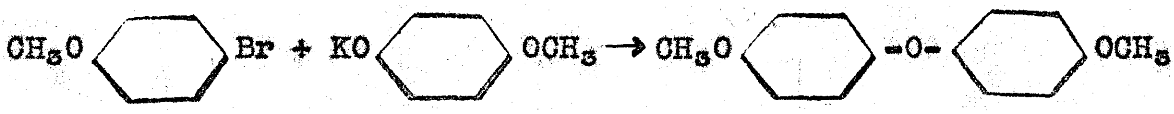
The reaction with mono chloracetic acid gives a high yield of 4-phenoxy phenoxy acetic acid.



This compound had been previously prepared by Hausermann[50]. It is interesting to note that 4-phenoxy phenoxy acetic acid has been recently patented for use as a germicidal[25].

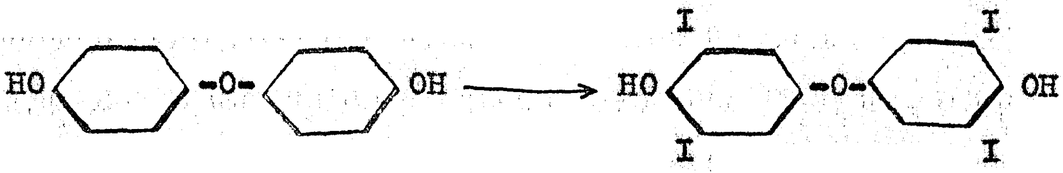
Attempts to nitrate this compound were unsuccessful. In all the nitrations used, only a gummy mass was obtained from which no satisfactory product could be isolated. The attempt to synthesize 4-(4'-hydroxy phenoxy) phenoxy acetic acid by this synthesis was also given up.

4-(4'-Hydroxy phenoxy) phenoxy acetic acid was obtained by making 4-(4'-hydroxy phenoxy) phenol and starting from this compound. The coupling of 4-brom anisole and 4-hydroxy anisole was employed to obtain the 4-(4'-methoxy phenoxy) anisole.

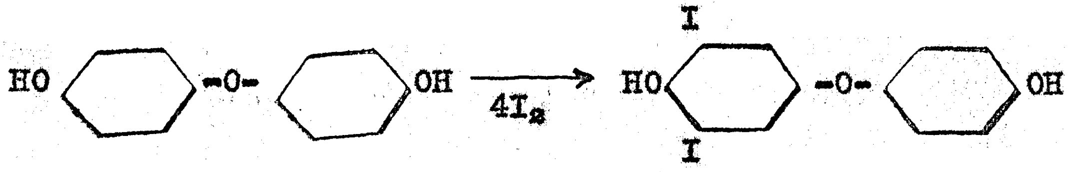


Good yields were obtained in this reaction. Oesterlin[78] as well as Choguill and Brewster[49] had previously prepared this compound which melts at 102°C. By the reaction of the di-methoxy derivative with aluminum chloride 4-(4'-hydroxy phenoxy) phenol was obtained. Hausermann and Bauer[80] and Oesterlin[48] had prepared this derivative which melts at 161°C.

Using 4-(4'-hydroxy phenoxy) phenol as a starting point, made possible quite a series of reactions. The compound was first iodinated, attempts being made to put four iodines in the ring.

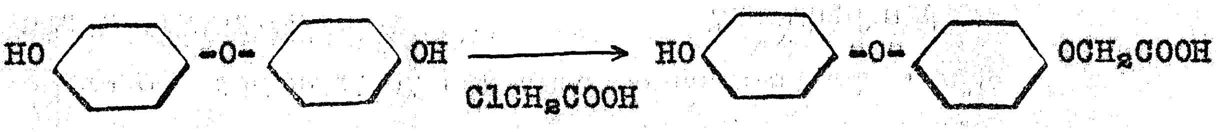


Choguill and Brewster[49] had previously worked on this and they were only able to obtain a di-iodo derivative. The results of this investigation agree with Choguill and Brewster's work, as only two iodines could be put into the ring. It is assumed that the iodines both go ortho to one of the hydroxyl groups and then refuse to allow the other two to enter.

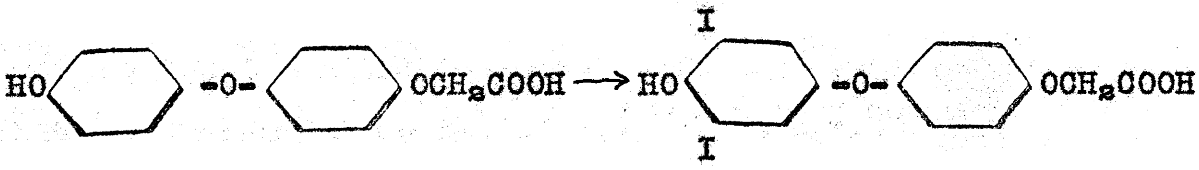


It was possible therefore to prepare mono and di acetic acid derivatives of 4-(4'-hydroxy phenoxy) phenol and also of 4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenol.

The first of these reactions was the synthesis of 4-(4'-hydroxy phenoxy) phenoxy acetic acid. This was accomplished by treating 4-(4'-hydroxy phenoxy) phenol with one mole of mono chloro acetic acid with sodium hydroxide solution.



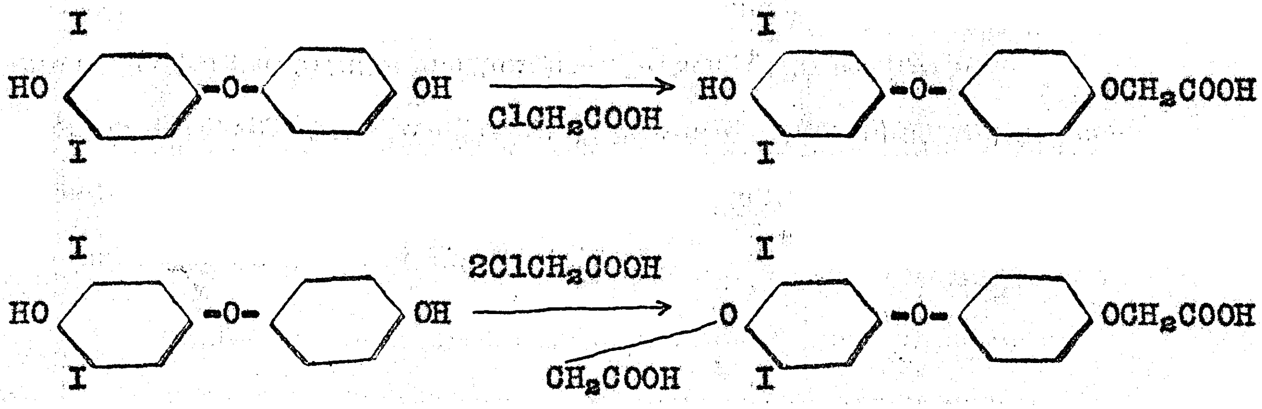
The 4-(4'-hydroxy phenoxy) phenoxy acetic acid was then iodinated, using ammonium hydroxide, iodine and potassium iodide. Two iodines entered into the rings presumably in ortho positions to the hydroxyl group. Attempts to substitute four iodines failed.



4-4'-Bis oxy acetic acid diphenyl ether was then prepared by taking 4-(4'-hydroxy phenoxy) phenol and treating it with two moles of chloro acetic acid. The sodium salt of the bis oxy acetic acid derivative is not so soluble in water as is the mono oxy acetic acid derivative, this providing a means of separation. 4-4'-Bis oxy acetic acid diphenyl ether was purified from heptane coming out as a white flocculent precipitate. A mixed melting point of the 4-(4'-hydroxy phenoxy) phenoxy acetic acid and 4-4'-bis oxy acetic acid diphenyl ether gave a depression which indicated that the two compounds are different.

4-4'-Bis oxy acetic acid diphenyl ether was then iodinated by using ammonia, iodine, and potassium iodide. Two iodines enter the ring forming 4-4'-(3',5'-di-iodo) bis oxy acetic acid diphenyl ether.

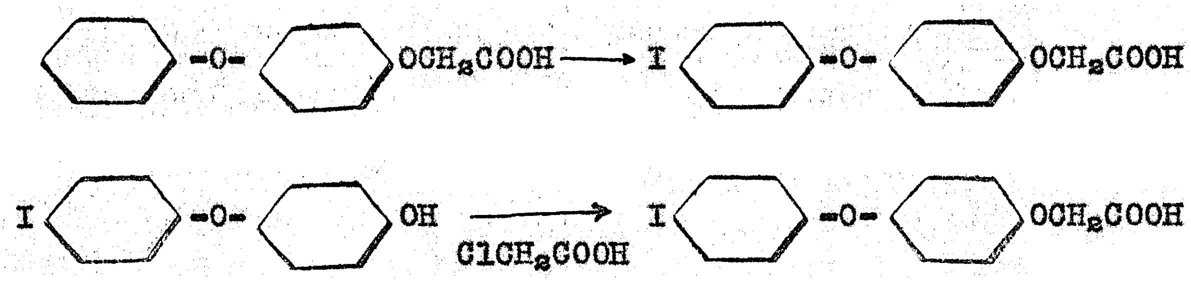
4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenol was then reacted with one and two moles of mono chloroacetic acid forming:



A mixed melting point of the compounds prepared first by iodination of 4-(4'-hydroxy phenoxy) phenoxy acetic acid and secondly by treatment of 4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenoxy acetic acid with chloro acetic acid did not give a depression, thus indicating that they are the same compound.

4-Phenoxy phenoxy acetic acid was then iodinated with iodine monochloride. This gave the 4-(4'-iodo phenoxy)

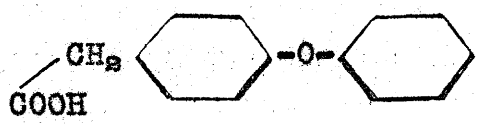
phenoxy acetic acid. The position of this iodine was proven by synthesizing the same compound by another method. 4-(4'-iodo phenoxy) phenol was treated with chloroacetic acid in sodium hydroxide solution. The compound formed by this reaction gave the same melting point as that prepared by the direct iodination of 4-phenoxy phenoxy acetic acid.



Physiological tests were made on the following compounds:

1) 4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenol
2) 4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenoxy acetic acid
3) 4-4'-(3',5'-di-iodo)-bis-oxy acetic acid diphenyl ether
4) 4-(3',5'-di-idod phenoxy) benzoic acid.

4-PHENOXY PHENYL ACETIC ACID SERIES

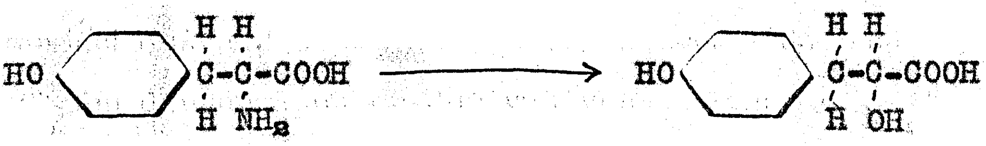


4-Hydroxy phenyl acetic acid was selected as the starting compound for this series. This substance was chosen because it was thought that the presence of the acetic acid group would greatly increase the solubility of the diphenyl ether derivatives. This proved to be the case as all the derivatives of 4-phenoxy phenyl acetic acid form very soluble sodium salts.

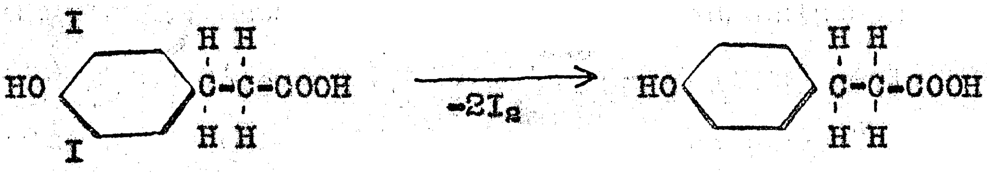
4-Hydroxy phenyl acetic acid has some biochemical significance, as it is one of the degradation products of tyrosine. 4-Hydroxy phenyl acetic acid is found in the human urine[40], in quantities of one half gram to twenty five liters of normal urine. 4-Hydroxy phenyl acetic acid is found along with tyrosine in the urine of dogs[41], Czapluki, Kostanecki, and Lampe[42] synthesized hydroxy phenyl acetic acid by treating 4-methoxy mandelo nitrile with hydeoiodic acid. Perkins and Newberry[43] prepared this compound by heating genistein with potassium hydroxide.

Erlonmeyer and Halsey[44] made 4-hydroxy phenyl acetic acid by treating 4-hydroxy benzaldehyde with hippuric acid and sodium acetate. Salkowski[45] was the first to synthesize 4-hydroxy phenyl acetic acid by the diazotization of 4-amino phenyl acetic acid. This method was also used in this investigation.

4-Hydroxy phenyl acetic acid is no doubt formed in the body by the degradation of tyrosine. This could be accomplished, simply by the deamination and subsequent oxidation of the hydroxy acid.



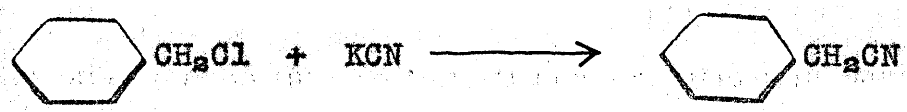
Di-iodo gorgoric acid may also be considered a precursor of 4-hydroxy phenyl acetic acid. This would of course necessitate the loss of two iodines.



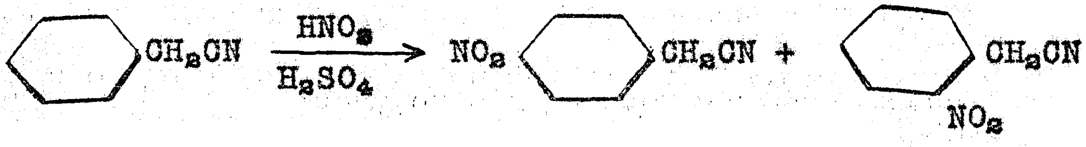
converting it to tyrosine, which then would react as shown above.

To prepare 4-hydroxy phenyl acetic acid in sufficient quantities requires many steps. The simplest procedure would be to nitrate phenyl acetic acid and then reduce this nitro compound to the amine. This can be done but the

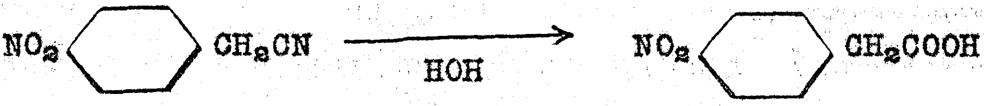
the mitration of phenyl acetic acid gives a mixture which is composed of the 2- nitro and the 4- nitro phenyl acetic acids. This mixture is very difficult to separate. The procedure decided upon was the treatment of benzyl chloride with potassium cyanide, giving benzyl cyanide.



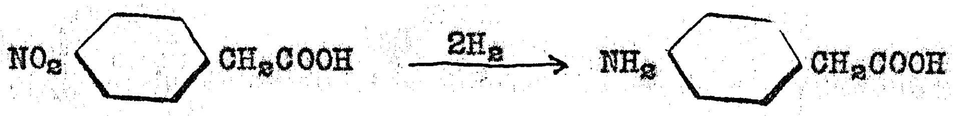
The cyano derivative was nitrated and gave a mixture of 2- and 4-benzyl cyanide. These isomers are easily separated as only the 4-nitro benzyl cyanide comes out from eighty percent ethyl alcohol. Further dilution separates the 2-nitro benzyl cyanide as a red oil. The reaction gives a fifty percent yield of each of these isomers.



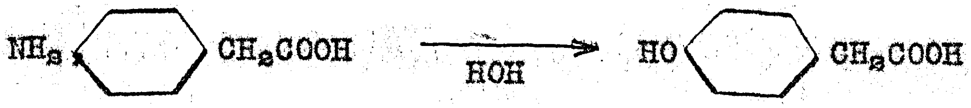
Hydrolysis of 4-nitro benzyl cyanide gave a good yield of 4-hydroxy phenyl acetic acid.

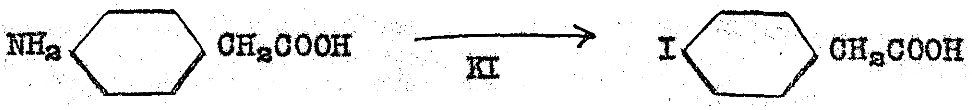


Two methods were employed to convert the nitro compound into 4-amino phenyl acetic acid. The first method was catalytic reduction using either platinum oxide or Raney's catalyst. The second method, by which much larger amounts could be reduced, was the use of hydrogen sulfide and ammonium hydroxide. Yields of eighty five percent of a very pure product were obtained by this procedure.

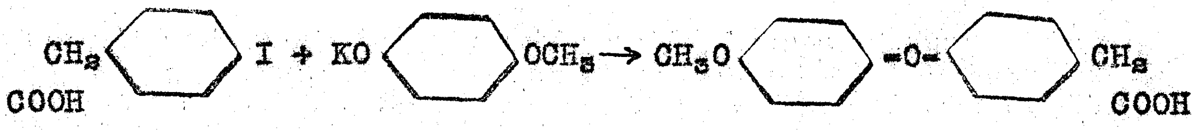


From the 4- amino phenyl acetic acid two products were synthesized; 4-iodo phenyl acetic acid and 4-hydroxy phenyl acetic acid. 4-Iodo phenyl acetic acid had previously been prepared by Malbery and Jackson[47].



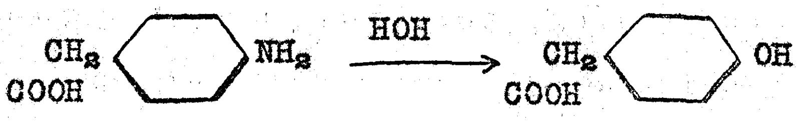


By making the sulfuric acid salt of the 4-amino phenyl acetic acid, diaztoizing, and adding to a cold solution of potassium iodide, a product was obtained which was easily purified from heptane. The melting point of the product was 135°C. which is the same as reported in the literature. The object of preparing this iodo compound was to attempt to couple it with monomethyl ether of hydroquinone.



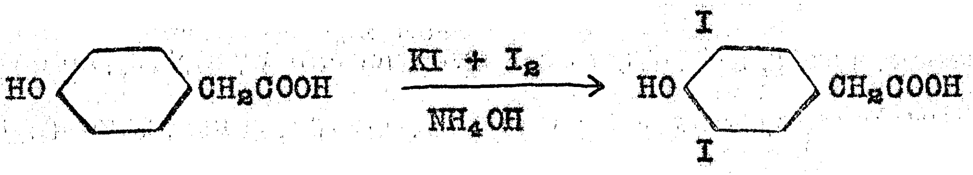
This would give 4-(4'-methoxy phenoxy) phenyl acetic acid which could have been converted to the hydroxy compound by treatment with aluminum chloride.

The second product prepared from 4-amino phenyl acetic acid was 4-hydroxy phenyl acetic acid. This compound has previously been prepared by Salkowski[45] by this same method. 4-Amino phenyl acetic acid was treated with sulfuric acid, diazotized with sodium nitrite, and added to a boiling solution of fifty percent sulfuric acid. Numerous experiments were done, using varying amounts of the amine in an attempt to increase the yield. In five and ten gram portions the yield was always less than fifty percent. By increasing the quantity of the amine to thirty grams, and extracting the solution at least three times with ether, the yield was increased to eighty five percent. This, thereby made possible a good supply of starting material. The 4-hydroxy phenyl acetic acid is very soluble in water, and must be extracted from the solution with an organic solvent. Salkowski reports that the hydroxy compound may be precipitated as the lead, calcium, barium, or silver salt.



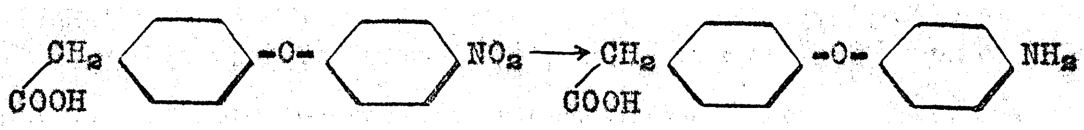
Starting with 4-hydroxy phenyl acetic acid, two compounds were synthesized: 3,5-di-iodo-4-hydroxy phenyl acetic acid and 4-(4'-nitro phenoxy) phenyl acetic acid.

The 3,5-di-iodo derivative of hydroxy phenyl acetic acid was prepared by making the ammonium salt of 4-hydroxy phenyl acetic acid and adding to this a calculated amount of iodine in potassium iodide solution. The solution is then acidified with dilute hydrochloric acid and washed thoroughly with water to remove any unreacted 4-hydroxy phenyl acetic acid. The iodo derivative is recrystallized from heptane, giving a white crystalline compound melting at 211°C. and analyzing correctly for two iodines. The use of this compound in further syntheses is discussed later.

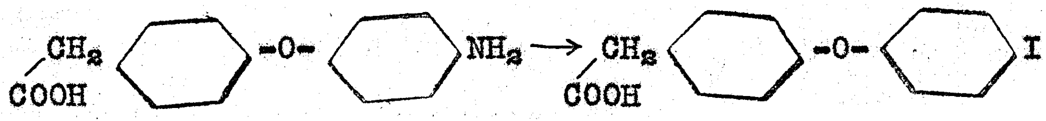


The potassium salt of 4-hydroxy phenyl acetic acid is prepared by dissolving the acid in alcohol and adding a calculated amount of alcoholic potassium hydroxide solution. It is not necessary to prepare the salt this was as the 4-hydroxy phenyl acetic acid and potassium hydroxide may be melted to gether and then reacted with nitro fluorobenzene. Better results were obtained by the former process. The 4-(4'-nitro phenoxy) phenyl acetic acid which results from the above reaction comes out in a gummy-mass, which is quite different from the other substituted phenolic fusions with nitro fluorobenzene. However, it can be purified with heptane and gives a yellowish compound which melts at 129°C. and gives a correct nitrogen analysis.

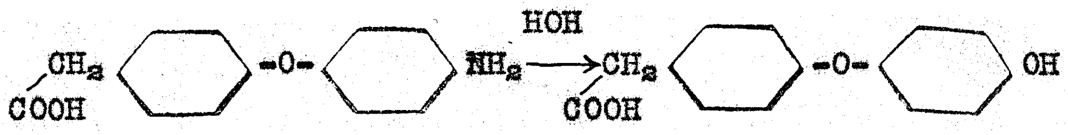
The 4-(4'-nitro phenoxy) phenyl acetic acid was reduced to the 4-(4'-amino phenoxy) phenyl acetic acid by catalytic hydrogenation and also by using iron and acetic acid. The amine is slightly yellow and melts at and analyzes correctly for nitrogen.



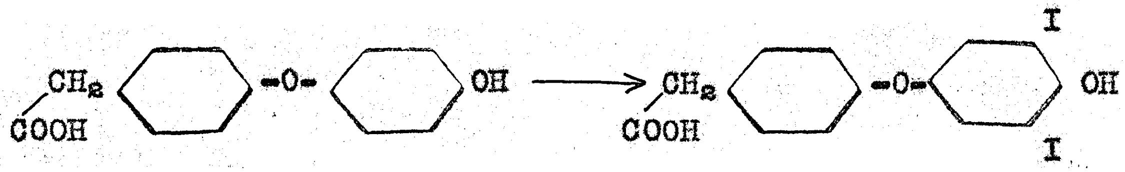
From 4-(4'-Amino phenxoy) phenyl acetic acid two compounds were prepared. 4-(4'-Iodo phenoxy) phenyl acetic acid was synthesized by treating the acid salt of the amine with sodium nitrite and potassium iodide.



4-(4'-Hydroxy phenoxy) phenyl acetic acid was prepared from the amine by treatment of amino acid salt with dilute sulfuric acid. The yield is very small being only 30% of the theoretical.



The preparation of 4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenyl acetic acid from 4-(4'-hydroxy phenoxy) phenyl acetic acid was the first reaction in thisseries. The iodination was accomplished by treating the hydroxy compound with ammonia, potassium iodide, and iodine. This iodo derivative has not been tested for physiological properties.

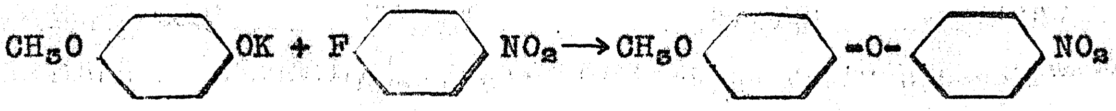


4-PHENOXY PHENYL GLYCINE SERIES

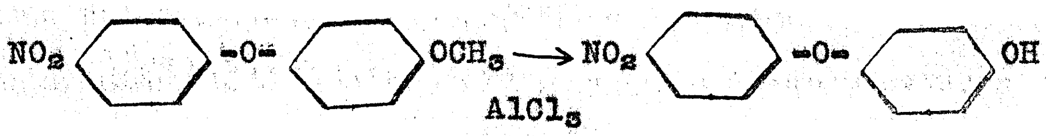
The 4-phenoxy phenyl glycine series was the last series to be studied. These glycine derivatives of diphenyl ether were not used because of any biochemical relationship with thyroxine, but rather to study the characteristics of diphenyl ether derivatives with a $-NHCH_2COOH$ grouping on the ring.

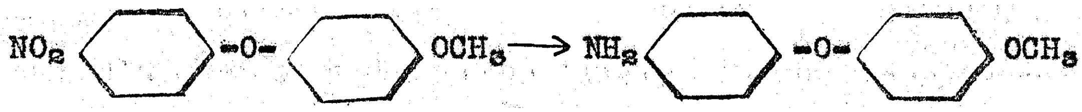
Attempts to couple 4-hydroxy phenyl glycine with 4-bromo anisole and 4-nitro fluorobenzene failed. The potassium salt of 4-hydroxy phenyl glycine was made and was heated with 4-nitro fluorobenzene at temperatures varying between 120° and 200°C. The nitro fluorobenzene was treated by steam distillation and hence removed and the remaining solution was neutralized. A black tarry mass which was formed proved to be the unchanged 4-hydroxy phenyl glycine. A similiar procedure was tried using 4-bromo anisole in place of 4-nitro fluorobenzene but to no avail.

It was necessary therefore, to prepare these phenoxy phenyl glycine derivatives by other means. This was accomplished by coupling 4-hydroxy anisole with 4-nitro fluorobenzene. This product had previously been prepared by Oesterlin[48], who used 4-nitro chlorobenzene in place of 4-nitro fluorobenzene. The reaction takes place at 135°-140°C. and is complete in a few minutes. 4-(4'-Nitro phenoxy) anisole can be purified from ethyl alcohol and the yield is very satisfactory.



From the 4-(4'-nitro phenoxy) anisole) two reactions were used. First, the splitting off of the methyl group with aluminum chloride and secondly, the reduction of the nitro group to the amino group.

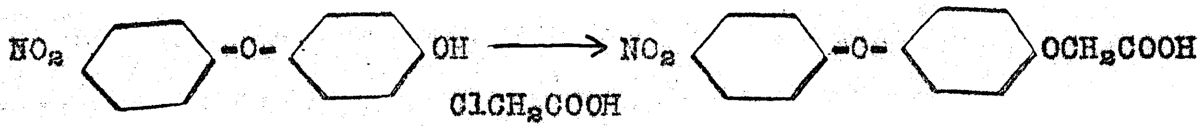




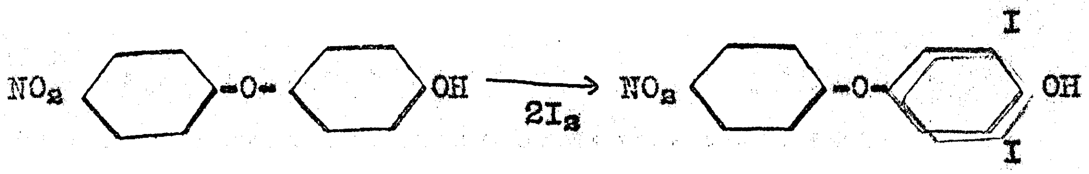
Both the above reactions give good yields, though special precautions must be taken in removing the methyl group with aluminum chloride. It is absolutely necessary that the reaction mixture of 4-(4'-nitro phenoxy) anisole and anhydrous aluminum chloride does not go above the temperature of 125°C. In this work several batches were decomposed at higher temperatures. After the reaction is complete the black solid left in the flask is treated with water to decompose the aluminum chloride. It is then filtered and washed and the precipitate extracted with alkali to remove the hydroxy compound.

The reduction of 4-(4'-nitro phenoxy) anisole was accomplished by using platinum oxide as a catalyst and an atmosphere of hydrogen. This amino compound crystallizes in white leaflets from heptane.

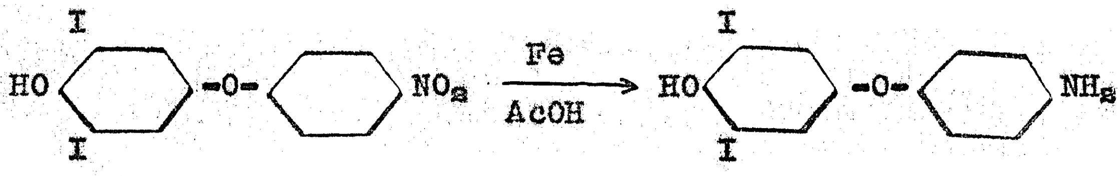
Many attempts were made to react chloroacetic acid with 4-(4'-nitro phenoxy) phenol. This would have made possible the synthesis of 4-(4'-nitro phenoxy) phenoxy acetic acid which is discussed in series III. The reaction in a sealed tube and at high temperature failed to produce any results.



The presence of the hydroxyl group in the four position provided the means to put two iodines in the ring. This was accomplished by using ammonium slat of 4-(4'-nitro phenoxy) phenol, and adding to this a calculated amount of iodine in a solution of ptassium iodido. The di-iodo compound separates out as the ammonium salt and is purified from dilute alcohol.



Reduction of 4-(3',5'-di-iodo-4'-nitro phenoxy) phenol without losing the iodine was accomplished by reduction with acetic acid and iron. The nitro compound was dissolved in acetic acid and ferric reductum was added slowly. The reaction mixture was refluxed for ten minutes and filtered. 4-(3',5'-di-iodo-4'-hydroxy phenoxy) aniline is precipitated by the addition of water to the acetic acid solution, and can be recrystallized from heptane. It is a white crystalline compound melting at 147°C.



4-(3',5'-di-iodo-phenoxy) aniline was fused with one mole of chloroacetic acid. This reaction gave very small amount of a brownish compound melting at 235°C. It is very hard to purify. It melts with decomposition.

No physiological tests were made with these iodinated compounds.

METHODS OF IODINATION

Since this investigation is concerned primarily with iodine derivatives of diphenyl ether, the methods of iodination employed are mentioned.

1) The addition of iodine-potassium iodide solution to an ammoniacal solution of the compound to be iodinated, was very successful when there was an hydroxyl group in position four. The entering iodines in all cases, but one, substituted in positions three and five, or ortho to the hydroxyl group.

2) As it was impossible to iodinate 4-(4'-hydroxy phenoxy) acetophenone with nitrogen iodide, a mixture of iodine, mercuric oxide and ethyl alcohol was employed. This procedure was satisfactory in this iodination, substituting iodines in the ortho positions to the hydroxyl gourp.

3) The replacement of an amine group with iodine was used. This is a standard reaction, being accomplished by making the acid salt, diazotizing with sodium nitrite and adding to cold solution of potassium iodide. Although this reaction gave a means of preparing iodine compounds it was mecessary in this investigation to aid in proving the position of the substituting iodine after iodination with iodine monochloride.

4) The addition of iodine monochloride to an acetic acid solution of the compound to be iodinated was employed entirely when the $4'$- position of diphenyl ether was not occupied. This reaction porceeds quickly but the resulting products are usually difficult to purify.

DISCUSSION OF TADPOLE IODINE ASSAY

The iodine compounds prepared in this investigation were tested for physiological properties by using Gaddum's Tadpole Thyroxine Assay[62]:

In 1912 Gudernatsch[63] discovered a remarkable effect of thyroid preparations on tadpoles. They shrink rapidly in size and their metamorphosis is hastened. This phenomenon has been described in great detail by Romeis[64], Kahns[65], and others. Numerous workers have suggested that thyroid preparation could be assayed depending on these phenomena. Swingle[66] discussed this previous work and criticizes them on the grounds that the results are not a specific effect of the active principle itself, but may be produced in verying degrees by almost <u>any iodine</u> compound. Gaddum[62] had revised these previous methods and gives a procedure for a quantitative measurement of tadpoles.

The most obvious change which occurs is a rapid diminution in size. This appears to be due partly to the hastening of the normal processes of metamorphosis and partly to the wasting which is associated with the increase in metabolic rate. The simplest measurements to make, and the one most usually made, is that of total length. Although a measurement of volume or weight would show much larger differences and might thus be thought likely to prove the most sensitive index of the effect. It was abandoned in favor of measureing the over-all length of each tadpole. The tadpoles were sucked up one by one into a piece of glass tubing and the water allowed to run out of the tube. When they became immobile in the extension they were held against a scale and measured to the nearest millimeter. Twelve tadpoles to a batch were used, and they were immersed in five hundred c.c. of clean solution, in tap water, of on of the compounds under test. Sodium carbonate was added in minute quantities to secure complete solution.

In this investigation, Gaddum's procedure was modified somewhat. The method of measuring the tadpoles was simplified. The tadpole to be measured was separated by means of a tea strainer and placed in a small crystallizing dish containing a small amount of tap water. Beaneath this dish was placed a sheet of ruled millimeter paper. After the tadpole had been in the dish for a minute or so, he comes to rest. By adjusting the paper without moving the dish quick measurement of the tadpole to within a millimeter is possible. This method is rap id and is quite accurate. The tadpoles are then placed (by means of a strainer) into a five hundred c.c. crystallizing dish, containing the solutions to be tested. It is necessary that the solution be changed daily. The tadpoles were fed on the whites of hard boiled eggs and a small amount of lettuce leaf.

None of the compounds tested gave any increased metabolism in tadpoles while using this method. The results are shown on page 147. More tests are being run at the present time and will be reported on at a later date.

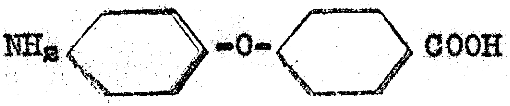
EXPERIMENTAL

SERIES I

4-PHENOXY BENZOIC ACID SERIES

SERIES I

SYNTHESIS OF



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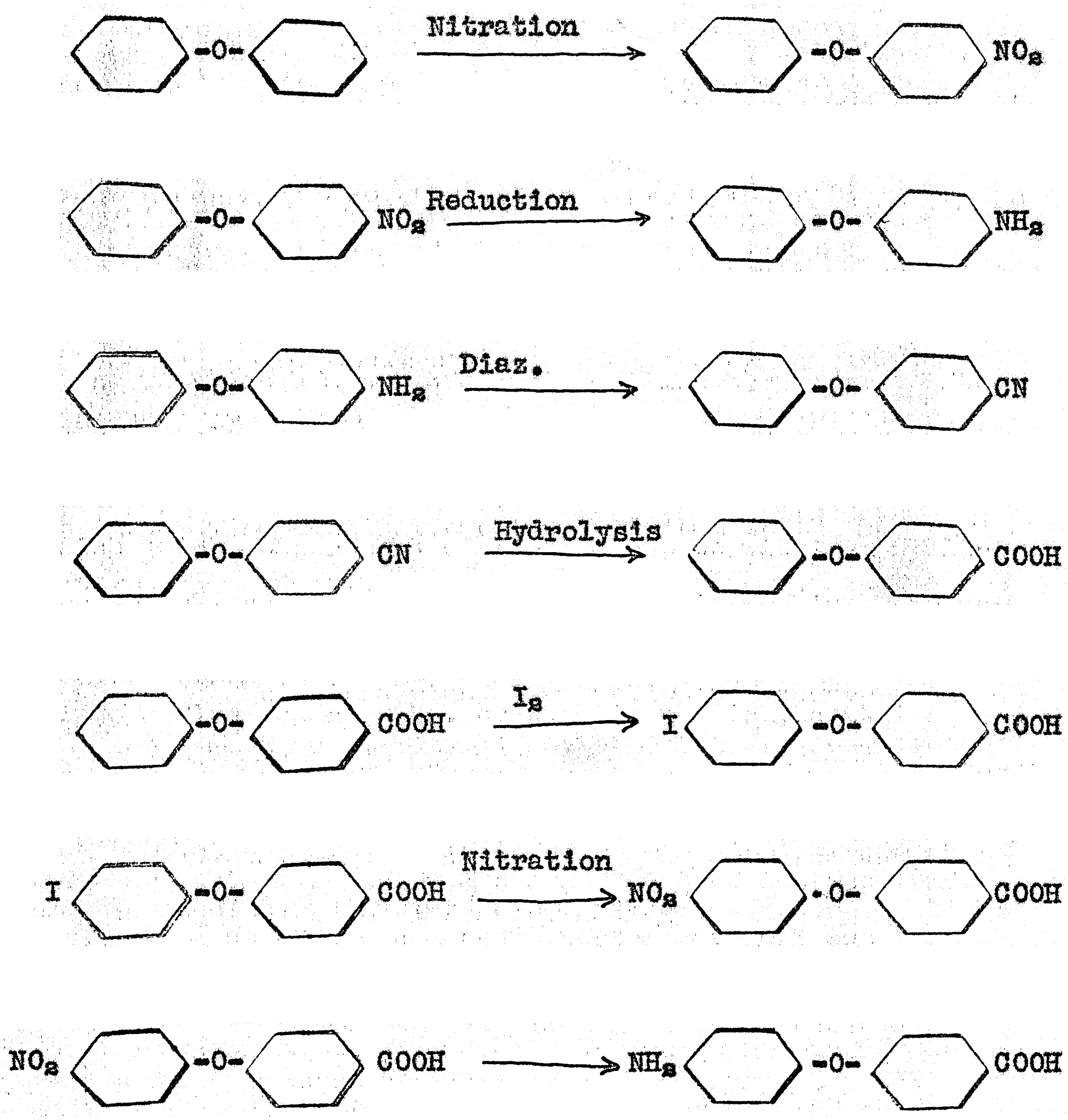

SERIES I

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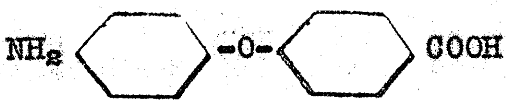

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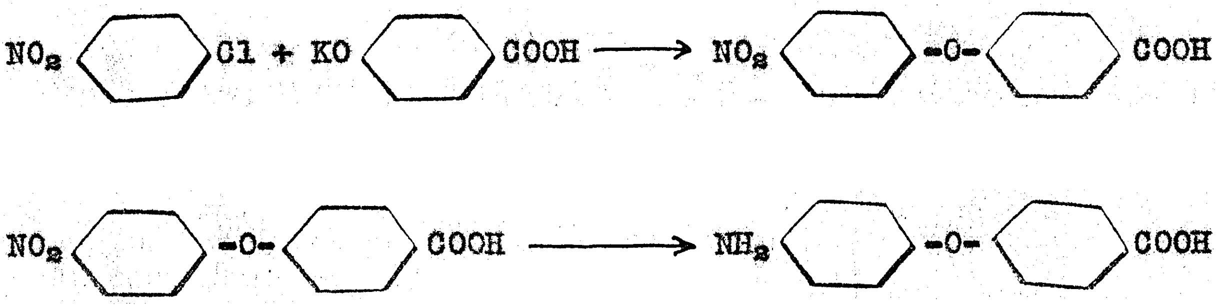

SERIES III

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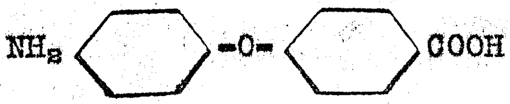

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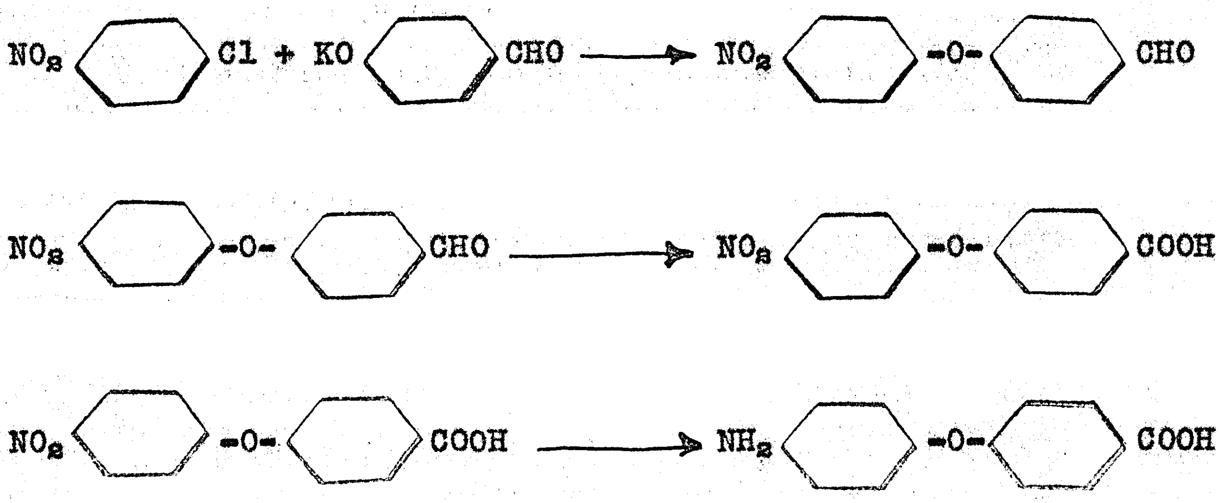

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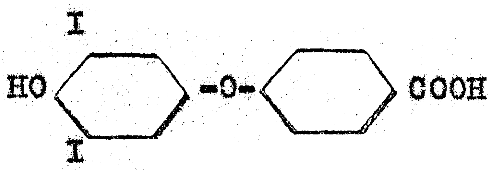

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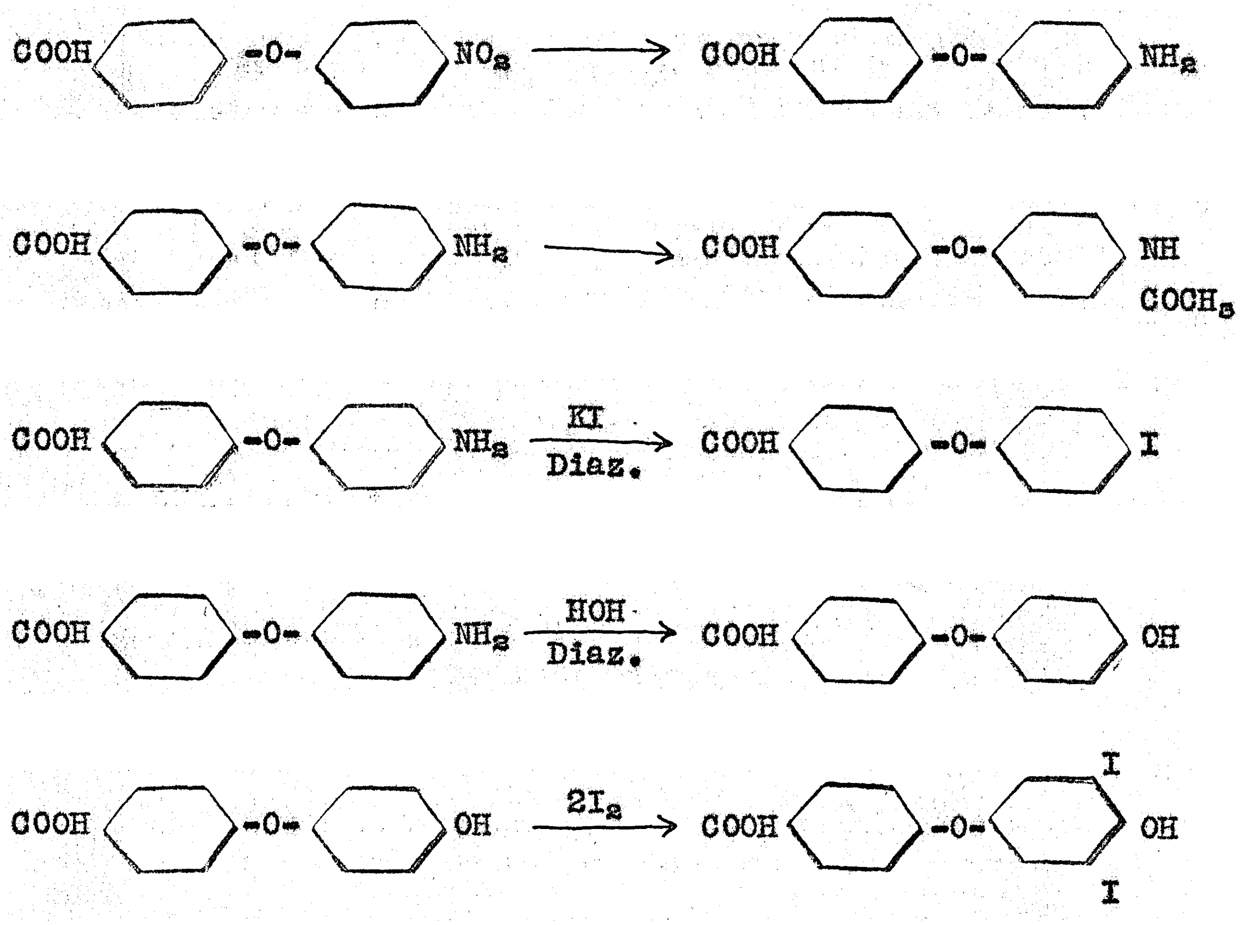
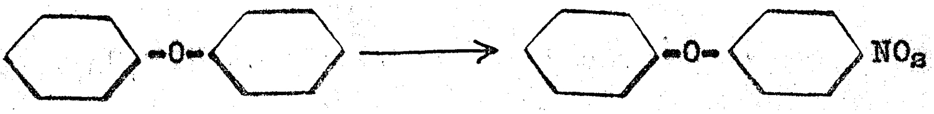


PREPARATION OF
4-NITRO DIPHENYL ETHER
from
DIPHENYL ETHER

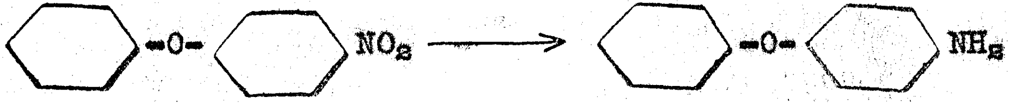


Procedure[21]:

One hundred c.c. of fuming nitric acid (specific gravity 1.52) in three hundred c.c. of glacial acetic acid were added over a period of two hours to a well-stirred solution of three hundred and forty grams of diphenyl ether in four hundred c.c. of acetic anhydride, kept in a water bath at a temperature of 25° to 30°C. After three and one half hours longer the reaction mixture was poured into water, the precipitated oil washed twice and distilled under reduced pressure. The mono-nitro compound distilled over at 193° to 210 °C. (uncorrected) at fourteen mm.

From seven hundred grams of the mono-nitro mixture kept at 0°C. overnight was obtained two hundred and seventy grams of practically pure 4-nitro diphenyl ether by filtering and washing the crystals with methyl alcohol. The melting point of the compound was found to be 57° to 60°C.; reported at 56°. 60°, and 61°C. The yield was eighty percent of the theoretical.

PREPARATION OF
4-AMINO DIPHENYL ETHER
by
REDUCTION OF 4-NITRO DIPHENYL ETHER with
ZINC AND CALCIUM CHLORIDE

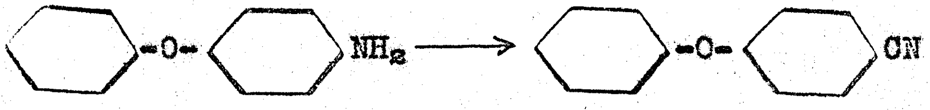


Procedure[21]:

To a well-stirred mixture of eighty grams of zinc dust and twenty grams of calcium chloride in seventy five c.c of water and two hundred c.c. of ninety five percent alcohol on a steam bath was added slowly forty three grams of the nitro compound. The reaction was very vigorous and after an hour the mixture was filtered to remove the zinc oxide and unchanged zinc. The filtrate was filtered again and deposited a few crystals of the hydrazo compound. These were removed and the solution diluted with water, which gave a light yellow mass of the amine.

A fair yield of the crude product was obtained and the melting point was 82°C.; reported melting point of the crude product was 75° to 80°C.; reported melting point for the pure amine was 83.5°C. It was found that the best yields could be obtained by the reduction of the nitro compound with catalytic hydrogenation.

PREPARATION OF
4-CYANO DIPHENYL ETHER
from
4-AMINO DIPHENYL ETHER

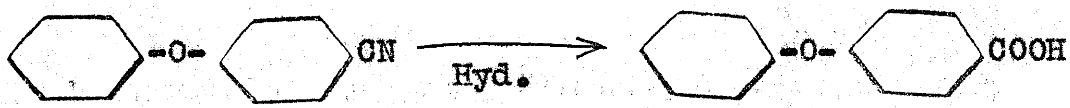


Procedure[21]:

Thirty seven grams of finely divided 4-amino diphenyl ether were warmed on a steam bath with sixty c.c. of concentrated hydrochloric acid and one hundred and fifty c.c. of water. The mixture was heated until the compound was a finely divided mass. The suspension of amino hydrochloride was cooled to 0°C. and diazotized with fifteen grams of sodium nitrite in forty c.c. of water. After one half hour the mixture was neutralized with sodium carbonate and poured into a cold solution of twenty five grams of sodium cyanide and twenty five grams of cuprous cyanide in one hundred and fifty c.c. of water. The brown precipitate first formed evolved nitrogen when warmed to room temperature.

The remaining oil was taken up with benzene. The benzene was evaporated and the oil distilled under vacuum, giving fifteen grams of light yellow oil. The boiling point of this compound at 14 mm. was 187°C. Upon standing the oil partially solidifies and was recrystallized from heptane giving colorless needles which melt at 47°C.

PREPARATION OF
4-PHENOXY BENZOIC ACID
from
4-CYANO DIPHENYL ETHER



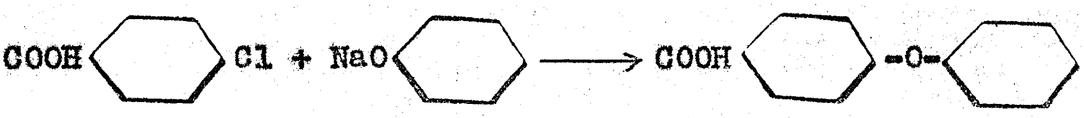
Procedure[21]:

By hydrolysis of 4-cyano diphenyl ether with alcoholic potassium hydroxide, the acid was formed in theoretical amounts.

This was accomplished by using fifty c.c. of ethyl alcohol, which was mixed with two grams of potassium hydroxide, and five grams of 4-cyano diphenyl ether. The mixture was refluxed on a water bath for three hours after which time the product was poured into a cold acidified solution of ice water. During the pouring the solution was stirred continously. 4-Phenoxy benzoic acid precipitates out as white crystals and is recrystallized from boiling ethyl alcohol.

An eighty percent yield of the final product was obtained and the melting was 160°C.; reported at 159° to 161°C.

PREPARATION OF
4-PHENOXY BENZOIC ACID
from
4-CHLOR BENZOIC ACID and SODIUM PHENYLATE

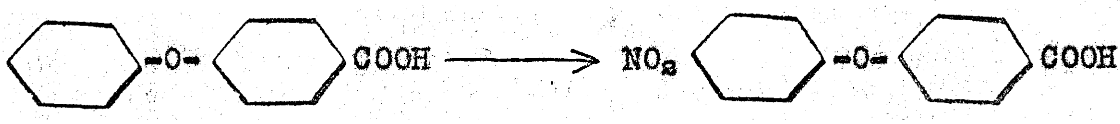


Procedure[87]:

To five grams of 4-chlor benzoic acid were added five grams of phenol, two and one half grams of sodium hydroxide, and some copper catalyst. This mixture was heated on an oil bath gradually until a temperature of 200°C. was reached. The temperature was allowed to remain constant for twenty minutes and stirred constantly with a copper wire. After taking up the melt in hot water, the solution was filtered and acidified with hydrochloric acid.

This procedure was tried several times and no quantity of the final product was obtained. Various proportions of the 4-chlor benzoic acid, phenol and sodium hydroxide were tried, but the reaction would not take place even when the temperature was raised to 250°C. and maintained there for several hours. Different catalysts were also used but no appreciable results were obtained.

PREPARATION OF
4-(4'-NITRO PHENOXY) BENZOIC ACID
from
4-CARBOXY DIPHENYL ETHER



Procedure:

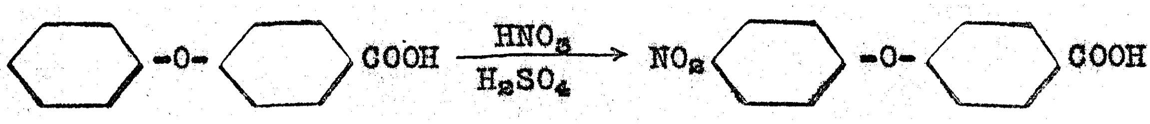
After trying many different methods of nitration the following procedure was found to give the best results. One mole (216 grams) of 4-carboxy diphenyl ether was added to one mole (63 grams) of concentrated nitric acid (specific gravity 1.52) and one mole of concentrated sulfuric acid (98 grams) When the mixture was heated to 75°C. there was suddenly a copious evolution of brown fumes. The 4-(4'-nitro phenoxy) benzoic acid crystallized from the solution to form yellow crystals which came to the surface of the liquid. The solution was filtered and the precipitate was recrystallized from benzene.

After several recrystallizations a melting point of 230°C. was obtained; reported at 236°C. The yield was sixty six grams. The melting point of the crude product was around 185°C. and it did not melt sharply, indicating apparently that there might be present both the 4-nitro and the 2-nitro compounds, the melting point for the ortho product being 182°C.

This method of nitration apparently is in contradiction to the ordinary methods, which report that the temperature should not go above 40° to 45°C., however, no results were obtained at these temperature, while results were obtained at 75°C.

Hausermann and Bauer reported that the product was insoluble in hot alcohol, however, it was found that the product was soluble in hot ethyl alcohol. The amount of alcohol used was considerable in proportion to the 4-(4'-nitro phenoxy) benzoic acid, however, it was soluble.

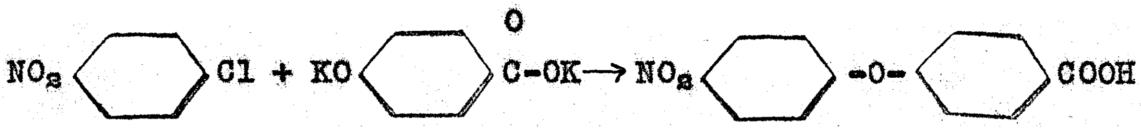
PREPARATION OF
4-(4'-NITRO PHENOXY) BENZOIC ACID
from
4-PHENOXY BENZOIC ACID



Procedure:

Twenty one grams of 4-carboxy benzoic acid were dissolved in one hundred to one hundred and twenty five c.c. of concentrated nitric acid. The solution was cooled by means of an ice-bath and then gently warmed to 45°C. until all the ether was in solution. The temperature was kept below 45°C. using an ice-bath for about one half hour, preventing an evolution of nitrogen dioxide as mush as possible. The solution was then allowed to set overnight. In the morning reddish brown crystals filtered off after cooling in ice-water. Water and ice added to the filtrate gave only a very small amount of a tarry gum. The filtered crystals were then washed and turned with ice-water. They were dissolved in dilute sodium hydroxide, boiled with charcoal , filtered, cooled with ice, acidified, and the product filtered off. The substance was purified by recrystallization from benzene.

PREPARATION OF
4-(4'-NITRO PHENOXY} BENZOIC ACID
from
4-NITRO CHLOROBENZENE and 4-HYDROXY BENZOIC ACID



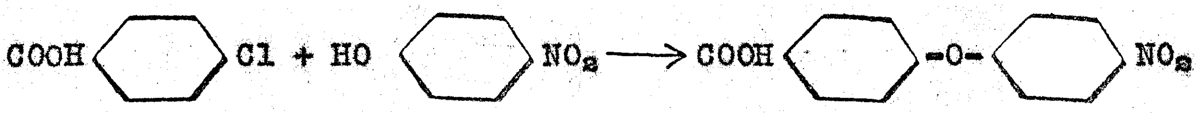
Procedure[30]:

Five grams of nitro chlorobenzene and six grams of the di-potassium salt of hydroxy benzoic acid were dissolved in fifty c.c. of nitrobenzene. The mixture was heated between 150° and 160°C. for five hours, and one half of the mixture worked up by adding water, and a little sodium hydroxide solution. When steam distilled, nitro benzene and nitro chlorobenzene was distilled over. The solution in the steam distillation flask was then filtered and made acidic. This solution was then heated five hours more and the other half of the solution worked up the same as the first half.

This procedure was tried and revised several times but no appreciable results were obtained, however, a very small amount of the 4-(4'-nitro phenoxy) benzoic acid was obtained but the yield was so small that other methods were used. Using the potassium salt of 4-hydroxy benzaldehyde instead of the 4-hydroxy benzoic acid gives a good yield of the aldehyde which can be oxidized to the acid.

(See page

PREPARATION OF
4-(4'-NITRO PHEN OXY) BENZOIC ACID
from
4-NITRO PHENOL and 4-CHLOROBENZOIC ACID

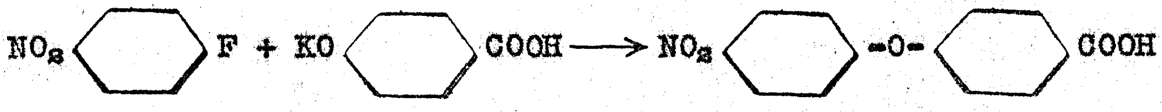


Procedure:

In coupling 4-nitro phenol and 4-chlorobenzoic acid, thirteen and five tenths grams of 4-nitro phenol and fifteen grams of 4-chlorobenzoic acid were dissolved in a solution of ten percent potassium hydroxide. This mixture was refluxed for six hours with occasional stirring. The contents were filtered and made acidic with hydrochloric acid. By means of fractional crystallization the final product was obtained and purified by dissolving in hot alcohol.

Experiments with this procedure gave varying results. At first no results were obtained but when the solution which was made acidic with hydrochloric acid, was allowed to stand for several days a product crystallized out which was 4-(4'-carboxy) nitro diphenyl ether, however, the yield was very small. The melting point of the compound was 220°C.; reported in literature at 236°C.

PREPARATION OF
4-(4'-NITRO PHENOXY) BENZOIC ACID
from
4-NITRO FLUOROBENZENE and 4-HYDROXY BENZOIC ACID



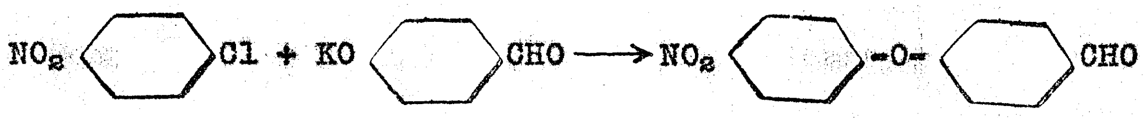
Procedure[26]:

Forty three grams (0.2 mole) of the dry potassium salt of 4-hydroxy benzoic acid (prepared by stirring the equivalent quantity of potassium hydroxide in water, into a water suspension of 4-hydroxy benzoic acid, then evaporating to dryness) were heated with 65 grams of 4-nitro fluorobenzene for one hour at 190° to 200°C. When cool, the excess 4-nitro fluorobenzene was removed by steam distillation (40 grams were recovered). After filtering off a small residue (2 grams) of a by product, 4-(4'-nitro phenoxy) benzoic acid, the solution remaining in the distillation flask, was acidified and the white precipitate washed with water. The yield was 37 grams of the crude product, which after recrystallization from glacial acetic acid and charcoal, melted at 235°C.; reported melting point was 235° to 236°C.

When the above acetic acid solution is diluted with water, more of the product will be obtained, however, the melting point of this product is around 190° to 200°C., showing the presence of some unchanged 4-hydroxy benzoic acid. But if this is recrystallized from glacial acetic acid pure 4-(4'-nitro phenoxy) benzoic acid will be obtained.

This method gives the best yields as well as the purest product of all other methods which were used in preparing 4-(4'-nitro phenoxy) benzoic acid.

PREPARATION OF
4-(4'-NITRO PHENOXY) BENZALDEHYDE
from
4-CHLORO NITRO BENZENE and 4-HYDROXY BENZALDEHYDE

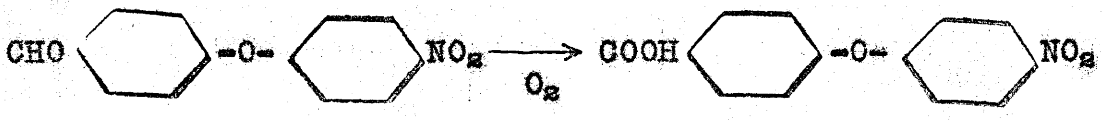


Procedure[22]:

A solution was made containing 45 grams of potassium hydroxide and twenty five c.c. of hot water. This solution was added with constant stirring to ninety seven grams of the crude 4-hydroxy benzaldehyde compound which previously had been dissolved in two hundred c.c. of ethyl alcohol. By cooling this mixture in ice there was obtained one hundred and sixteen grams or 91% of the theoretical of the potassium salt. The material which was obtained was of a dark red color but was found to be satisfactory for the following reaction.

To two hundred grams (1.27 mole) of 4-chloro nitro benzene kept at 165-170°C. was added in small portions with stirring during one hour, ninety three grams (.58 mole) of the dry potassium salt. The mix was then kept at 190-200°C. for six hours, cooled and steam distilled to remove excess 4-chloro nitrobenzene. On crystallization from dilute acetic acid and charcoal gave 106 grams or 75% of the theoretical of a brown product, which after several crystallizations with charcoal and alcohol gave colorless needles, which melted at 104° and 105°C.

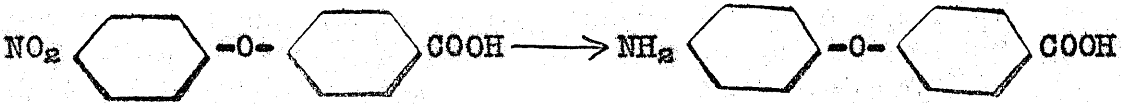
PREPARATION OF
4-(4'-NITRO PHENOXY) BENZOIC ACID
from
4-(4'-NITRO PHENXOY) BENZALDEHYDE



Procedure:

A mixture of sixty grams of sodium dichromate in one hundred c.c. of water and forty nine grams of the 4-(4'-nitro phenoxy) benzaldehyde was heated until the aldehyde was just about to melt, then as soon as it had completely melted, forty three c.c. of concentrated sulfuric acid were added to the stirred mixture during the half hour. After an hour, the mixture was allowed to cool, then diluted with water and the solid residue extracted several times with hot dilute sodium hydroxide solution. By acidifying this alkaline solution, there was obtained forty one grams of 4-(4'-nitro phenoxy) benzoic acid or seventy nine percent of the theoretical. The melting point was found to be 235°C.; reported at 235° to 236°C.

PREPARATION OF
4-(4'-AMINO PHENOXY) BENZOIC ACID
from
4-(4'-NITRO PHENOXY) BENZOIC ACID by REDUCTION WITH CATALYTIC HYDROGEN



Procedure:

Twenty grams of the 4-(4'-nitro phenoxy) benzoic acid were dissolved in hot ethyl alcohol. As this nitro product is not readily soluble in alcohol, a sufficient quality was used to insure complete solution of the compound. The solution was heated to boiling and placed in a liter bottle which had previously been heated to approximately the same temperature of the solution. The bottle was then placed in a special catalytic hydrogen reducing apparatus and two tenths grams of the platinum oxide catalyst were added.

The mixture was then shook vigorously and at the same time hydrogen was passed into the bottle under pressure. The skaing was continued until complete reduction had taken place. In this case the amount of hydrogen utilized was thirty pounds. After repeated experiments the best results wereobtained when the pressure was amintained at fifty pounds. When the compound had taken on the necessary amount of hydrogen it was left in the bottle under pressure and continued shaking to insure complete reduction.

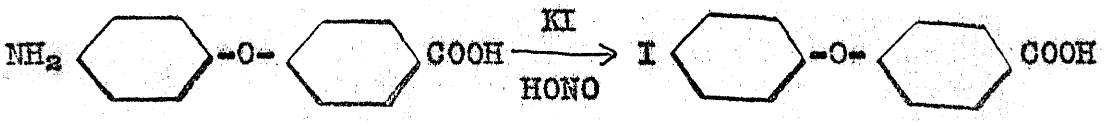
The reduced compound was then filtered, by suction, to remove the catalyst and any insoluble impurities that may have been in the solution. The solution after reduction turned a deep greenish color and the amine was brought down by adding to a solution and ice and water. The final product was of a white creamy nature, which melted at 193° to 194°C.; reported at 193° to 194°C. by Hausermann and Bauer[80].

The scarcity of the nitro product and the long procedure required to obtain the 4-(4'-amino phenoxy) benzoic acid makes it necessary that the reduction of the compound be one giving a very high yield. Large quantities could not be reduced at one time because of the difficulty of dissolving the 4-(4'-nitro phenoxy) benzoic acid in alcohol. Hausermann and Bauer[80] have reported that this nitro compound was insoluble in hot alcohol, but it was found that with sufficient alcohol it will go into solution so that the reduction can be easily carried out.

The nitro product was found to reduce much better if the solution was taken out of the bottle occasionally and heated and a fresh portion of the datalyst added.

In order to obtain the best results, the nitro product must be of the highest purity. Attempts to reduce the nitro product melting at two or three degrees lower than 235-236°C. were very unsatisfactory.

PREPARATION OF 4-(4'-IODO PHENOXY) BENZOIC ACID from 4-(4'-AMINO PHENOXY) BENZOIC ACID



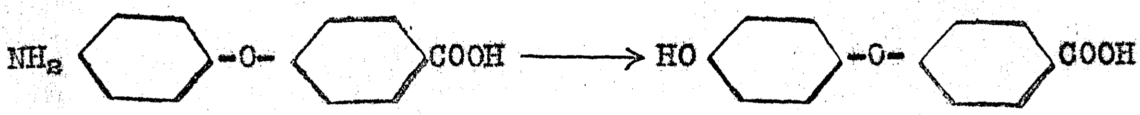
Procedure[e]:

To a solution of five grams of 4-(4'-amino phenoxy) benzoic acid in twenty c.c. of glacial acetic acid was added a cooled solution of ten c.c. of concentrated sulfuric acid in fifty c.c. of water, and the resulting mixture m was cooled to 0°C. The sulfuric acid salt of the amine separated out considerably. While stirring rapidly, there was then added drop by drop an ice cold solution of 1.8m grams of sodium hydroxide in ten c.c. of water.

The nitrous acid formed was used up immediately, with very little evolution of oxides of nitrogen, but the appearance and mushy conditon of the solution changed only slightly. No clear oragne diazonium solution is formed. After standing for ten minutes, stirring frequently, the mixture was poured with rapid stirring into a solution of four grams of potassium iodide in twenty five c.c. of water to which fifty grams of ice had been added. A deep brick red addition product formed immediately. The mixture was then diluted to five hundred c.c., then warmed slowly to

95°C. The red color gradually changed to light brown during the heating, but very little decomposition occurred until approximately eighty percent had been reached, when the precipitate rose to the surface in the form of froth. After keeping at 95°C. for a few minutes to complete the decomposition, the mixture was cooled well, and the cream colored product (7 grams) filtered off. An attempt to dissolve the latter in dilute sodium hydroxide solution precipitated the salt in practically quantitative yield when only a very slight excess of alkali had been added. This filtered off and acidified gave six grams (eighty one percent of the theoretical) of the crude iodo acid, which by recrystallization from alcohol, was obtained as fine nearly colorless crystals, melting at 216° to 217°C. The product was soluble in ether, hot benzene, acetic acid, but insoluble in water.

PREPARATION OF
4-(4'-HYDROXY PHENOXY) BENZOIC ACID
from
4-(4'-AMINO PHENOXY) BENZOIC ACID



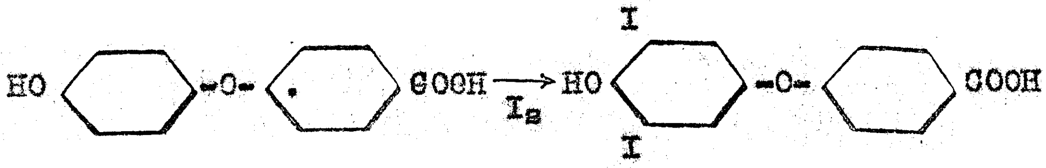
Procedure:

Five and one half grams of finely powdered 4-(4'-amino phenoxy) benzoic acid were stirred into a slightly warmed mixture of fifteen c.c. of concentrated sulfuric acid and twenty c.c. of water, then abour fifty grams of crushed ice added. With a thermometer in the mixture, an ice cold solution of 1.8 grams of sodium nitrite in ten c.c. of ice water was slowly added with stirring, keeping the temperature at 0°C. by immersion in an ice salt bath, when necessary. The mushy consistency of the sulfate salt was changed bery little by conversion to the diazonium salt, and the appearance after the diazotization was about the same as before. After allowing to stand for fifteen minutes with frequent stirring the cold diazo mixture was added slowly through a reflux condenser (to prevent losing water) to a boiling mixture of one hundred and twenty c.c. of concentrated sulfuric acid and ninety c.c. of water, taking care that the addition did not occasion too great a frothing as the nitrogen excaped, and the acid solution kept boiling during the addition, which required about fifteen minutes. The solution was cooled with ice and filtered, and washed several times to remove the acid. After a thorough washing a grayish brown product resulted yielding five grams of the product which melted indefinitely at approximately 170°C.

After drying the product it was then recrystallized from hot benzene and charcoal. Repeated crystallizations yielded a white product melting sharply at 193°C. As the amine melts at 192°C., a mixed melting point was made, giving a melting point of 168°C., showing that the product was not the amine. This product forms the sodium salt and it is very soluble in water. It was also very soluble in cold ethyl alcohol and acetic acid. It was also recrystallized from hot water and melts at 192°C. The yield of the pure product was only about twenty percent.

Analysis:

PREPARATION OF
4-(3',5'-DI-IODO-4'-HYDROXY PHENOXY) BENZOIC ACID
from
4-(4'-HYDROXY PHENOXY) BENZOIC ACID



Procedure:

To two grams of the 4-(4'-hydroxy phenoxy) benzoic acid was added sixteen c.c. of ammonium hydroxide (specific gravity 0.88) and two c.c. of dilute sodium hydroxide solution. To this was added with constant stirring, the calculated amount of a normal solution of iodine in potassium iodide. This was performed as a titration, the iodine solution being added by means of a burette.

Black NI_3 forms and disappears slowly. After the addition of the theoretical amount of iodine, sodium disulfite was added to remove any excess iodine that may have been formed. The solution was then made acid with hydrochloric acid. The precipitate formed is of a gelatinous nature and can be recrystallized from heptane. The crystals formed were white and decomposed at 225°C. with the liberation of iodine and finally melted at 255°C.

There was obtained three grams of this compound which was about 60(of the theoretical yield.

Analysis:

Calculated percent Iodine (for $C_{13}H_8O_4I_2$; molecular weight = 482) = 52.71%

1) Found 52.43%

Weight of sample - - - - - - - - - - - - - - - - .1892

Std. $AgNO_3$ sol'n used (1 c.c. .00635 g. of I) - - 15.61

Weight of Iodine - - - - - - - - - - - - - - - - .0992

Percent of Iodine - - - - - - - - - - - - - - - 52.43%

2) Found 52.55%

Weight of sample - - - - - - - - - - - - - - - - .1640

Std. $AgNO_3$ sol'n used (as above) - - - - - - - - - 13.57

Weight of Iodine - - - - - - - - - - - - - - - - .0862

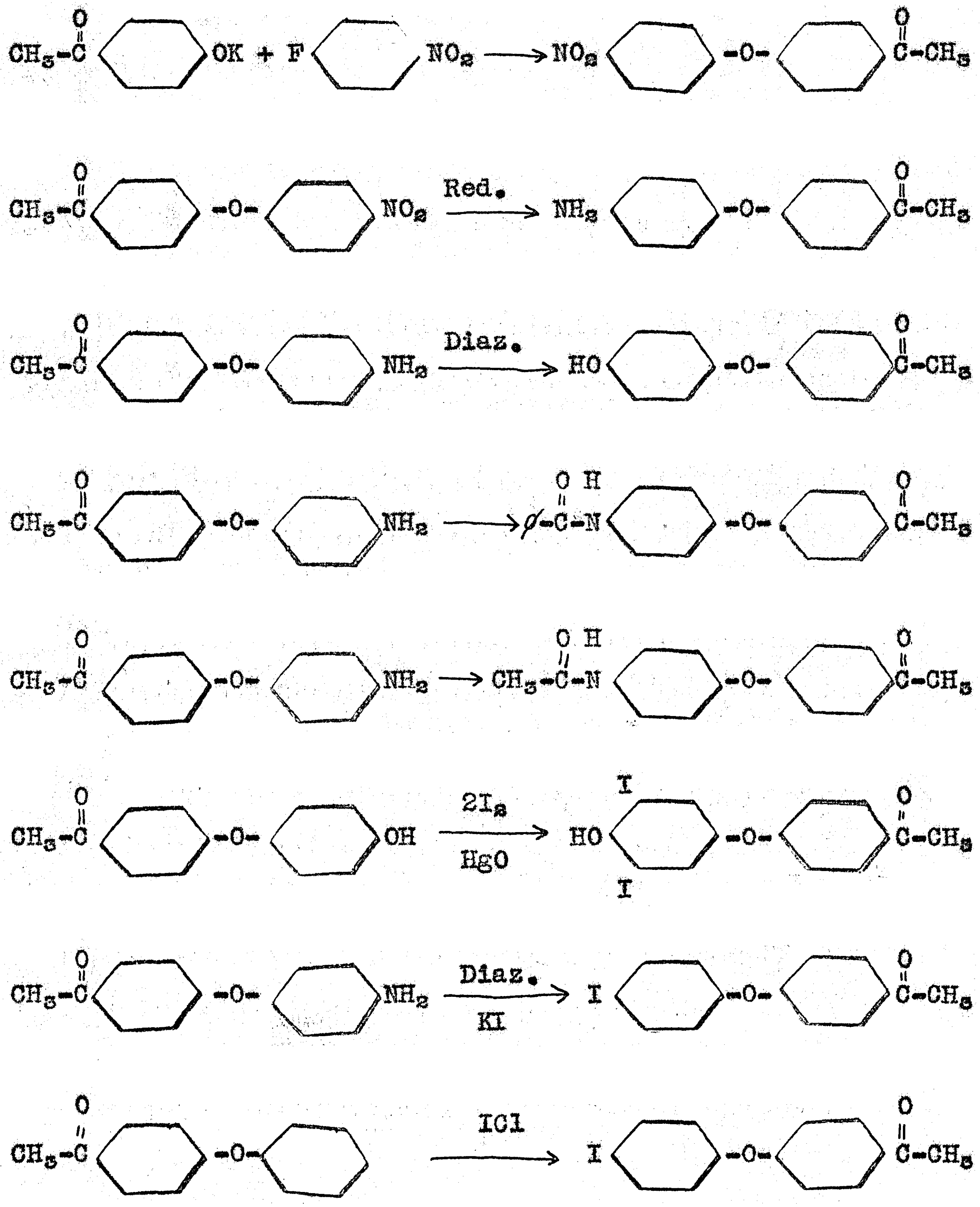
Percent of Iodine - - - - - - - - - - - - - - - 52.55%

EXPERIMENTAL

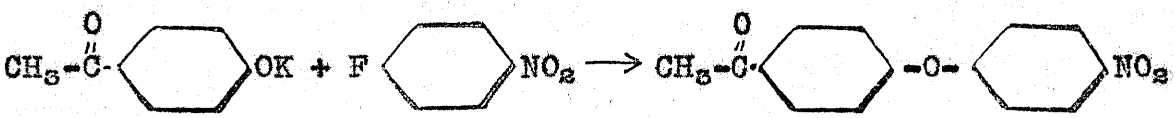
SERIES II

4-PHENOXY ACETOPHENONE DERIVATIVES

4-PHENOXY ACETOPHENONE SERIES



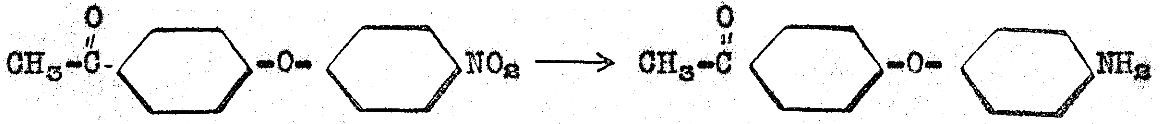
PREPARATION OF
4-(4'-NITRO PHENOXY) ACETOPHENONE
from
4-HYDROXY ACETOPHENONE and 4-NITRO FLUOROBENZENE



Procedure[28]:

To ten grams of the potassium salt of 4-hydroxy acetophenone, add fifty grams of 4-nitro fluorobenzene. (Using a large excess of 4-nitro fluorobenzene will give a better results). This mixture is then heated for one hour in an oil bath at about 160°C. The mixture is cooled, steam distilled to remove the excess 4-nitro fluorobenzene, and filtered white hot to remove the tarry materials. The crude 4-(4'-nitro phenoxy) acetophenone separates partially as an oil but upon cooling solidifies and is purified by recrystallizing from hot alcohol. The alcoholic filtrate is diluted with water and more of the compound will precipitate. The two precipitates added together give almost a quantitative yield. The compound is repurified by boiling in hot alcohol and charcoal. Pure 4-(4'-nitro phenoxy) acetophenone separates out as a heavy, flaky, white precipitate and melts sharply at 83°C. The yield was 12.5 grams which eighty nine perdent of the theoretical yield.

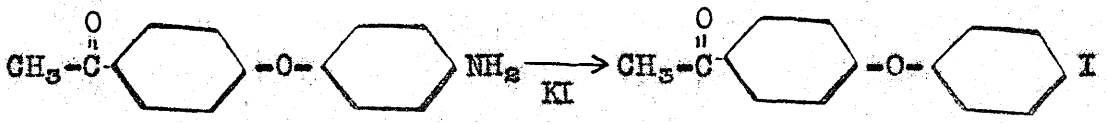
PREPARATION OF
4-(4'-AMINO PHENOXY) ACETOPHENONE
from
4-(4'-NITRO PHENOXY) ACETOPHENONE



Procedure:

Dissolve 5 grams of 4-(4'-nitro phenoxy) acetophenone in one hundred and fifty c.c. of hot alcohol and place in the reducing machine. Larger quantities may be used if desired as the product is readily soluble in hot alcohol. Use 0.2 grams of platinum oxide as a catalyst and reduce in a hydrogenation machine under 45-50 pounds of pressure. The reaction is complete in about fifteen minutes, absorbing the theoretical amount of hydrogen. The mixture was filtered to remove the platinum oxide and poured into finely crushed ice. The amine product separates out as a fine white flaky precipitate, giving a quantitative yield of the compound. 4-(4'-Amino phenoxy) acetophenone crystallized from ethyl alcohol and the melting point of the purified compound is 123°C. The yield was 3.98 grams which is ninety percent of the theoretical yield.

PREPARATION OF
4-(4'-IODO PHENOXY) ACETOPHENONE
from
4-(4'-AMINO PHENOXY) ACETOPHENONE



Procedure:

Five grams of 4-(4'-amino phenoxy) acetophenone, finely powdered are dissolved in fifteen to twenty c.c. of glacial acetic acid. To this solution is added fifteen c.c. of concentrated sulfuric acid (the sulfate does not go into solution).m Cool the mixture to 0° C. and add 2.5 grams of sodium nitrite dissolved in ten to fifteen c.c. of water. Add the sodium nitrite solution slowly and keep the temperature of the mixture below 5°C. After all the sodium nitrite solution has been added let the solution stand in the ice bath for ten minutes. The diazo compound is then added slowly to a solution of four grams of potassium iodide dissolved in twenty five c.c. of water, containing crushed ice. Continue stirring for a few minutes after all the diazo product has been added. Place the solution on a water bath and gradually bring to 70°C. and maintain this temperature until the evolution of gases ceases. A brown precipitate of 4-(4'-iodo phenoxy) acetophenone separates from the solution upon cooling. Sodium acid sulfate is added to remove the excess iodine. The solution is filtered and washed thoroughly with water.

4-(4'-Iodo phenxoy) acetophenone crystallizes from heptane giving a light yellow product which melts sharply at 96.5°C.

Analysis:

Calculated percent iodine (for $C_{14}H_{11}O_2I$; molecular weight of 338.0) = 37.57% Found: 37.22%

1) Weight of sample - - - - - - - - - - - - - - 0.1758

Standard $AgNO_3$ solution used (1 c.c. .00635 grams of Iodine) - - - - - - - - - - - - - - 10.32 c.c.

Weight of iodine in sample - - - - - - - - - - - 0.0655 gm.

Percent of Iodine in sample - - - - - - - - - - 37.22

Found 37.08%

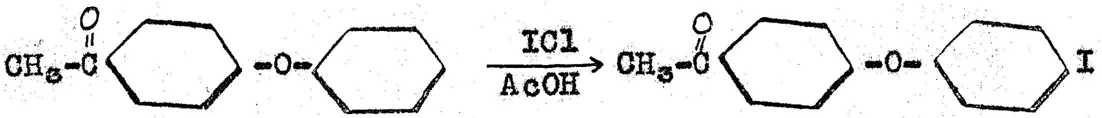
2) Weight of sample - - - - - - - - - - - - - - 0.1586 gm.

Standard $AgNO_3$ solution used (as above) - - - - 9.27 c.c.

Weight of iodine is sample - - - - - - - - - - 0.0588

Percent of Iodine in sample - - - - - - - - - - 37.08%

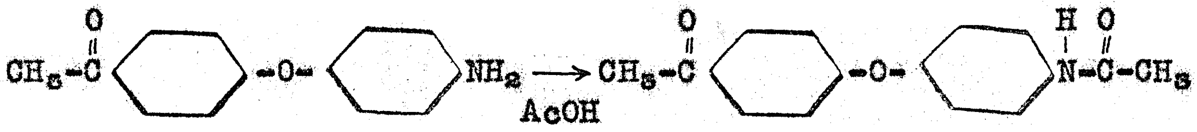
PREPARATION OF
4-(4'-IODO PHENOXY)ACETOPHENONE
from
4-PHENOXY ACETOPHENONE



Procedure:

Five grams of 4-phenoxy acetophenone were dissolved in 15 c.c. of glacial acetic acid. To this was added a calculated amount of iodine monochloride (4 grams) in small portions. The reaction is spontaneous with much hydrogen being given off. After all the iodine monochloride has been added the solution was refluxed for three hours. The mixture was then poured into cracked ice and the product separates out as a black tarry mass. A solution of sodium disulfite was added to remove any free iodine. The mass was then extracted with ether, separated and dried. The ether was allowed to evaporate leaving a reddish oil. This was taken up in heptane and allowed to slowly evaporate. Yellow crystals separated out which gave a melting point of 96°C. A mixed melting point of this iodo compound and that prepared from 4-(4'-amino phenoxy) acetophenone gave no depression, thus proving that the iodine entered the ring in the 4'- position.

PREPARATION OF
4-(4'-ACETAMINO PHENOXY) ACETOPHENONE
from
4-(4'-AMINO PHENOXY) ACETOPHENONE



Procedure:

Twenty two grams of 4-(4'-amino phenoxy) acetophenone were dissolved in thirty c.c. of acetic acid (glacial), thirty c.c. of acetic anhydride added, and the resulting solution was boiled under reflux for fifty hours. The reaction is complete if one drop of the solution when placed in cold water crystallizes out as a solid; if as an oil, reflux some more. When the reaction is complete add enough acetic acid to quadruple the volume. Then pour slowly into cold water, agitating at the same time. A brown precipitate is obtained, which can be purified from hot water and charcoal. As the product is only slightly soluble in water, it takes a large volume of water and considerable time to purify a small amount. However, the product comes out as a white flaky compound, which melts sharply at 146°C. The yield was seventy percent of the theoretical.

Analysis:

Sample No. 1 Wt. of sample = 0.3784 gm.

c.c. of acid used = 3.02 N of acid = .4733N

$$x = \frac{(3.02)(.4733)(.03505)(.3977)}{.3784}$$

x = 5.27% of Nitrogen

Sample No. 2 Wt. of sample = 0.4125 gm.

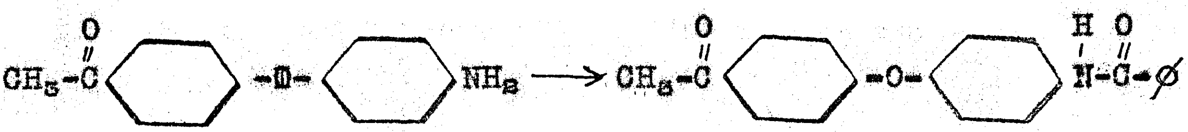
c.c of acid used = 3.22 N of acid = .4733N

$$x = \frac{(3.22)(.4733)(.03505)(.3977)}{.4125}$$

x = 5.15% of nitrogen

Calculated theoretical percent of nitrogen = 5.20%

PREPARATION OF
4-(4'-BENZOYL AMINO PHENOXY) ACETOPHENONE
from
4-(4'-AMINO PHENOXY) ACETOPHENONE



Procedure:

To ten grams of 4-(4'-amino phenoxy) acetophenone add the theoretical amount (6.25 grams) of benzoyl chloride and fifty c.c. of ten percent sodium hydroxide solution. Shake in a stoppered flask until the odor of the bengoyl chloride has completely disappeared. The mass becomes whiter and finally a white solid. After thoroughly washing with water, the product is recrystallized from ethyl alcohol. The melting point is from 144° to 145°C. The yield is ninety percent of the theoretical.

Analysis:

Sample No. 1 Wt. of sample = 0.4946 gm.

c.c. of acid used = 3.29 c.c. N of acid = .4733N

$$x = \frac{3.29(.4733)(.03505)(.3997)}{.4946}$$

x = 4.41%

Sample No. 2 Wt. of sample = 0.5394 gm.

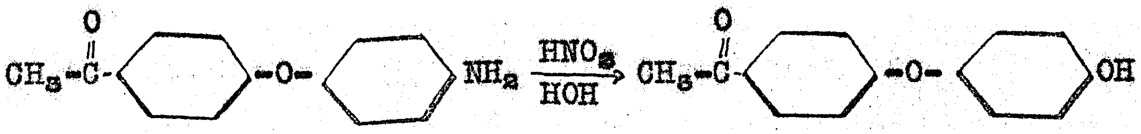
$$x = \frac{(3.50)(.4733)(.03505)(.3997)}{.5394}$$

c.c. of acid = 3.50

x = 4.30%

Calculated theoretical % of N = 4.23%

PREPARATION OF
4-(4'-HYDROXY PHENOXY) ACETOPHENOME
from
4-(4'°AMINO PHENOXY PHENXOY) ACETOPHENONE



Procedure:

Five grams of 4-(4'-amino phenoxy) acetophenone are finely powdered and stirred into a slightly warmed mixture of fifteen c.c. of concentrated sulfuric acid and twenty c.c. of water, giving a greenish-colored mixture. Fifty grams of crushed ice were added to the solution which had been placed in and ice-salt bath, lowering the temperature to 0°C. Then 1.8 grams of sodium nitrite in ten c.c. of water were added. The greenish-colored mixture then turned a brownish color, and was completely in solution. After allowing the solution to stand for ten to fifteen minutes with frequent stirring the cold diazo product was added to a boiling solution of 120 grams of concentrated sulfuric aicd and 90 grams of water. The solution will boil around 155° to 160°C. It is better to add this product by means of a reflux condenser, in this way preventing the loss of water. The product should not be added too rapidly as it will froth up a great deal, due to the liberation of nitrogen. This addition should require ten to fifteen minutes. The solution is cooled with ice which produces a flaky brown precipitate. The product is filtered and washed thoroughly to remove all the sulfuric acid. 4-(4'-Hydroxy phenoxy) acetophenone is purified by recrystallizing from hot water, in which it is only slightly soluble. It can also be recrystallized from heptane. The melting point of this compound is 153°C., and the yield was about sixty percent of the theoretical.

ATTEMPTED PREPARATION OF
4-(3',5'-DI-IODO-4'-HYDROXY PHENOXY) ACETOPHENONE
with NI_3

Procedure:

Five grams of 4-(4'-hydroxy phenoxy) acetophenone is dissolved in forty c.c. of ammonium hydroxide. To this ammoniacal solution is added eleven grams of iodine dissolved in potassium iodide. After one half of the iodine has been added the iodo compound begins to separate from the solution as a brownish black substance. When the addition of iodine-potassium iodide is complete, the solution is made acid and filtered. The precipitate is washed thoroughly with a dilute soldium bisulfite solution and then with water.

Attempts to purify this light yellow colored compound, which had a distinct odor of iodoform, failed. The iodine analysis was not satisfactory. This iodo compound proved to be very toxic to tadpoles, killing all of the test batch within thirty minutes.

The explanation of the formation of iodoform is given on page 21. It was therefore necessary to use some other method of iodination besides NI_3 and 4-(4'-hydroxy phenoxy) acetophenone. The procedure found to be successful was the treatment of 4-(4'-hydroxy phenoxy) acetophenone with iodine, mercuric oxide, and alcohol.

EXPERIMENTAL

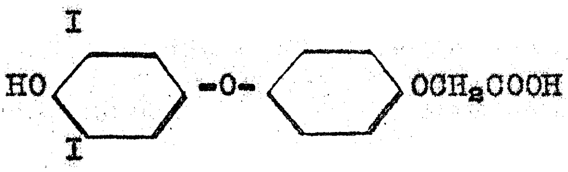
SERIES III

4-PHENOXY PHENOXY ACETIC ACID DERIVATIVES

SERIES III

4-Phenoxy Phenoxy Acetic Acid Series

Synthesis of



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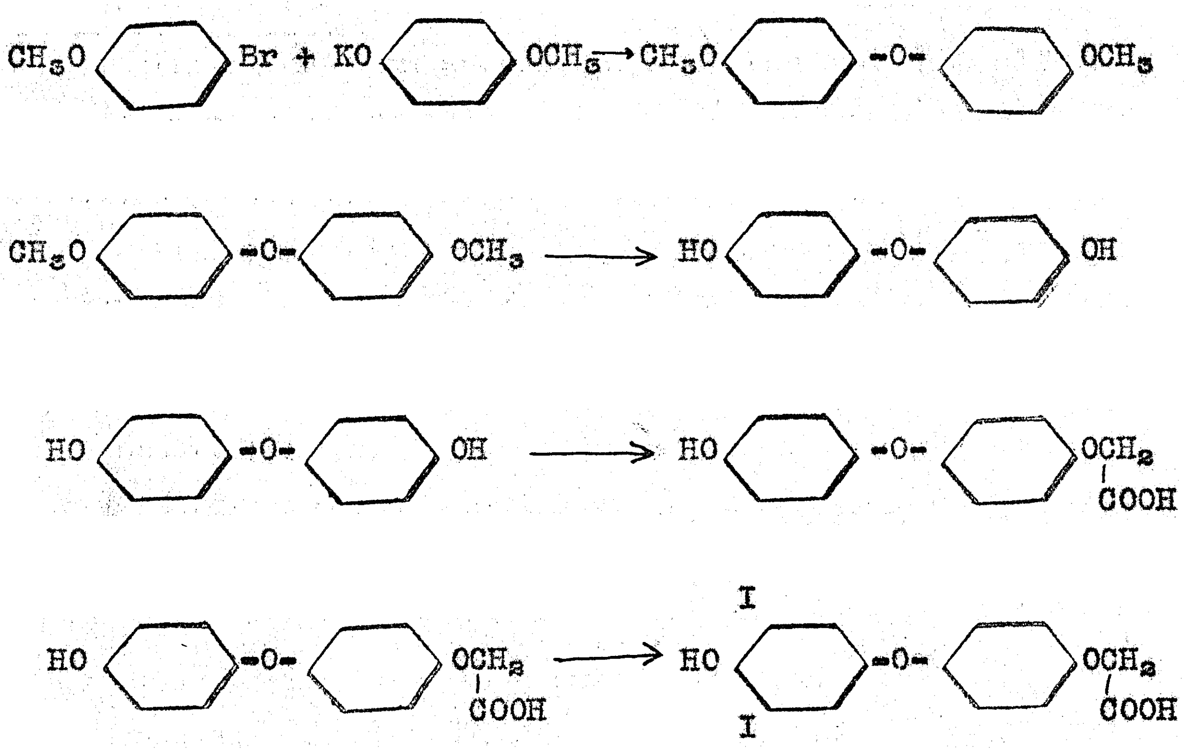
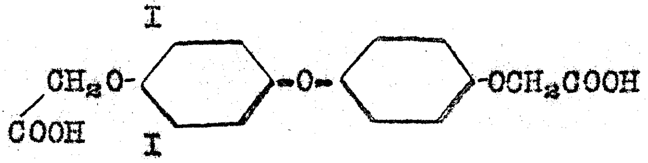


SERIES III
(CONTINUED)

Synthesis of



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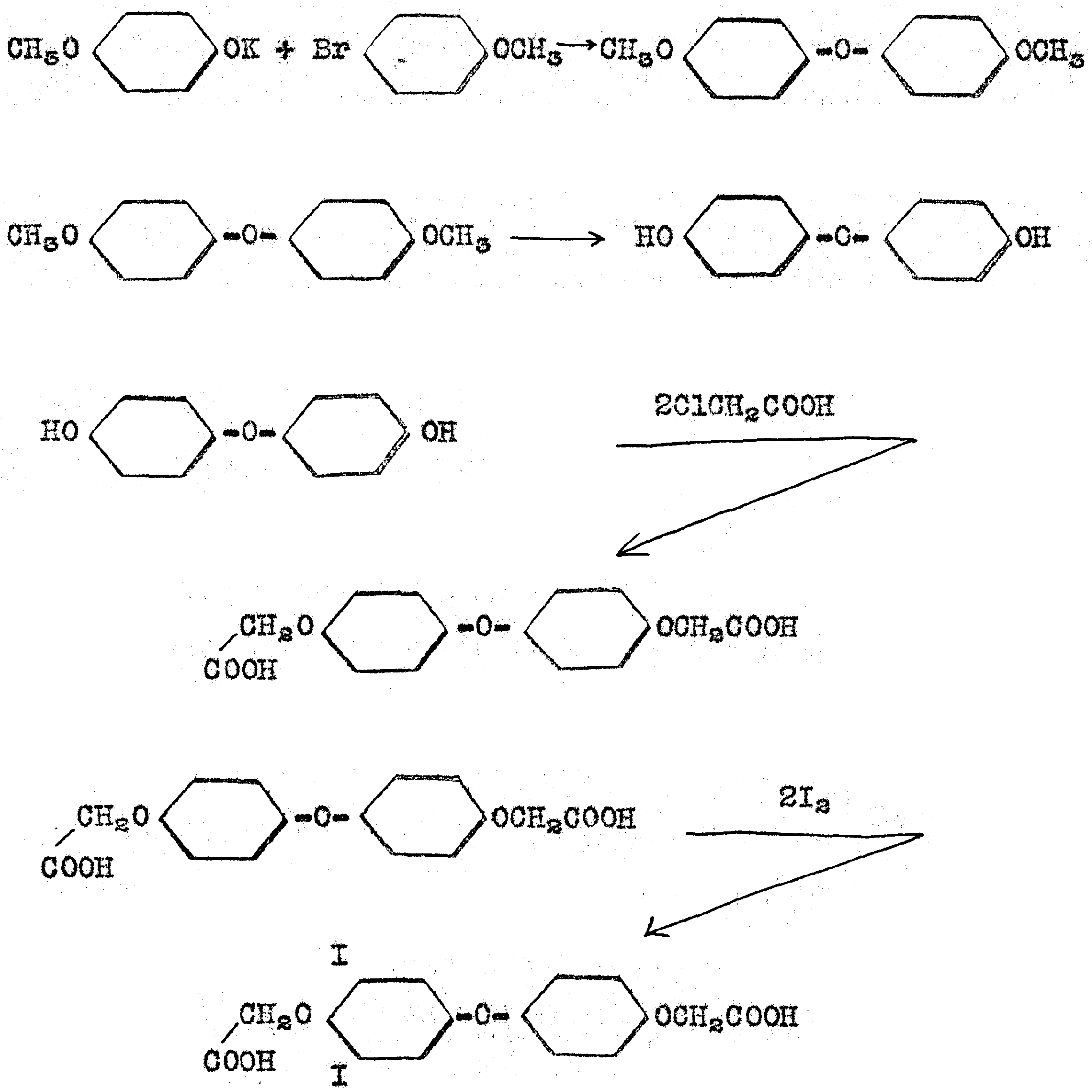
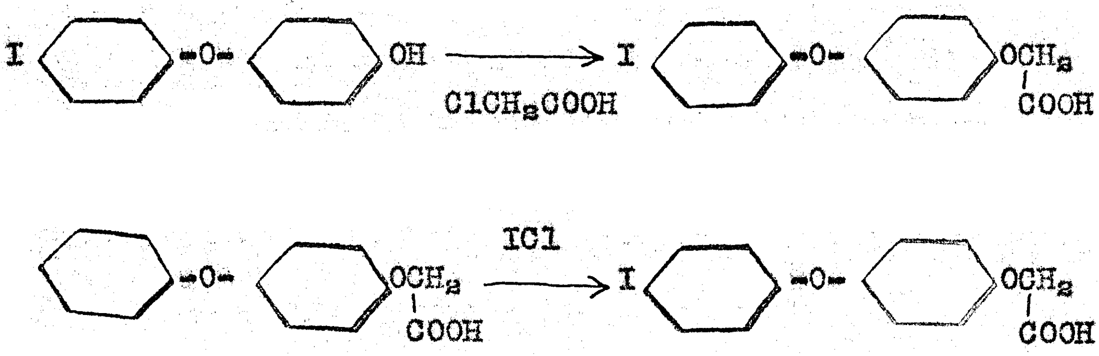


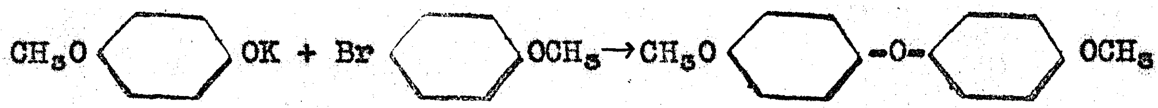
4-(4'-IODO PHENOXY) PHENOXY ACETIC ACID

Synthesis of

by



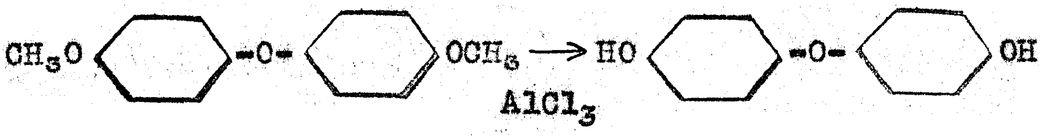
PREPARATION OF
4-4'-DIMETHOXY DIPHENYL ETHER
from
MONOMETHYL ETHER OF HYDROQUINONE and BROMANISOLE



Procedure:

Seventy grams of monomethyl ether of hydroquinone were melted and heated to reaction with 28.4 grams of potassium hydroxide. The salt formed was heated to 160°C. on an oil bath to remove the water formed. When cooled, 90 grams of p-bromo-anisole were added with a little copper bronze. The mixture was heated under a reflux condenser on an oil bath at 200°C. for three and one half hours. The solid was extracted with dilute alkali to recover the excess monomethyl ether, and steam distilled to remove the excess bromo-anisole. The residue was washed with water several times, filtered, and the solid crystallized from hot alcohol. The product formed white leaf crystals which melted at 103 to 104°C. The yield was sixty grams.

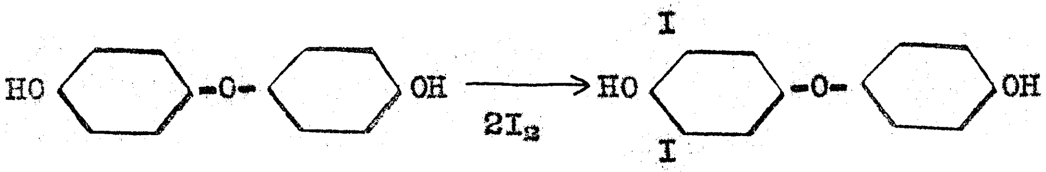
PREPARATION OF
4-(4'-HYDROXY PHENOXY) PHENOL



Procedure:

Twenty grams of 4-4'-dimethoxy diphenyl ether were heated with forty grams of anhydrous aluminum chloride and the product fused with the evolution of hydrogen chloride on an oil bath for one and one half hours at 145° to 150°C. Water and hydrochloric acid (3:1) were slowly added to decompose the aluminum salts. The mixture was allowed to stand overnight. The solid formed was filtered off, extracted with sodium hydroxide solution, filtered, and precipitated cold with dilute hydrochloric acid. The precipitate crystallized from boiling water in gray flakes which melted at 160°C. The yield is fourteen grams.

PREPARATION OF
4-(3',5'-DI-IODO-4'-HYDROXY PHENOXY) PHENOL
from
4-(4'-HYDROXY PHENOXY) PHENOL and NITROGEN IODIDE



Procedure:

Four grams of 4-(4'-hydroxy phenoxy) phenol were dissolved in fifty c.c. of ammonium hydroxide. Ten grams of iodine were dissolved in a solution of potassium iodide and added to the above ammonium salt. After the addition of the iodine was complete the solution was stirred for thirty minutes more. The mix was poured into a dilute hydrochloric acid solution, which separates the 4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenol as a black mass. A dilute solution of sodium bisulfite was added to remove any excess iodine. The solution is filtered and washed with hot alcohol as the di-iodo compound is not soluble, while the 4-(4'-hydroxy phenoxy) phenol is. Attempts to obtain the product other than black failed although the analysis checks with the calculated amount for iodine. The yield is two grams and the melting point of the 4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenol is 240°C. with liberation of iodine.

Analysis:

Calculated percent of iodine (for $C_{12}H_8O_3I_2$; molecular weight of 454) = 55.94%

1) Found 55.01%

Weight of sample - - - - - - - - - - - - - - - - - - .188

Std. $AgNO_3$ sol'n used (1 c.c. .00635 g. of I)- - - 16.28

Wt. of Iodine in sample - - - - - - - - - - - - - - .1034

Percent of Iodine in sample - - - - - - - - - - - - 55.01%

2) Found 54.88%

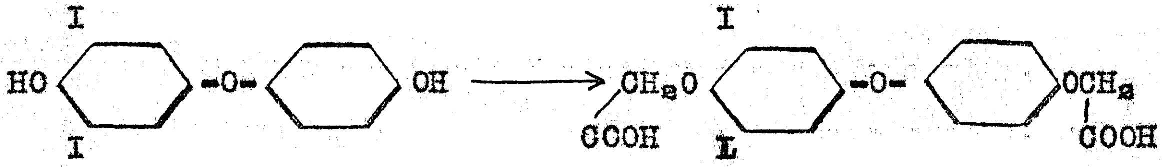
Weight of sample - - - - - - - - - - - - - - - - - - .1348

Std. $AgNO_3$ sol'n used (1 c.c. .00635 g. of I)- - - 11.65

Wt. of Iodine in sample - - - - - - - - - - - - - - .0739

Percent of Iodine in sample - - - - - - - - - - - - 54.88%

PREPARATION OF 4-4'-(3',5'-DI-IODO)-BIS-OXY ACETIC ACID DIPHENYL ETHER from 4-4'-(3',5'-DI-IODO) DIHYDROXY DIPHENYL ETHER and CHLORO ACETIC ACID



Procedure:

Two grams of 4-4'-(3',5'-di-iodo) dihydroxy diphenyl ether were mixed with one gram of chloro acetic acid. To this was added a strong solution of sodium hydroxide. After the reaction which is spontaneous had subsided the mixture is heated for fifteen minutes. The mix is diluted with water and the sodium salt of the di-iodo compound does not go in solution. The precipitate is made acid and filtered. The yield was about 1.5 grams of a dark brown compound. The melting point of 4-4'-(3',5'-di-iodo)-bis-oxy acetic acid diphenyl ether was above 285°C. although iodine is liberated at 250°C.

Analysis:

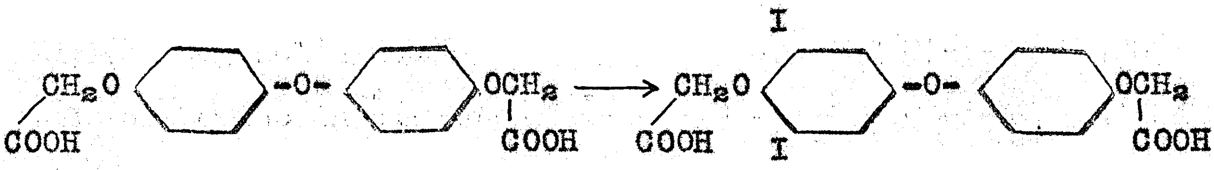
Calculated percent of Iodine (for $C_{16}H_{12}O_7I_2$; molecular weight = 570) = 43.33%

1) Found 42.93%

Weight of sample - - - - - - - - - - - - - - - - .1280

Std. $AgNO_3$ sol'n used (1 c.c. .00635 g. of I)	8.67
Weight of Iodine in sample	.0550
Percent of Iodine in sample	42.93%
2) Found 43.01%	
Weight of sample	.1456
Std. $AgNO_3$ sol'n used (as above)	10.01
Weight of Iodine in sample	.0636
Percent of Iodine in sample	43.01%

PREPARATION OF
4-4'-(3'5'-DI-IODO)-BIS-OXY ACETIC DIPHENYL ETHER
from
4-4'-BIS-OXY ACETIC ACID DIPHENYL ETHER and NITROGEN IODIDE



Procedure:

Three grams of 4-4'-bis-oxy acetic acid diphenyl ether is dissolved in thirty five c.c. of ammonium hydroxide. To this is added thirty seven c.c. of 0.1N solution of iodine in potassium iodide. This solution is stirred during the addition of the iodine and one half hour longer to complete the reaction. The mix is poured in ice and dilute hydrochloric acid, and the product separates out as a dark brown mass. A dilute solution of sodium bisulfite is added to remove the excess iodine. The mixture is then filtered and washed with water. The melting point of the impure product is 110°C. As the di-iodo product is not soluble in hot ethyl alcohol, and the 4-4'-di-oxy acetic acid diphenyl ether is, this gave a method to remove any unreacted starting products. The precipitate was refluxed with ethyl alcohol and filtered while hot. The di-iodo compound became lighter in color.

The melting point of the compound was above 285°C. liberating iodine at 250°C.

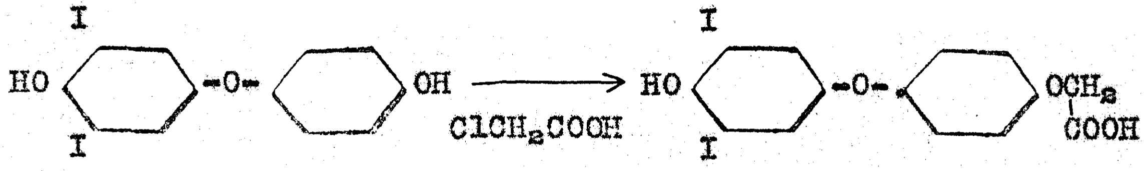
Analysis:

Calculated percent of Iodine (for $C_{16}H_{12}O_7I_2$; molecular weight = 570) = 43.33%

1) Found 43.61%

Weight of sample	.1545
Std. $AgNO_3$ sol'n used (1 c.c. .00635 g. of I)	10.60
Weight of Iodine in sample	.0674
Percent of Iodine	43.61%

PREPARATION OF
4-(3',5'-DI-IODO-4'-HYDROXY PHENOXY) PHENOXY ACETIC ACID
from
4-(3',5'-DI-IODO-4'-HYDROXY PHENOXY) PHENOL and CHLORACETIC ACID



Procedure:

Two grams of 4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenol were reacted with one half gram of chloro acetic acid and a concentrated sodium hydroxide solution. The mixture was heated for one hour on the water bath and then poured into ice and dilute hydrochloric acid which separates out a brownish crystalline mass. 4-(3'5'-di-iodo-4'-hydroxy phenoxy) phenoxy acetic acid was exceedingly difficult to purify as it is very insoluble in most of the ordinary solvents. Making the sodium salt of this di-iodo compound, boiling with charcoal and acidifying with hydrochloric acid gave a compound which analyzed satisfactorily. The melting point of the product was above 250°C., although iodine is liberated at 230°C. As this is supposed to be the same product as that formed by iodination of 4-(4'-hydroxy phenoxy) phenol, a mixed melting point was made. The melting point of the mixture was undepressed, thereby indicating that the compounds were identical.

Analysis:

Calculated percent for iodine (for $C_{14}H_{10}O_5I_2$; molecular weight = 512) = 49.60%

1) Found 48.9%

Weight of sample - - - - - - - - - - - - - - - - .1423

Std. $AgNO_3$ sol'n used (1 c.c. .00635 g of I) - 10.95

Weight of Iodine - - - - - - - - - - - - - - - .0695

Percent of Iodine - - - - - - - - - - - - - - 48.90%

2) Found 49.13%

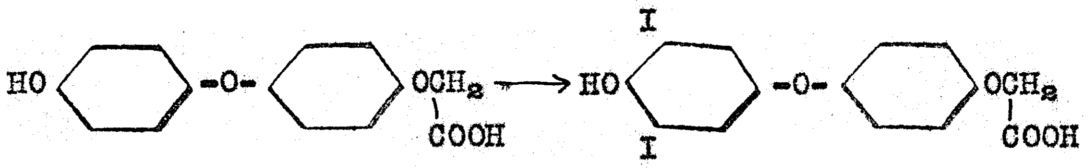
Weight of sample - - - - - - - - - - - - - - - .1227

Std. $AgNO_3$ Sol'n used (as above) - - - - - - - - 9.49

Weight of Iodine - - - - - - - - - - - - - - - .0603

Percent of Iodine - - - - - - - - - - - - - - 49.13%

PREPARATION OF
4-(3',5'-DI-IODO-4'-HYDROXY PHENOXY) PHENOXY ACETIC ACID
from
4-(4'-HYDROXY PHENOXY) PHENOXY ACETIC ACID and IODINE



Procedure:

Three grams of 4-(4'-hydroxy phenoxy) phenoxy acid were dissolved in ammonium hydroxide. To this mixture while being mechanically stirred is added six grams of iodine dissolved in potassium iodide solution. The mix is allowed to stir for one hour after the iodine solution has been added. The solution is then poured into dilute hydrochloric acid containing cracked ice. Sodium bisulfite is added to remove the excess iodine. The precipitate that comes down is brownish black and formed a soluble sodium salt, which was boiled with charcoal and reacidified. The product thus formed was light brown and gave an iodine test with concentrated sulfuric acid. As this brownish precipitate was not soluble in heptane it was washed thoroughly with heptane to remove the unchanged 4-(4'-hydroxy phenoxy) phenoxy acetic acid. The yield was only about 60%, and the melting point was above 250°C. Analysis of the compound shows that it contains two iodines.

Analysis:

Calculated percent of Iodine)for $C_{14}H_{10}O_5I_2$; molecular weight = 512) = 49.60%

1) Found 48.73%

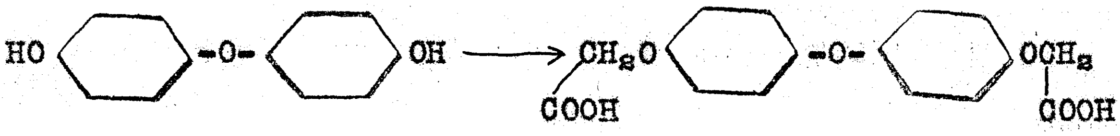
Weight of Sample - - - - - - - - - - - - - - - - - - .1657

Std. $AgNO_3$ Sol'n used (1 c.c. .00635 g. of I) - - - 12.71

Weight of Iodine - - - - - - - - - - - - - - - - - - .0807

Percent of Iodine - - - - - - - - - - - - - - - - - 48.73%

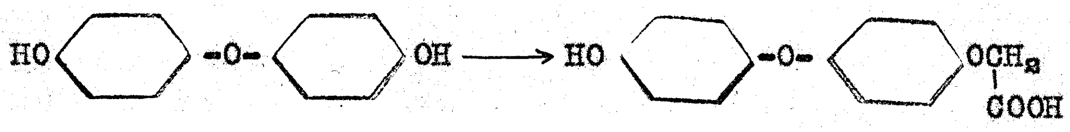
PREPARATION OF
4-4'-BIS-OXY ACETIC ACID DIPHENYL ETHER
from
4-4'-DIHYDROXY DIPHENYL ETHER and CHLOROACETIC ACID



Procedure:

Five grams of 4-4'-dihydroxy diphenyl ether and eleven grams of chloroacetic acid were melted together. To this was added a concentrated solution of sodium hydroxide. The reaction is spontaneous and evolves much heat. After the addition of sodium hydroxide is complete the mixture is diluted with water and boiled for ten to fifteen minutes. The solution is acidified, filtered and washed thoroughly with water. The product comes out as white flakes which turn brown upon drying. The compound can be purified from heptane, and benzene and comes out as snowy white flakes. The yield is seventy five percent of the theoretical and the melting point of the pure compound is 188°C.

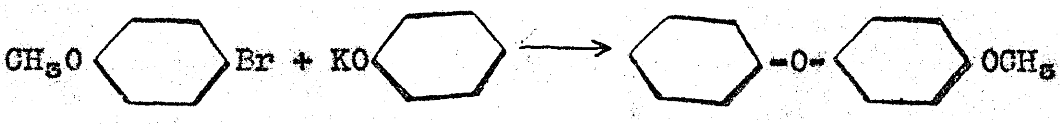
PREPARATION OF
4-(4'-HYDROXY PHENOXY) PHENOXY ACETIC ACID
from
4-(4'-HYDROXY PHENOXY) PHENOL and CHLOROACETIC ACID



Procedure:

Five grams of 4-(4'-hydroxy phenoxy) phenol were melted with three grams of mono chloro acetic acid. To this melt was added two grams of sodium hydroxide in just enough water to dissolve it. The reaction is spontaneous and care should be taken not to add the sodium hydroxide solution too rapidly. After the initial reaction had 10 c.c. of water was added and the solution heated for fifteen minutes. The solution was then poured into ice and dilute hydrochloric acid. 4-(4'-Hydroxy phenoxy) phenoxy acetic acid is precipitated as a white solid. It is then dried on a plate and repurified from heptane. The product comes out white and melts sharply at 147°C. The yield was seventy percent of the theoretical.

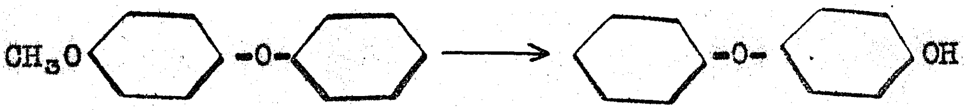
PREPARATION OF 4-METHOXY DIPHENYL ETHER from 4-BROMO ANISOLE and POTASSIUM PHENOLATE



Procedure:

To sixty seven grams (slight excess) of phenol add fifty grams of solid potassium hydroxide. Without a reflux condenser heat this mixture to 185°C. on an oil bath, stirring frequently, to drive off the water. Keep the substance at 185°C. for ten minutes and then allow it to cool to 145°C. and add 122 grams of 4-bromo anisole and copper catalyst. Then heat the mixture at 190°C. for one hour. After one hour continue heating at 210°C. for another hour. Pour the mixture into five hundred c.c. of water and add three hundred c.c. of chloroform. Stir the mixture well and separate the chloroform layer which contains the methoxy product. Shake the aqueous portion again with more chloroform and separate as before. The chloroform was distilled off and the remaining oil distilled in vacuum. That portion distilling between 150° and 185°C. was collected. The product is a pâle yellow liquid whose boiling point is 178°C. at 20 mm. of pressure. The yield was fifty three percent of the theoretical.

PREPARATION OF
4-HYDROXY DIPHENYL ETHER
from
4-METHOXY DIPHENYL ETHER

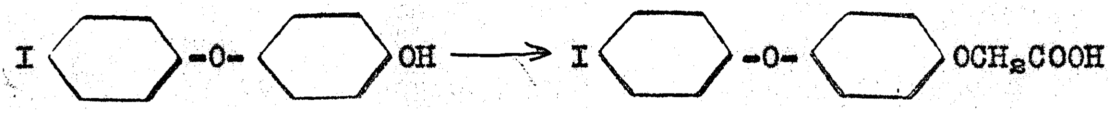


Procedure:

Seventeen grams of aluminum chloride was added in small portions to twenty five grams of 4-methoxy diphenyl ether. The mixture was shaken a fter each addition with occasional warming in an oil bath which was never over 110°C. until dissolved. This was continued until all the aluminum chloride was added. The mixture was then heated for thirty minutes in an oil bath, the temperature being kept at 120° to 130°C. Two grams of aluminum chloride was then added and shaken into solution as before. The mix was then heated another thirty minutes between 140° and 150°C. The mix was then cooled, powdered, and added to four hundred c.c. of water containing a small amount of hydrochloric acid. After this addition the mixture was allowed to stand for twenty minutes with occasional stirring. A little chloroform was then added to dissolved the oils. The chloroform layer was separated and the other fraction was haken with another portion of chloroform.

The chloroform mixture was twice treated with five percent sodium hydroxide solution to remove the 4-hydroxy diphenyl ether. This portion was then removed and acidified. The hydroxy product which separates is then redissolved in chloroform and the chloroform is recovered by distillation. The hydroxy product is distilled in vacuum. That fraction which distills between the temperatures of 180° and 215°C. is collected. The boiling point of the pure 4-hydroxy diphenyl ether is 195°C.

PREPARATION OF
4-(4'-IODO PHENOXY) PHENOXY ACETIC ACID
from
4-(4'-IODO PHENOXY) PHENOL and CHLOROACETIC ACID
METHOD I



Procedure:

To two grams of 4-(4'iodo phenoxy) phenol there was added one gram of chloroacetic acid. To this mixture a strong sodium hydroxide solution was added. An instantaneous reaction occurs, and the mixture is then heated for fifteen minutes to insure complete reaction. The mixture is then filtered to remove the sodium salt of 4-(4'-iodo phenoxy) phenoxy acetic acetic acid from the starting material as the sodium salt of 4-(4'-iodo phenoxy) phenol is soluble. This precipitate which is white is made acid with dilute hydrochloric acid. The 4-(4'-iodo phenoxy) phenoxy acetic acid is purified from ethyl alcohol and begins to shrink at 200°C. and finally melts at 304°C. A mixed melting point of this compound with that prepared from direct iodination of 4-phenoxy phenoxy acetic acid showed no depression, thus proving that the two compounds are identical.

Analysis:

Calculated percent of Iodine (for $C_{14}H_{11}O_4I_1$; molecular weight = 370) = 34.32%

1) Found 34.12%

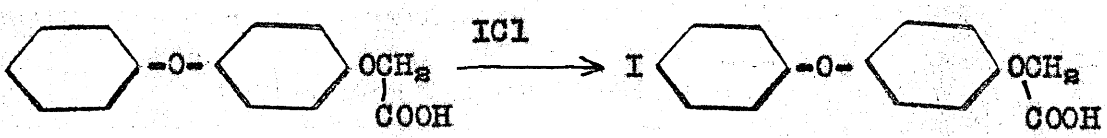
Weight of sample - - - - - - - - - - - - - - - - - .1330

Std. $AgNO_3$ sol'n used (1 c.c. .00635 g. of I)- - 7.15

Weight of Iodine in sample - - - - - - - - - - - - .0453

Percent of Iodine in sample - - - - - - - - - - - 34.12%

PREPARATION OF
4-(4'-IODO PHENOXY) PHENOXY ACETIC ACID
from
4-PHENOXY PHENOXY ACETIC ACID and IODINE MONOCHLORIDE
METHOD II



Procedure:

Dissolve three grams of 4-phenoxy phenoxy acetic acid in ten c.c. of glacial acetic acid. To this is then slowly added 3.37 grams of iodine monochloride dissolved in a small amount of acetic acid. The solution is refluxed for three hours on a water bath, after which it is poured into cracked ice. A dilute solution of sodium bisulfite is added to remove any excess iodine, and the mixture is filtered. 4-(4'-Iodo phenoxy) phenoxy acetic acid can be purified by recrystallization from heptane, giving a compound which melts above 250°C. A mixed melting point made using the above compound with the iodo product obtained from 4-(4'-iodo phenoxy) phenol, gave no depression thus indicating that the two compounds are the same.

EXPERIMENTAL

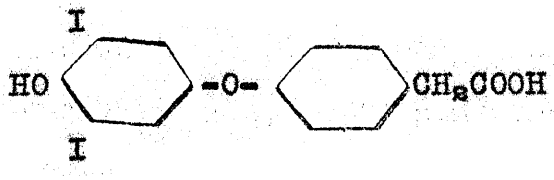
SERIES IV

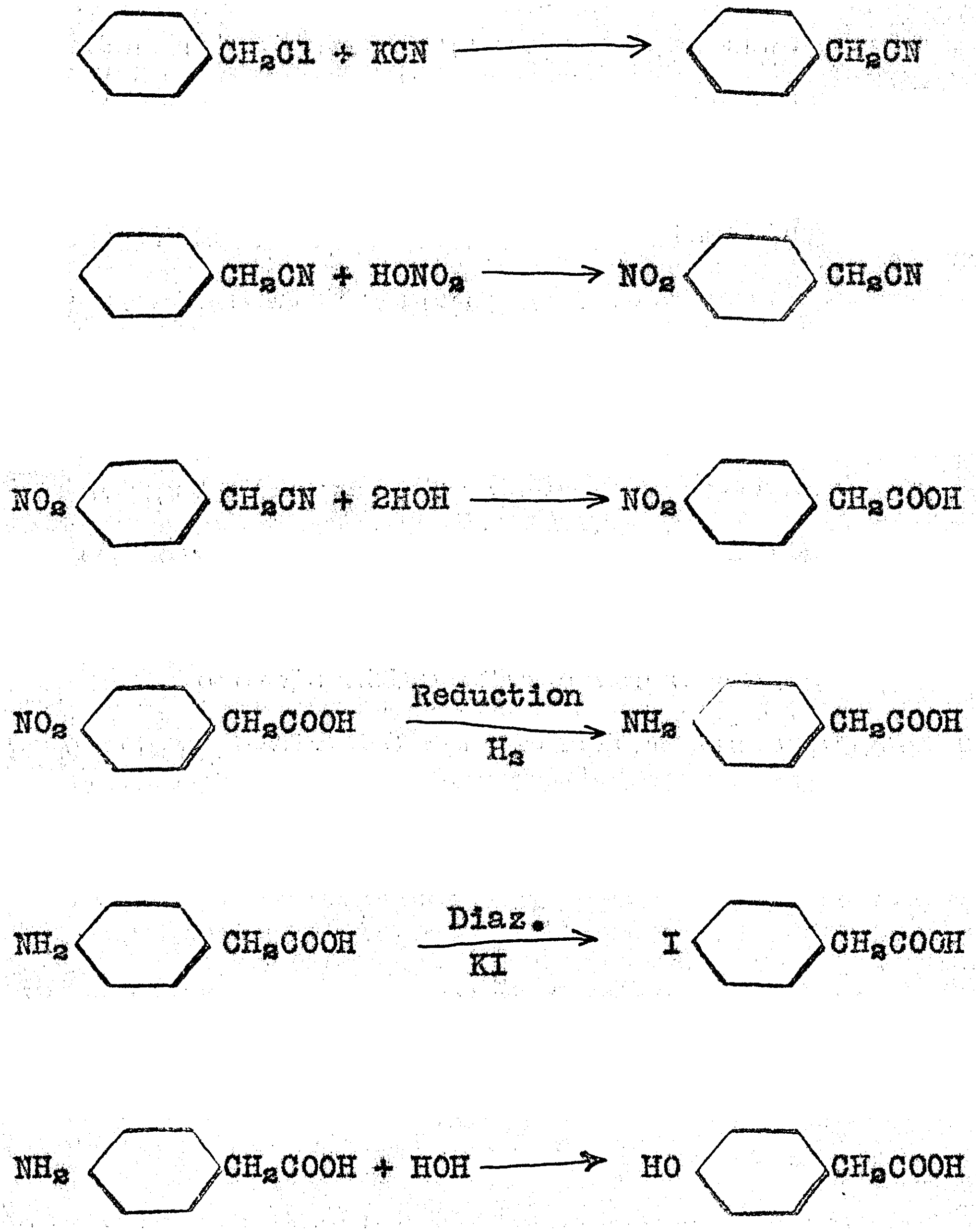
4-PHENOXY PHENYL ACETIC ACID DERIVATIVES

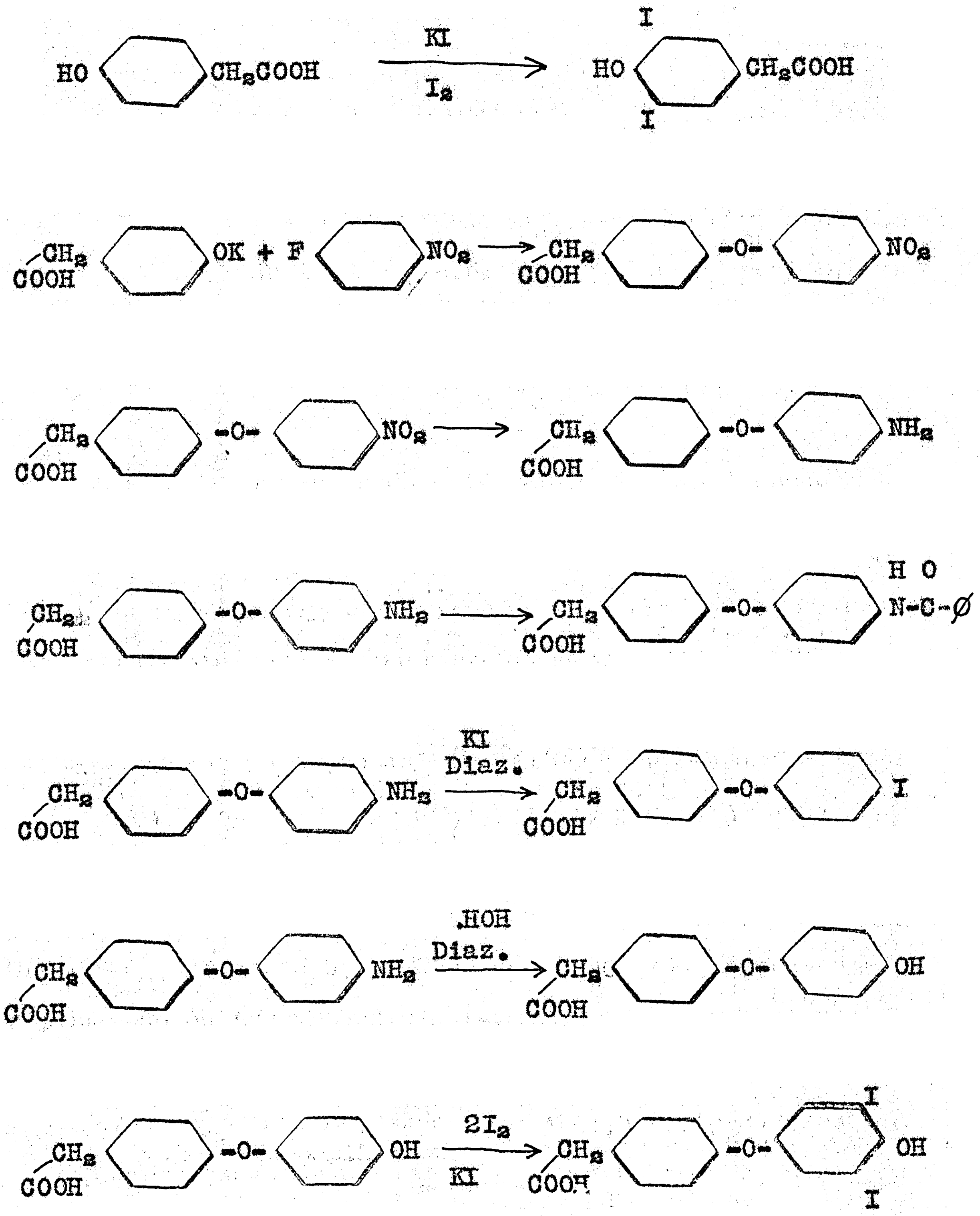
SERIES IV

4-PHENOXY PHENYL ACETIC ACID SERIES

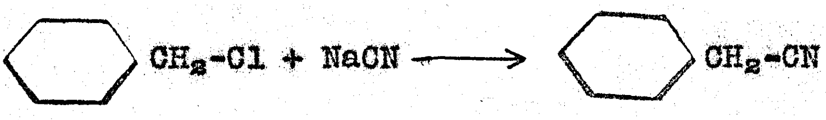
SYNTHESIS OF






HO
CH2COOH
KI
I2
I
OK + F
NO2
CH2
COOH
-O-
NH2
H O
N-C-Ø
KI
Diaz.
.HOH
OH
2I2

PREPARATION OF BENZYL CYANIDE from BENZYL CHLORIDE and SODIUM CYANIDE



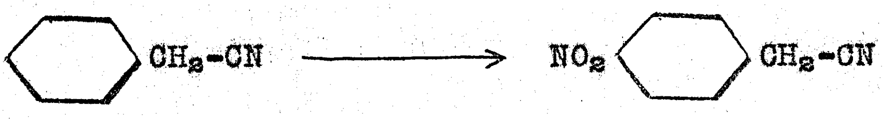
Procedure[87]:

In a five liter round-bottom flask, fitted with a stopper holding a reflux condenser and separatory funnel, are placed five hundred grams of powdered sodium cyanide and 450 c.c. of water. The mixtureis warmed on a water bath in order to dissolve most of the sodium cyanide, and then 1000 grams of benzyl chloride mixed with 1000 grams of 95% ethyl alcohol is run through the separatory funnel in the course of one-half to three quarters of an hour. The mixture is heated under a reflux condenser on the steam bath for four hours, cooled and filtered with suction to remove most of the sodium chloride. It is well to wash the filtered salt with a small portion of alcohol in order to remove any benzyl cyanide which may have been mechanically held.

The flask is now fitted with a condenser, and as mush alcohol as possible is distilled off on the steam bath. The residual liquid is cooled, filtered if necessary and the layer of benzyl cyanide is now placed in a

Claisen flask and distilled under reduced pressure, the water coming over first, and finally the benzyl cyanide. It is advantageous to use a fractionating column or, bettersstill, a Claisen flask with a modified side arm which gives the same effect as a fractionating column. The material is collec ted at 120° to 135°C. and the yield is 740 to 830 grams.

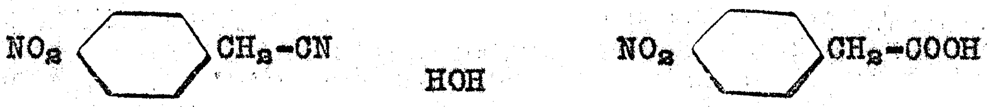
PREPARATION OF
4-NITRO BENZYL CYANIDE
from
BENZYL CYANIDE and NITRIC ACID



Procedure[37]:

In a 2 liter round bottom flask, fitted with a stopper holding a dropping funnel and a mechanical stirrer, is placed a mixture of 275 c.c. of concentrated sulfuric acid(4.9 m., sp.gr. 1.8) and concentrated nitric acid (4.3 m. sp. gr. 1.4). This is cooled to 10°C. in a freezing mixture and 100 grams of benzyl cyanide is run in slowly at such a rate that the temperature is about 10°C. and does not exceed 20°C. After all the benzyl cyanide has been added, the ice bath is removed, the mixture stirred for an hour and then poured into 1200 grams of ice. A pasty mass slowly separates; more than half of this mass is 4-nitro benzyl cyanide, the other constituents being o-nitro benzyl cyanide and a variable amount of an oil which resists hydrolysis; apparently no dinitro compounds are formed. The mass is filtered on a steam funnel and dissolved in 500 c.c. of boiling 95% alcohol. On cooling 4-nitro benzyl cyanide crystallizes; the mother liquid, on distillation, give an impure alcohol which can be used for the next run. Recrystallization from 550 c.c. of 80% alcohol yield 70 to 75 grams of product which melts at 115° to 116°C.

PREPARATION OF
4-NITRO PHENYL ACETIC ACID
from
4-NITRO BENZYL CYANIDE by HYDROLYSIS

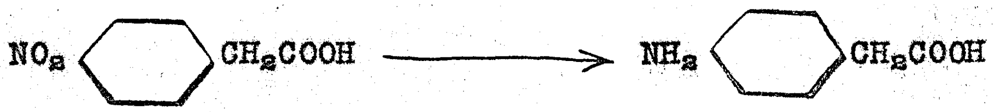


Procedure:

In a 1 liter round bottom flask is placed 100 grams of 4-nitro benzyl cyanide. A solution of 300 c.c. of concentrated sulfuric acid in 280 c.c. of water is prepared, and two-thirds of this solution is poured onto the 4-nitro benzyl cyanide. The mixture is shaken well, until the solid is all moistened with the acid. Any solid matter adhering to the walls of the vessel is now washed down into the liquid with the remainder of the acid; the flask is attached to a reflux condenser and set without shaking over a 10 centimeter hole in a large sheet of asbestos board which rests on a tripod., and heated until the mixture boils. The boiling is continued for fifteen minutes.

The reaction mixture, which now becomes rather dark is distilled with an equal volume of coldwater and cooled to 0°C. or below. The solution is filtered, the precipitate is washed several times with ice water and dissolved in 1600 c.c. of boiling water. This solution is filtered as rapidly as possible through a large folded filter, preferably with a steam funnel. In spite of all precautions, however, some solid usually separates on the filter. This must be redissolved in a minimum quantity of boiling water and this final solution filtered into the same solution. The 4-nitro phenyl acetic acid separates in long, pale yellow needles, which melt at 151°-152°C. The yield is 103 to 106 grams.

PREPARATION OF
4-AMINO PHENYL ACETIC ACID
from
4-NITRO PHENYL ACETIC ACID by REDUCTION with HYDROGEN



Procedure:

Dissolve thirteen grams of 4-nitro phenyl acetic acid in about one hundred and fifty c.c. of alcohol. It is best to heat the solution to boiling despite the fact that the nitro product is very soluble in alcohol. The solution is then placed in the reducing machine with about one-half gram of Raney's catalyst added. The process of reduction begins at once. During the reaction thirteen pounds of hydrogen were absorbed. After the reaction heat the solution to boiling and filter from the catalyst while the solution is still warm. The amino product precipitates out without dilution with water. If the reduction is complete further purification is unnecessary. The melting point of the product is 199° to 200°C. The yield is nine grams which is 82.7% of the theoretical.

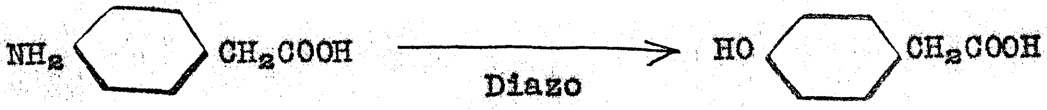
PREPARATION OF
4-AMINO PHENYL ACETIC ACID
from
4-NITRO PHENYL ACETIC ACID by REDUCTION with HYDROGEN SULFIDE

Procedure[87]:

A 1500 c.c. flask is fitted with a two-holed rubber stopper carrying a glass tube which ends below the middle of the flask. The second hole is fitted with a common glass stopcock. To the flask is added 500 c.c. of 6N aqueous ammonia and 100 grams of 4-nitro phenyl acetic acid is now slowly introduced, with shaking. The flask is then placed in an ice bath, and the mixture saturated with hydrogen sulfide. The temperature being held below 50°C.

The stopper is removed from the reaction flask and the solution of ammonium 4-amino phenyl acetate gently boiled under the hood until nearly all the excess hydrogen sulfide and ammonia have escaped. The solution changes from a dark-orange-red to a pale yellow. The deposited sulfur is filtered off by suction, and 40 c.c. of glacial acetic acid rapidly stirred into the hot filtrate. The 4-amino phenyl acetic acid which precipitates weighs 69 to 70 grams, but is contaminated with a small amount of free sulfur. On evaporating the mother liquid to small volume, about five grams more can be obtained. The crude material is recrystallized from four liters of distilled water about seventy grams of product being obtained which melts at 199° to 200° C.

PREPARATION OF
4-HYDROXY PHENYL ACETIC ACID
from
4-AMINO PHENYL ACETIC ACID



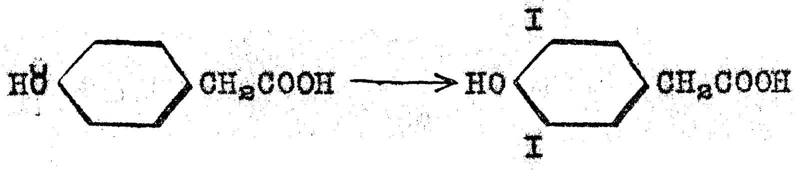
Procedure:

Thirty grams of 4-amino phenyl acetic acid are added to 75 c.c. of water and 45 c.c. of sulfuric acid (sp.gr. of 1.84). The solution is warmed until most all of the precipitate is in solution. It is then cooled to 30°C. in an ice bath and then 100 grams of ice is added. To this cooled mix then is added slowly a cooled solution of 14 grams of $NaNO_2$ in 30 c.c. of water. The diazonium compound should go complete into solution. If, after standing 15 minutes in an excess of nitrous acid, there remains any precipitate, it should be removed by filtration. If the amino compound has been purified thoroughly there will be no remaining precipitate, which is uaually unchnaged 4-nitro phenyl acetic acid and may be reduced to the amino compound.

The clear solution is added slowly to a boiling solution of 50 c.c. of sulfuric acid (sp.gr. of 1.8) and 100 c.c. of water. It is advisable to add the solution slowly through a reflux condenser, thus preventing a loss of water. If added slowly there should be no tarry substances formed in the solution. Allow to continue boiling for ten minutes, after the addition of the diazonium compound.

The solution containing the 4-hydroxy phenyl acetic acid is allowed to cool and extracted with ether at least three times. The hydroxy compound is so soluble in water that it will not precipitate out even slightly on chilling. The ether is evaporated off ~~en~~ a water bath and may be used for the next extractions. There remains in the flask, a dark brown, semi-oily mass. Pour into an evaporating dish and allow to stand in the open to remove the remaining ether. 4-Hydroxy phenyl acetic acid solidifies and may be purified from heptane. The melting point of the purified compound is 130°C. It has a characteristic penetrating odor. The yield is very good, 85 to 90% of the theoretical.

PREPARATION OF
3,5,-DI-IODO-4-HYDROXY PHENYL ACETIC ACID
from
4-HYDROXY PHENYL ACETIC ACID



Procedure:

Make the ammonium salt of 4-hydroxy phenyl acetic acid by dissolving ten grams of the product in at least fifty c.c. of concentrated ammonium hydroxide. If necessary ten to fifteen c.c. of water may be added. This solution is stirred mechanically and to it is added the calculated amount of I_2 (33 grams) dissolved in potassium iodide and water. Best results were obtained by adding the potassium iodide - iodine solution through a dropping funnel.

As the ammonium slat is dark brown it is impossible to see the end point. However, after all the iodine solution has been added, the stirring was continued for one hour. The solution was poured into dilute hydrochloric acid and ice. The di-iodo compound separates out at once. After it has been acidified, a dilute solution of sodium bisulfite is added to remove any free iodine. The unchanged 4-hydroxy phenyl acetic acid and the inorganic salts are removed on filtering and washing with water.

The 3,5-di-iodo-4-hydroxy phenyl acetic acid comes out as a light brown solic, which melts around 195° to 200°C. It may be purified from boiling water or heptane. The pure product comes out white and melts very sharply at 211°C. without any loss of iodine.

Analysis:

Calculated % of iodine (for $C_8H_6O_3I_2$; molecular weight is 404.0 = 62.8%

1) Found 62.4% - - - - - - - - - - - - - - - - -

Wt. of sample - - - - - - - - - - - - - - - - - - .1168 g.

Std. $AgNO_3$ solution used (1 c.c. .0127 g. of I) = 5.80 cc.

Weight of iodine in sample - - - - - - - - - - - .07366

Percent of Iodine in sample - - - - - - - - - - - = 62.4%

2) Found 62.5%

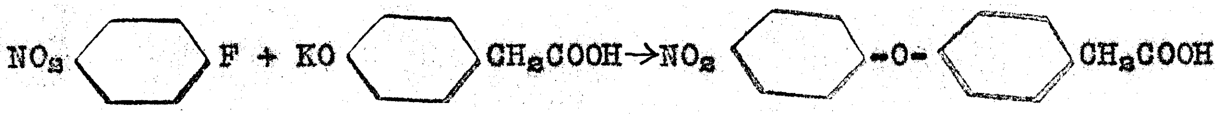
Wt. of sample - - - - - - - - - - - - - - - - - - .1671 g.

Std. $AgNO_3$ solution used (as above) - - - - - - - 8.23 cc.

Wt. of idoine in sample - - - - - - - - - - - - - - .1045

Percent of iodine in sample - - - - - - - - - - - 62.5%

PREPARATION OF
4-(4'-NITRO PHENOXY) PHENYL ACETIC ACID
from
4-NITRO FLUOROBENZENE and 4-HYDROXY PHENYL ACETIC ACID



Procedure:

Make the potassium salt of 4-hydroxy phenyl acetic acid by dissolving twelve grams of the acid in ethyl alcohol. To this add an alcoholic solution of potassium hydroxide (containing 16 grams of potassium hydroxide). Evaporate off the alcohol. The potassium salt settles out in a tarry mass unless the solution is evaporated carefully. To the potassium salt of the acid is added 30 grams of 4-nitro fluorobenzene (11 grams excess). Vigorous reaction takes place at 145° to 150°C. The flask is removed from the oil bath while the reaction continues. The reaction is apparently complete in a few minutes. However, the product is heated for 30 minutes longer at 140 to 145°C.

The mass is then steam distilled to remove an unchanged nitro fluorobenzene. There was recovered about 12 c.c. of which is nearly the theoretical (11.5 grams) . The solution is then cooled and added to cold dilute hydrochloric acid. The product separates out gummy. This is washed and allowed to dry, at which time it becomes crystalline. The yield was 60% of the theoretical.

The compound was crystallized from heptane, and benzene, or a mixture of both. It is very soluble in hot benzene and fairly soluble in cold benzene. After dissolving in benzene add to an equal volume of heptane. The product comes out as yellow crystals. The melting point of this compound is 110 to 111°C. Continued purification from the benzene-heptane solutions gives pale yellow crystals having a melting point of 128°C.

Analysis:

Sample 1 = .2055 grams

c.c. of acid used = 7.58

N of acid = 0.1N

Percent of nitrogen = 5.16%

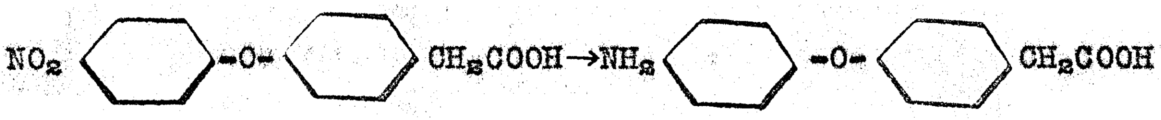
Sample 2 = .1942 grams

c.c. of acid used = 7.11

Percent of nitrogen = 5.11%

Calculated theoretical percent of Nitrogen = 5.12%

PREPARATION OF
4-(4'-AMINO PHENOXY) PHENYL ACETIC ACID
from
4-(4'-NITRO PHENOXY) PHENYL ACETIC ACID by REDUCTION



Procedure:

Dissolve five grams of the nitro product in about 200 c.c. of alcohol. Warm the solution and reduce in the special hydrogenation machine, using platinum as the catalyst. The product seemingly is very hard to reduce. Filter to remove the catalyst that remains and pour the filtrate into ice water. The product is now purified from heptane. The yield of the purified product is low; around forty percent. It crystallizes out as a white precipitate. The melting point of the compound before purification is about 145°C. After purifying from heptane it is 158°C.

Analysis:

Sample 1 = .22.2 g. c.c. of acid used = 2.22 c.c.

$$x = \frac{(2.22)(.0066)}{.2212}$$

x = 6.62% of Nitrogen

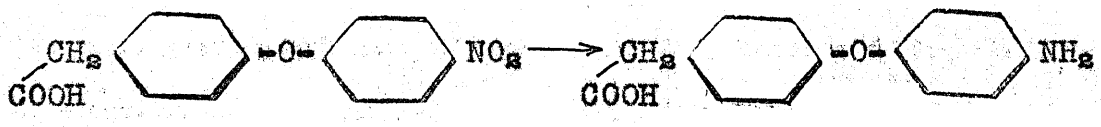
Sample 2 = .2081 grams c.c. of acid used = 2.06 c.c.

$$x = \frac{2.06(.0066)}{.2081}$$

x = 6.53% of Nitrogen

Calculated % of Nitrogen = 5.76%

PREPARATION OF
4-(4'-AMINO PHENOXY) PHENYL ACETIC ACID
from
4-(4'-NITRO PHENOXY) PHENYL ACETIC ACID by REDUCTION



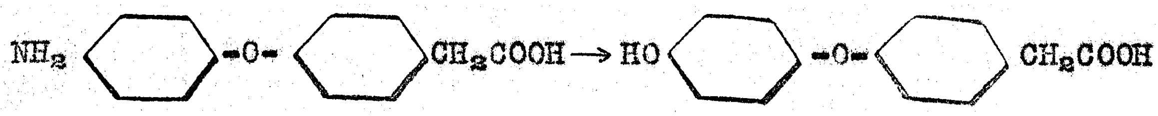
Procedure:

The amino compound was prepared by reducing the nitro compound. Two different methods were used. One with hydrogen sulfide and the other with catalytic hydrogen.

Dissolve 4-(4'-nitro phenoxy) phenyl acetic acid by making the ammonium salt with ammonium hydroxide. Saturate the compound with hydrogen sulfide, until the calculated amount of increase in weight has been obtained. (See the procedure on Page for details of this method). Boil to remove the excess hydrogen sulfide and ammonia. The dark colored solution becomes pale yellow due to the precipitate of sulfur. Add more ammonium hydroxide and saturate with hydrogen sulfide to insure complete reduction. Boil out as above.

Filter, cool with ice and acidify with acetic acid. A yellow precipitate forms. Wash thoroughly and dry. The product is resrystallized from equal parts of benzene and heptane. The melting point of the compound is 159°C. and the yield is only about 60% of the theoretical.

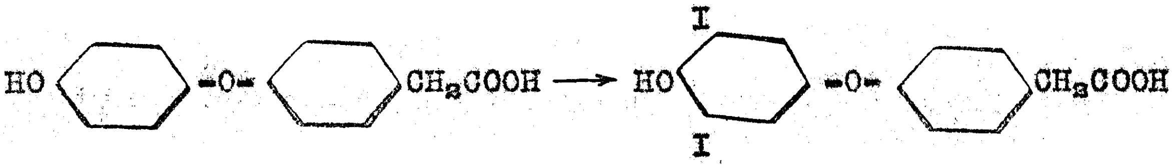
PREPARATION OF
4-(4'-HYDROXY PHENOXY) PHENYL ACETIC ACID
from
4-(4'-AMINO PHENOXY) PHENYL ACETIC ACID



Procedure:

Stir 5 grams of powdered 4-(4'-amino phenoxy) phenyl acetic acid into a mixture of 15 c.c. of concentrated sulfuric acid and 20 c.c. of water. The solution is cooled to 0°C. and crushed ice (about 50 grams) is also added to the solution. Slowly add to this solution an aqueous solution of 1.8 grams of sodium nitrite. Allow this to stand for 15 minutes, but stir continuously. Then add the cold diazo product, in small quantities, trough a reflux condenser, to a boiling solution of 60 c.c. of concentrated sulfuric acid and 100 c.c. of water. Slow boiling and slow addition of the ciazo product is necessary for the success of this reaction, about twenty minutes being required for this step pf the production. The solution should be cooled by pouring into a cold beaker which is placed in a salted ice bath. Several grams of ice may be added to the solution itself. The solution is then filtered washed thoroughly with water to remove all the sulfuric acid. 4-(4'-Hydroxy phenoxy) phenyl acetic acid is purified from heptane, melting at 188°C. The yield is only 50% of the theoretical.

PREPARATION OF
4-(3',5'-DI-IODO-4'-HYDROXY PHENOXY) PHENYL ACETIC ACID
from
4-(4'-HYDROXY PHENOXY) PHENYL ACETIC ACID



Procedure:

Two grams of 4-(4'-hydroxy phenoxy) phenyl acetic acid were dissolved in twenty five c.c. of ammonium hydroxide. To this solution was added with constant stirring, the calculated amount of a normal solution of iodine in potassium iodide. After the addition of iodine is complete the solution is acidified with hydrochloric acid, precipitating the 4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenyl acetic acid as a dark brown substance. Heptane proved to be the best solvent for the purification of this di-iodo compound. The sodium salt of 4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenyl acetic acid is very soluble in water and may also be used as a means of purification. The compound decomposed at 220°C. liberating iodine.

Analysis:

Calculated percent of iodine (for $C_{14}H_{10}O_4I_2$; molecular weight is 496) = 51.20%

1) Found 50.81%

Wt. of sample - - - - - - - - - - - - - - - - .1453 grams

Std. $AgNO_3$ solution used (1 cc. .00635g. I_2) = 11.62 c.c.

Wt. of Iodine in sample - - - - - - - - - - - .0737 g.

Percent of Iodine in sample - - - - - - - - - 50.81%

2) Found 50.72%

Wt. of sample - - - - - - - - - - - - - - - - .1694 grams

Std. $AgNO_3$ solution used (1 cc. .00635g. I_2) = 13.52 c.c.

Wt. of Iodine in sample - - - - - - - - - - - .0859 g.

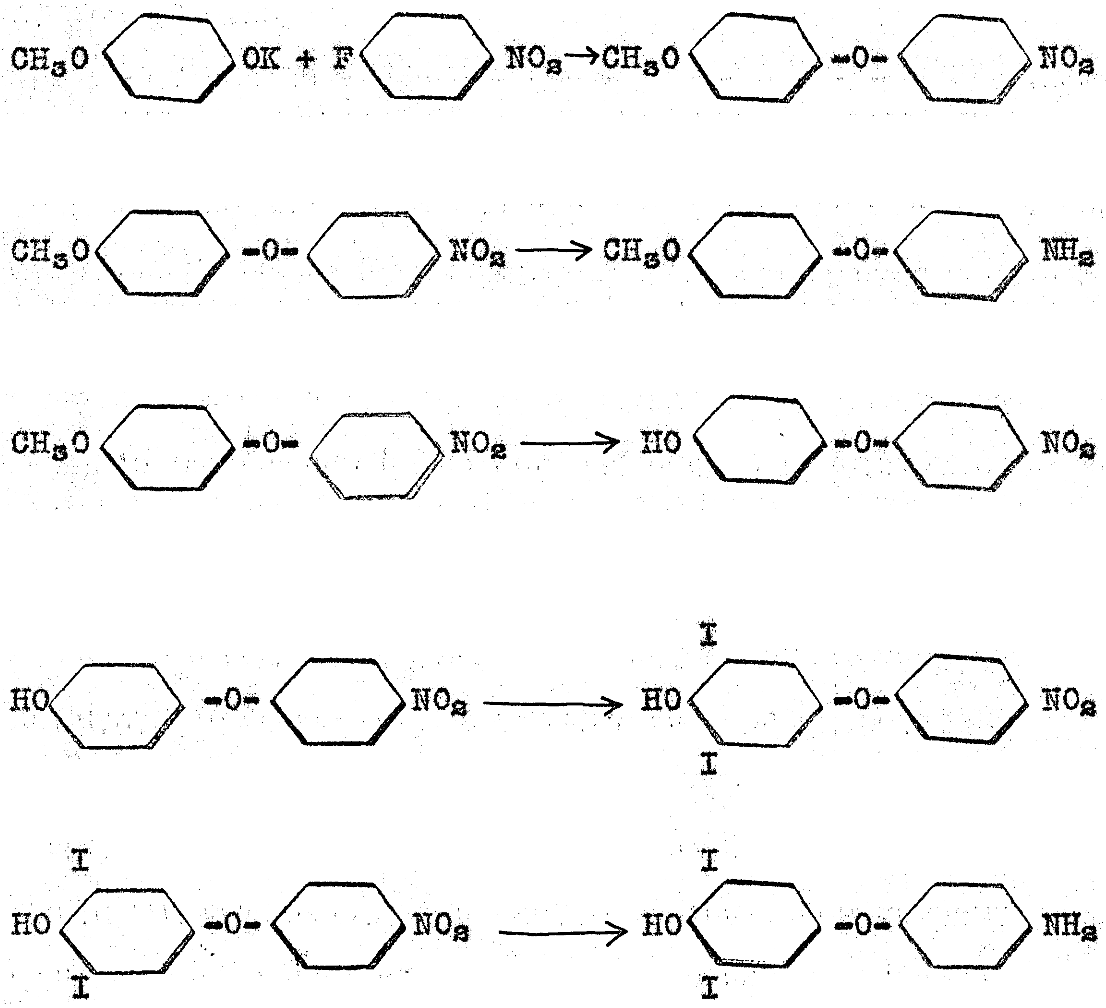
Percent of Iodine in sample - - - - - - - - - 50.72%

EXPERIMENTAL

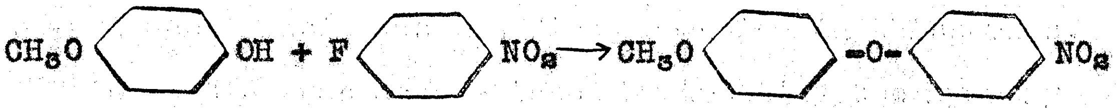
4-PHENOXY PHENYL GLYCINE SERIES

SERIES V

PHENOXY PHENYL GLYCINE SERIES



PREPARATION OF
4'-METHOXY-4-NITRO DIPHENYL ETHER
from
4-HYDROXY ANISOLE and 4-NITRO FLUOROBENZENE

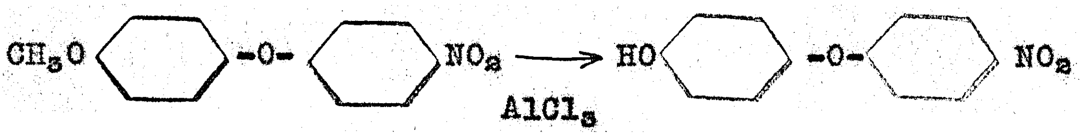


Procedure:

4'-Methoxy-4-nitro diphenyl ether has been previously prepared by Oesterlin[48] and also by Brewster and Choguill[49].

Melt 0.2 mole of 4-hydroxy anisole with the calculated amount of potassium hydroxide (11.2 grams). Heat to a temperature of 120°C. and keep this temperature for ten minutes. Cool to 100°C. and add forty grams of nitro fluorobenzene (12 grams excess). Raise the temperature of the oil bath to 130°C. when the reaction takes place sponstaneously. After allowing the reaction to subside, heat to 140°C. and keept at this temperature for twenty minutes. Steam distill to remove the excess nitro fluorobenzene. The solution is allowed to cool and is filtered and washed thoroughly to remove the unchanged monomethyl ether of hydroquinono. The product is then recrystllized from alcohol. Heptane is also very satisfactory for purification. The compound comes out as yellow glistening flakes, melting at 111°C. The yield is about 80%.

PREPARATION OF
4-(4'-NITRO PHENOXY) PHENOL
from
4-(4'-NITRO PHENOXY) ANISOLE



Procedure:

Take twenty grams of 4-(4'-nitro phenoxy) anisole and mix thoroughly with twnety grams of anhydrous aluminum chloride. The reaction begins at once with mich evolution of HCl. The mix is placed on an oil bath and heated slowly to 120°C. If the temperature is allowed to go above 120°C. decomposition usually takes place. Continue heating at 115°C. to 120°C. for 45 to 60 minutes.

Add 150 c.c. of water with some HCl in it to the mix, and shake thoroughly. The solution becomes quite hot. Filter and wash thoroughly.

Take up the precipitate with dilute sodium hydroxide and filter to remove the unchanged methoxy product. A second extraction with hot dilute sodium hydroxide solution, extracted hydroxy compound. The solution is then poured into dilute hydrochloric acid solution. The compound separates out at once. One recrystallization from water gave a melting point of 160 to 165°C. Compound can be recrystallized from heptane, benzene, alcohol, or water. Best results were obtained with heptane. The product comes out as white needles melting at 168°C. The yield was 75% of the theoretical.

Analysis:

Sample 1 = .2191 grams

c.c. of acid used = 9.53

N of acid used = 0.1N

% of nitrogen = 6.08% nitrogen

Sample 2 = .2420 grams

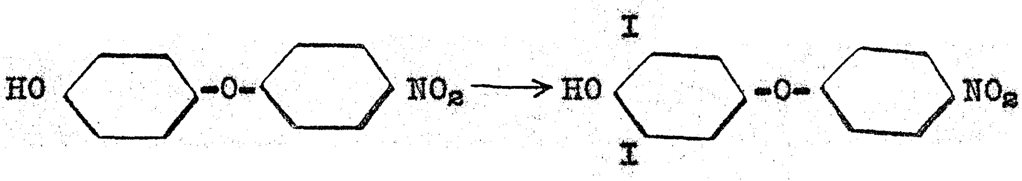
c.c. of acid used = 10.45 c.c.

N of acid used = 0.1N

% of nitrogen = 6.05%

Calculated theoretical % of nitrogen = 6.06%

PREPARATION OF
4-(4'-NITRO PHENOXY)-2,6-DI-IODO PHENOL
from
4-(4'-NITRO PHENOXY) PHENOL



Procedure:

Dissolve 5 grams of 4-(4'-nitro phenoxy) phenol in 40 c.c. of ammonium hydroxide and a little dilute sodium hydroxide solution. The sodium hydroxide solution is necessary as the ammonium salt is not very soluble.

While stirring add the calculated amount of iodine (11 grams) in potassium iodide solution. After addition of one third solution, the di-iodo product begins to separate out. Continue adding the iodine potassium iodide solution and stir for one hour after the addition is complete. Practically all the di-iodo compound precipitates out and the solution is filtered. The filtrate is made acid to recover the amount of the di-iodo that remained in solution. However, the unchanged hydroxy compound also comes down with this. The ammonium slat of the di-iodo compound is dissolved in acetic acid and precipitated by pouring the mix in ice. This brings the compound out as a grey precipitate. It is then dried and recrystallized from 50% alcohol. The compound is light yellow and has a melting point of 153°C. The yield is only about 55% of the theoretical. The di-iodo compound is only very slightly soluble in heptane, however, a small amount can be repurified from it.

Analysis:

Calculated percent of Iodine (for $C_{12}H_7O_4I_2$; molecular weight = 469) = 54.15%

1) Found 53.80%

Weight of Sample - - - - - - - - - - - - - - - - - .1500

Std. $AgNO_3$ sol'n used (1 c.c. .00635 g. of I) - 12.70

Weight of Iodine in sample - - - - - - - - - - - - .0807

Percent of Iodine in sample - - - - - - - - - - - 53.80%

2) Found 53.92%

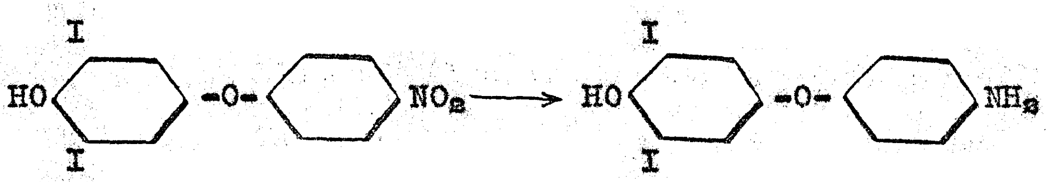
Weight of sample - - - - - - - - - - - - - - - - - .1528

Std. $AgNO_3$ sol'n used (as above) - - - - - - - - - 12.97

Weight of Iodine in sample - - - - - - - - - - - - .0824

Percent of Iodine in sample - - - - - - - - - - - 53.92%

PREPARATION OF
4-(4'-AMINO PHENOXY)-2,6-DI-IODO PHENOL
from
4-(4'-NITRO PHENOXY)-2,6-DI-IODO PHENOL



Procedure:

Dissolve 5 grams of 4-(4'-nitro phenoxy)-2,6-di-iodo phenol in 30 c.c. of glacial acetic acid. It is necessary to warm the product in solution.

Six grams of iron powder (ferric reductum) was added in small portions. The reaction becomes quite violent . After all the iron has been added, the solution is refluxed for 15 minutes. The solution is filtered while hot and the residue is extracted again with hot acetic acid. Allow to cool and pour in ice. The amino product comes out as a brown solid, which is recrystallized from heptane. The purified product is white and melts at 147°C. The hydrochloride salt is soluble in water and a mixed melting point with 4-(4'-nitro phen~~my~~y)-2,6-di-iodo phenol gave a depression.

Analysis:

Calculated percent for iodine (for $C_{12}H_9O_2I_2$; molecular weight = 439) = 57.85%

1) Found 57.30%

Weight of sample - - - - - - - - - - - - - - - - .1465

Std. AgNO$_3$ sol'n used (1 c.c. .00635 g. of I)- 13.20

Weight of Iodine - - - - - - - - - - - - - - - - .0839

Percent of Iodine - - - - - - - - - - - - - - - 57.30

2) Found 57.42%

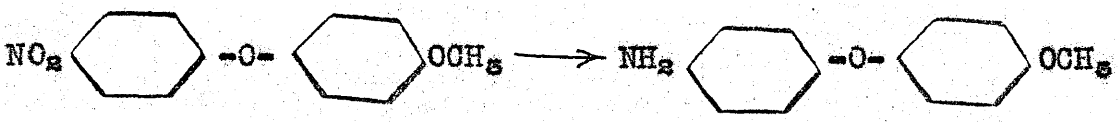
Weight of sample - - - - - - - - - - - - - - - - .1232

Std. AgNO$_3$ sol'n used (as above) - - - - - - - - 11.13

Weight of Iodine - - - - - - - - - - - - - - - - .0707

Percent of Iodine - - - - - - - - - - - - - - - 57.43%

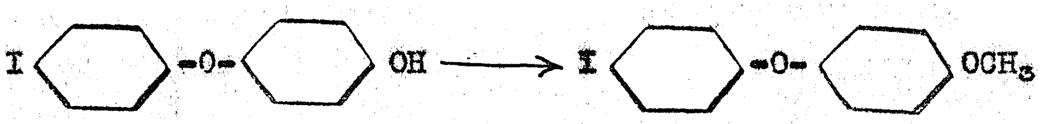
PREPARATION OF
4-(4'-AMINO PHENOXY) ANISOLE
from
4-(4'-NITRO PHENOXY) ANISOLE BY REDUCTION



Procedure:

Dissolve ten grams of 4-(4'-nitro phenoxy) anisole in fifty c.c. of ethyl alcohol. Transfer to the reducing machine and add 0.2 grams of platinum oxide. The calculated amount of hydrogen is used in a few minutes. Solution is filtered to remove the catalyst and poured into finely divided ice. The amino product separates out as a yellow crystalline mass. The melting point of this unpurified product is 65° to 70°C. Recrystallization from heptane gives good results and after two purifications gives a melting point of 82°C. The yield is eighty percent of the theoretical. This nitro compound can also be reduced by using acetic acid and iron. However, the yield is not as high and requires more time than the above reaction.

PREPARATION OF
4-(4'-IODO PHENOXY) ANISOLE
from
4-(4'-IODO PHENOXY) PHENOL

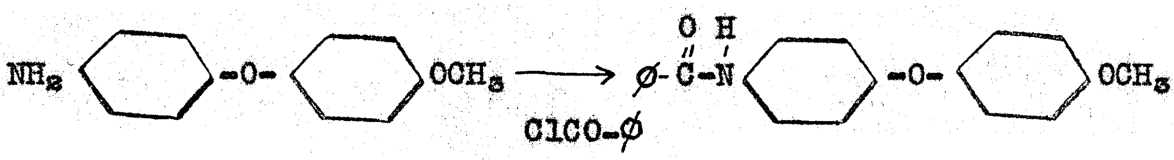


Procedure:

Two grams of 4-(4'-iodo phenoxy) phenol were dissolved in twenty c.c. of ten percent sodium hydroxide solution. Add three c.c. of dimethyl sulfate to this solution, after warming to 50° or 60°C. and shake. The reaction is spontaneous and comes to a boil precipitating a white solid. Continue to shake the solution and let it stand for fifteen minutes. Coolin ice and filter. The methoxy compound is purified from alcohol and melts at 113°C. The yield was two grams.

A mixed melting point of 4-(4'-iodo phenoxy) anisole made by methylation and 4-(4'-iodo phenoxy) anisole made by direct iodination gave no depression, thus showing that the two compounds are the same.

PREPARATION OF
4-(4'-BENZOYL AMINO PHENOXY) ANISOLE
from
4-(4'-AMINO PHENOXY) ANISOLE



Procedure:

Take two grams of the amino compound and mix thoroughly with a ten percent solution of sodium hydroxide. Add benzoyl chloride and shake until the odor of the benzoyl chloride has disappeared. The reaction is complete in twenty minutes. The brown amino compound changes to a grayish colored product. This is washed thoroughly to remove sodium benzoate. The residue is dissolved in ethyl alcohol and precipitated by adding to ice water. The product comes out lighter and has a melting point of 125°C. Recrystallization from heptane gives a white crystalline product which melts sharply at 137°C.

Analysis:

PREPARATION OF
CATALYST - PLATINUM OXIDE[37]

Procedure:

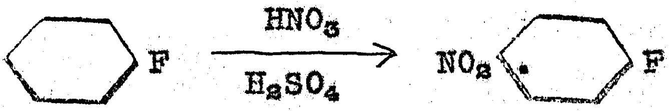
In a 150 c.c. porcelain casserole was prepared a solution of crystals of chloroplatinic acid corresponding to one gram of platinum in five c.c. of water. To this was added twenty grams of sodium nitrate. The mixture was heated gently over a bunsen burner and stirred with a glass rod while the water was expelled. The mixture was then heated gently over a bunsen glame again and the intensity of the flame gradually increased until the maximum heat was obtained, at which time the substance is completely fused. The stirring and heating was continued until the evolution of the oxides of nitrogen had practically ceased. The mass was allowed to cool, with stirring and fifty c.c. of water added. The brown precipitate which remained undissolved was filtered off and washed free from inorganic salts. The precipitate was washed several times with hot water to remove the soluble sodium salts. The filtrate will contain some colloidal platinum which can be recovered. The product was then dried in an oven and kept in a dessicator until used.

PREPARATION OF
RANEY'S CATALYST

Procedure:

To twnety five grams of sodium hydroxide dissolved in 113 c.c. of water is added, a little at a time, twenty five grams of Raney's Catalyst powder with constant stirring. Each addition causes considerable violent reaction. When all the powder has been added, heat to boiling point and hold there about two hours. Replace with water the liquid lost through evaporation. At the end of two hours discontinue adding water, and heat to 142°C. The soluble solids are dissolved by bringing solution back to original amount while heating. The solution is decanted from the sludge and the sludge is washed with water by decantation until it is neutral to litmus. (It must be kept thoroughly wet at all times.) It is washed three times by decantation with 95% ethyl alcohol, to remove the water, and is placed in a glass stoppered bottle where it is kept covered with alcohol, and then is ready for use. Its activity may be tested by allowing a little to dry on filter paper, and if the paper ignites spontaneously the catalyst is active.

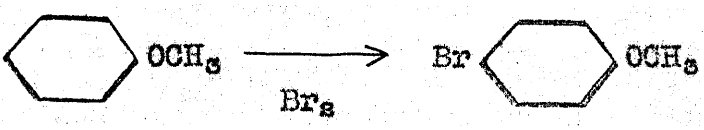
PREPARATION OF
4-NITRO FLUOROBENZENE
from
FLUOROBENZENE



Procedure[26]:

Fluorobenzene was first nitrated to 4-nitro fluorobenzene by adding twenty five grams of fluorobenzen with stirring to a mixture of nitric acid (30 c.c.)(specific gravity of 1.42), sulfuric acid (40 c.c.)(specific gravity of 1.84) and nitric acid (15 c.c.)(specific gravity of 1.5). While this mixture was stirring, care was taken to keep the temperature from rising above 25°C. during the addition, by cooling the flask in cold water. The stirring was continued for an hour, maintaining the temperature at the above value or slightly below. The mixture was diluted with water, the oily layer separated, washed with dilute sodium carbonate solution, dried over calcium chloride and slowly distilled. The product boiled at 205°C. and was shown by its use in the synthesis of diphenyl ether derivatives to be practically pure 4-nitro fluorobenzene. The yields were between 85% and 90%.

PREPARATION OF
4-BROMO AINSOLE
from
ANISOLE and BROMINE



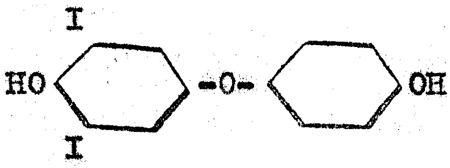
Procedure:

To one mole of anisole (108 grams) in one hundred and fifty c.c. of fifty percent acetic acid there is added one tenth mole (16 grams) of bromine. <u>This addition must take place slowly.</u> The temperature of the reaction must not go above 20°C.

After the bromine has been added the mixture is poured into water and the oily layer separated. It is thoroughly washed with water, dried over calcium chloride and distilled. The boiling point of the 4-bromo anisole is 215°C. and the boiling point of the anisole is 155°C. Ninety seven grams of 4-bromo anisole were obtained, this amount being ninety percent of the theoretical yield.

PHYSIOLOGICAL TESTS

Compound:



4-(3',5'-DI-IODO-4'-HYDROXY PHENOXY) PHENOL

Sample: .0125 gram of compound in 500 c.c. of tap water.

.0030 gram of compound in = 25 p.p.m.

Using crystallizing dishes ; height of dish = 8.0 cm.

depth of water = 3.8 cm.

Length of tadpole

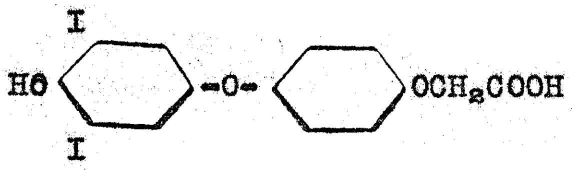
7-10-36	7-20-36
28.0 mm.	27.0 mm.
26.0	24.0
23.0	28.0
26.0	25.0
26.0	26.0
24.0	27.0
25.0	25.0
27.0	25.0
25.0	
24.0	
25.4 Average	25.8 Average

Controls:

7.10-36	7-20-36
25.0 mm.	24.0 mm.
23.0	28.0
24.0	29.5
27.5	29.0
26.0	27.0
26.0	25.0
26.0	25.0
24.5	27.0
25.0	
25.45 Average	26.8 Average

PHYSIOLOGICAL TESTS

Compound:



4-(3',5'-DI-IODO-4'-HYDROXY PHENOXY) PHENOXY ACETIC ACID

Sample: .0125 gram of compound in 500 c.c. of tap water.

.0030 gram of Na_2CO_3 = 25 p.p.m.

Using crystallizing dishes; height of dish 8.0 cm.

depth of water 3.8 cm.

Length of Tadpole

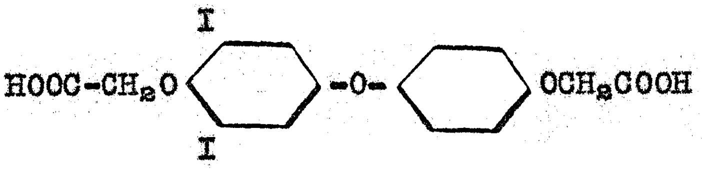
7-8-36	7-20-36
26.0 mm.	24.0 mm.
28.0	31.0
26.5	25.0
25.0	28.0
23.0	29.5
23.5	32.0
23.0	25.5
24.0	26.0
23.0	29.0
27.0	
25.4 Average	27.8 Average

Controls:

7-8-36	7-20-36
25.0 mm.	24.0 mm.
23.0	28.0
24.0	29.5
27.5	29.0
26.0	27.0
26.0	25.0
26.0	25.0
24.5	27.0
25.0	
25.45 Average	26.8 Average

PHYSIOLOGICAL TESTS

Compound:



4-4'-(3'5'-DI-IODO)-BIS-OXY ACETIC ACID DIPHENYL ETHER

Sample: .0125 gram of compound in 500 c.c. of tap water

.0030 gram of Na_2CO_3 = 25 p.p.m.

Using crystallizing dishes; height of dish 8.0 cm.

depth of water 5.8 cm.

Length of Tadpole

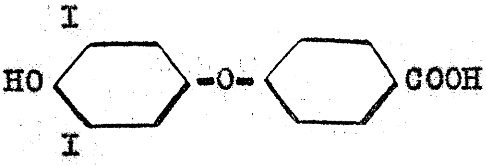
7-1-36	7-17-36
23.0 mm.	23.0 mm.
22.5	25.0
22.0	31.0
21.0	27.0
26.0	26.0
23.5	27.0
25.0	25.0
22.0	26.3 Average
21.5	
21.5	
22.8 Average	

Controls:

7-1-36	7-17-36
27.0 mm.	28.0 mm.
23.0	25.0
21.0	22.0
22.0	22.0
26.0	28.0
25.5	25.0 Average
23.5	
26.0	
24.25 Average	

PHYSIOLOGICAL TESTS

Compound:



4-(3',5'-DI-IODO PHENOXY) BENZOIC ACID

Sample: .0125 gram of compound in 500 c.c. of tap water.

.0030 gram of Na_2CO_3 = 25 p.p.m.

Length of tadpole

6-24-36	6-30-36	7-3-36
26.5 mm.	30.0 mm.	28.0 mm.
25.5	28.0	26.5
25.0	27.0	26.5
26.0	27.5	27.0
24.0	27.0	27.5
24.0	26.0	28.0
24.5	27.0	27.0
24.0	26.0	27.0
25.0 Average	27.3 Average	27.3 Average

Controls:

6-24-36	6-30-36	7-3-36
27.0 mm.	27.5 mm.	23.0 mm.
23.0	28.0	28.0
26.0	26.0	23.0
25.0	22.0	27.0
21.5	25.0	27.0
21.0	24.0	23.0
23.0	23.0	
23.6 Average	25.1 Average	25.1 Average

SUMMARY

1) Seven di-iodo derivatives of diphenyl ether have been synthesized.

2) One di-iodo derivative of 4-hydroxy phenyl acetic acid has been prepared.

3) Two mono-iodo derivatives of diphenyl ether have been prepared. The position of the iodine in both compounds was 4'-.

4) Five of the di-iodo derivatives of diphenyl ether were tested for physiological activity, using Gaddum's Tadpole Iodine Assay. No significant results were obtained.

5) The advantageous use of 4-nitro fluorobenzene in the syntheses of diphenyl ether deriavtives has been demonstrated.

6) All attempts to add hydrocyanic acid to the phenoxy acetophenone derivatives failed.

7) Iodine in ammonium hydroxide solution could not be used as a means to iodinate 4-hydroxy acetophenone although it worked satisfactorily in the other iodinations attempted.

8) The melting points of all the 3,5-di-iodo derivatives of diphenyl ether were found to be

above 200°C., and in all cases the compounds decomposed.

9) Physiological tests of those iodo compounds not previously tested are being performed at the present time. The results of these tests will be reported later.

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ABSTRACT

The object of this investigation is to prepare and study various mono- and di-iodo derivatives of substituted diphenyl ethers and their intermediate compounds. Positions 4 and 4' have been studied chiefly, especially with reference to the difference in solubility which is found upon changing the groups in position 4.

In some of the compounds here reported the iodinated diphenyl ether nucleus is somewhat similiar to that of thyroxine, but physiological tests upon some of the substances have not revealed any marked influence upon the basal metabolic rate. Gaddum's Tadpole Iodine Assay was used to make the physiological tests.

The following new compounds were synthesized and and analyzed:

4-(4'-hydroxy phenoxy) benzoic acid,
4-(3',5'-di-iodo-4'-hydroxy phenoxy) benzoic acid,
4-(4'-iodo phenoxy) acetophenone,
4-(4'-acetamino phenoxy) acetophenone,
4-(4'-benzoyl amino phenoxy) acetophenone,
4-(4'-hydroxy phenoxy) acetophenone,
4-(3',5'-di-iodo-4'-hydroxy phenoxy) acetophenone,
4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenol,

4-4'-(3',5'-di-iodo)-bis-oxy acetic acid diphenyl ether,

4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenoxy acetic acid,

4-4'-bis-oxy acetic acid diphenyl ether,

4-(4'-hydroxy phenoxy) phenoxy acetic acid,

4-(4'-iodo phenoxy) phenoxy acetic acid,

3,5-di-iodo-4-hydroxy phenyl acetic acid,

4-(4'-nitro phenoxy) phenyl acetic acid,

4-(4'-amino phenoxy) phenyl acetic acid,

4-(4'-hydroxy phenoxy) phenyl acetic acid,

4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenyl acetic acid,

4-(4'-nitro phenoxy)-2,6-di-iodo phenol,

4-(4'-amino phenoxy)-2,6-di-iodo phenol,

4-(4'-benzoyl amino phenoxy) anisole.

Physiological tests were made on the following compounds:

4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenol,

4-(3',5'-di-iodo-4'-hydroxy phenoxy) phenoxy acetic acid,

4-4'-(3',5'-di-iodo)-bis-oxy acetic acid diphenyl ether,

4-(3',5'-di-iodo phenoxy) benzoic acid.

These diphenyl ether derivatives were prepared partly by the Ullmann synthesis. Three separate methods of iodination were employed successfully in this work: (1) Iodination with iodine monochloride in acetic acid, (2) iodine in ammonium hydroxide solution, and (3) Iodine and mercuric oxide in alcohol solution.

Physiological tests of those iodo compounds not previously tested are being performed at the present time. The results of these tests will be reported later.