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THE REACTION BETWEEN BARBITAL (DIETHYLBARBITURIC ACID) AND PHOSPHORUS PENTACHLORIDE

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The 5,5-dialkylbarbituric acids, of which barbital is the oldest and most familiar example, are surprisingly inert chemically despite their powerful physiological action as hypnotics. Barbital is one of the least reactive members of the series, presumably because of a molecular stability conferred by its paired ethyl groups. It is resistant to most oxidizing and reducing agents, to high temperatures, and is not easily hydrolyzed. Aside from its imide hydrogen it may be said to possess no functionally reactive groupings. Consequently very few derivatives have been prepared from it. These few comprise desoxyveronal,[2] a xanthydrol condensation product,[3] the Grignard reaction products,[4] and several N-alkyl derivatives.[5] These represent practically all the derivatives that have been prepared directly from a 5,5-dialkylbarbituric acid without breaking open the pyrimidine ring.

In view of the fact that other pyrimidones have been converted into corresponding chloropyrimidines by means of phosphorus oxychloride and pentachloride, it seemed reasonable to expect that barbital would undergo the same reaction. Our purpose was to replace the three oxygens by six chlorines, two of which would then split off as hydrogen chloride, leaving a tetrachloropyrimidine derivative with paired ethyls in the 5-position; and then to replace the four chlorines by hydrogen and obtain the structural base, *viz.*, 5,5-diethyldihydropyrimidine. The first of the above reactions was successfully accomplished and the tetrachloro derivative obtained beautifully crystalline. The yield, however, was small, due to a side reaction of an intermediate chlorination product. Removal of the four chlorines to obtain the structural base has thus far been unsuccessful because of the ease with which the tetrachloro derivative is hydrolyzed by water alone into a nitrile. An unexpected reaction occurs here. Hydrogen chloride is split off quantitatively, but the pyrimidine ring then breaks down into diethylmalononitrile and presumably water and carbon dioxide. In the presence of zinc dust there is formed also a diethyldichloropyrimidine by replacement of two chlorines by hydrogens. This substance is much

[1] Most of the analyses reported in this paper were made by Dr. I. W. Grote of this Laboratory, using the Pregl micro technique.

[2] Tafel and Thompson, *Ber.*, **40**, 4489 (1907).

[3] Fabre, *J. pharm. chim.*, **26**, 241 (1922).

[4] Dox, THIS JOURNAL, **49**, 2275 (1927).

[5] Dox and Jones, *ibid.*, **51**, 316 (1929); Lyons and Dox, *ibid.*, **51**, 288 (1929).

more stable and may be steam distilled without decomposition. It is also resistant to further reduction, so that our attempts thus far to replace the two remaining chlorines by hydrogen have not been successful.

Experimental

In the first attempts to chlorinate barbital, phosphorus oxychloride was used. The parent barbituric acid had previously been converted into trichloropyrimidine,[6] by heating for one hour in a sealed tube at 130–140° with phosphorus oxychloride. Under these conditions barbital failed to react. Even when the temperature was raised to 175–180° and the heating prolonged six hours, there was very little evidence of reaction. The barbital was recovered almost quantitatively and identified by its melting point. The only indication of a slight reaction was a terpene-like odor of the steam distillate obtained after decomposition of the phosphorus oxychloride by pouring the reaction mixture on ice.

2,4,6-Trichloro-5-*sec.*-butylpyrimidine.—The stability of the dialkylbarbituric acids, as illustrated by barbital, toward phosphorus oxychloride is in striking contrast to the readiness with which a monoalkylbarbituric acid reacts. A tube containing 5 g. of *sec.*-butylbarbituric acid and 15 cc. of phosphorus oxychloride was heated at 175–180° simultaneously with the barbital in the preceding experiment. The reaction mixture was poured on ice and after decomposition of the excess phosphorus oxychloride the residual oil was extracted with ether. Evaporation of the solvent then left a white crystalline mass which after recrystallization from alcohol melted at 40°. The yield was 5.157 g. from 5 g. of *sec.*-butylbarbituric acid, or 79% of the theoretical.

Anal. Calcd. for $C_8H_9N_2Cl_3$: N, 11.69; Cl, 44.47. Found: N, 11.65, 11.53; Cl, 44.53.

As pointed out by Behrend,[7] in the analogous reaction with methyluracil, each oxygen atom is evidently replaced by two chlorines, then one chlorine from each pair is split out with an adjacent hydrogen as hydrogen chloride, leaving three double bonds in the ring.

A lower homolog, 2,4,6-trichloro-5-ethylpyrimidine, has been prepared by v. Merkatz[8] from 5-ethylbarbituric acid and phosphorus oxychloride.

Reaction with Barbital

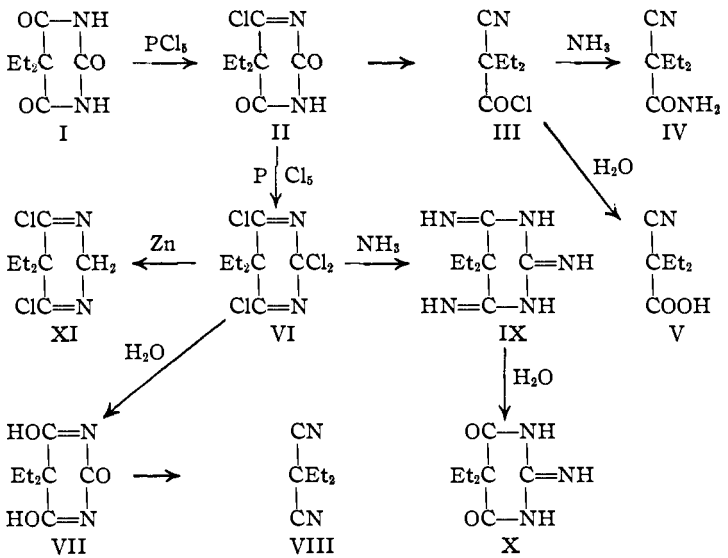
In subsequent experiments with barbital, phosphorus pentachloride was used in place of phosphorus oxychloride because of its greater reactivity. Even here the reaction appears to reach an equilibrium, so that phosphorus pentachloride and unreacted barbital are still present although the mixture may have been heated for two or three days after the evolution of hydrogen chloride had ceased. The phosphorus pentachloride exchanges 2Cl for each O of the barbital, and the resulting phosphorus oxychloride can for the most part be removed readily by distillation. It is unlikely that complete chlorination of the barbital molecule occurs before the splitting out of hydrogen chloride begins. If the reaction proceeds stepwise and in a definite sequence, replacement of oxygen being followed by removal of hydrogen chloride, there would be four intermediate products between Formulas II and VI. It is obvious that one of the carbons must retain both its chlorines, since there are three pairs of chlorines but only two adjacent hydrogens. The final product would be a tetrachloro derivative with two

[6] Gabriel, *Ber.*, **33**, 3666 (1900).

[7] Behrend, *Ann.*, **227**, 25 (1885).

[8] v. Merkatz, *Ber.*, **52**, 869 (1919).

double bonds, instead of a trichloro derivative with three double bonds as illustrated by the *sec.*-butyl compound above.



Theoretical proportions for this reaction would be $3PCl_5$ to 1 barbital. Actually this represents an excess of phosphorus pentachloride, for the reason that the reaction does not proceed entirely in this manner. Another and entirely different reaction occurs simultaneously, yielding a product which retains one of the barbital oxygens. This will be discussed presently.

In the case of barbituric acid or its monoalkyl derivatives only the first of these reactions seems to occur. The reaction mixture may be poured on ice to decompose the remaining phosphorus chlorides, and a good yield of the chlorinated pyrimidine thus obtained. With barbital, however, a viscous product remains which reacts slowly with water and has the characteristic odor of organic acid chlorides. In the first experiments where the reaction mixture, after hydrolysis of the phosphorus chlorides, was extracted with ether and the tetrachloropyrimidine derivative crystallized by evaporation of the solvent, a viscous mother liquor remained. Distillation of this with steam gave an oily product with a strong camphoraceous odor. The oil solidified in crystals, melting at 44°, which were identified as diethylmalononitrile, while extraction of the aqueous layer with ether gave a crystalline substance which was identified as diethylcyanoacetic acid. These obviously were secondary products formed during the steam distillation. In subsequent experiments steam distillation was therefore avoided.

A number of chlorinations were made, using barbital and phosphorus pentachloride. In several of these a small quantity of phosphorus oxychloride was added to moisten the mixture but no advantage appeared to be gained by so doing. The following experiment was performed on a somewhat larger scale and illustrates the typical reaction.

An intimate mixture of 96 g. of barbital and 376 g. of phosphorus pentachloride was placed in a 1-liter distilling flask connected with a downward condenser and receiver, the latter provided with an outlet tube leading through dry calcium chloride and terminating over a quantity of water contained in a flask. The mixture was heated by immersing the distilling flask in an oil-bath maintained at 115–120°. The mass slowly sintered while a vigorous evolution of hydrogen chloride occurred. The hydrogen

chloride was absorbed by the water beneath the end of the outlet tube. After six hours' heating the mass had become liquid and the evolution of gas had practically ceased. On cooling overnight the excess phosphorus pentachloride formed a crystalline crust on the walls of the flask. Titration of an aliquot of the hydrogen chloride collected indicated the equivalent of 40.8 g. compared to a theoretical value of 38.1 g., hence the escaping vapors had carried over some of the phosphorus oxychloride. The apparatus was then connected to a water pump and the bath gradually warmed. At first more hydrogen chloride came off at 65 mm. and bath temperature of 55–60°. At 80° and 80 mm. distillation of the phosphorus oxychloride began. At 110° and 80 mm. the distillation was practically complete and the sublimation of phosphorus pentachloride began. The phosphorus oxychloride thus collected weighed 45.5 g. This does not represent the entire yield since no attempt was made at quantitative recovery by providing adequate cooling. Atmospheric pressure was then restored and the bath temperature raised to 135° for four hours to insure as complete a reaction as possible. The reaction mixture was again cooled overnight, and the viscous amber-colored liquid was filtered through dry asbestos to remove the phosphorus pentachloride that had separated. The filtrate was collected directly in a Claisen distilling flask.

Distillation of this filtrate gave a further yield of phosphorus oxychloride. Between 50 and 55° at 65 mm. 25 g. was collected, and a further sublimation of phosphorus pentachloride occurred. Distillation was then continued at 5–6 mm. pressure, 20.6 g. of colorless liquid passing over between 60 and 80°. Although the bath temperature was raised to 150°, no more distillate was obtained. The bath was then removed and the flask carefully heated over a free flame. Practically no further distillate was thus obtained, but a rise of mercury in the manometer from 5 to 15 mm. indicated an incipient decomposition, hence the distillation was discontinued.

Diethylcyanoacetyl Chloride (Formula III).—The distillate thus obtained had the characteristic odor of organic acid chlorides, and a test portion treated with water slowly decomposed with liberation of acid. Owing to the difficulty of removing traces of phosphorus chlorides the product was not analyzed, but was converted into crystalline derivatives for identification.

Diethylcyanoacetamide (Formula IV).—The above distillate was dissolved in 300 cc. of benzene and saturated with dry ammonia. A copious separation of ammonium chloride was filtered off and washed with ether. Evaporation of the combined mother liquor and washings left a white crystalline residue which on recrystallization from hot water gave long needles (5 cm.) melting at 121°.

Anal. Calcd. for $C_7H_{12}ON_2$: N, 20.0. Found: N, 19.81.

Diethylcyanoacetic Acid (Formula V).—Another portion of the distillate was distilled with steam and the distillate extracted with ether. Evaporation of the solvent and recrystallization of the residue by dissolving in benzene and adding petroleum ether gave a crystalline product, very soluble in water, alcohol and benzene, strongly acid and melting at 68°.[9]

Anal. Calcd. for $C_7H_{11}O_2N$: N, 10.07. Found: N, 9.93. Mol. wt. by titration, 143; calcd., 141.

2,2,4,6-Tetrachloro-5,5-diethyldihydropyrimidine (Formula VI).[10]—The undistilled

[9] The melting point of diethylcyanoacetic acid is given by Hesse (*Am. Chem. J.*, **18**, 748 (1896), as 57°, and by Hessler, THIS JOURNAL, **38**, 939 (1916), as 61°.

[10] The difference in conjugated structure between this substance and the 2,4,5,6-tetrachloropyrimidine prepared by Ciamician and Magnaghi, [*Ber.*, **18**, 3444 (1885)] from alloxan and by Emery. [*Ber.*, **34**, 4178 (1901)] from dialuric acid will be seen by a glance at the formula.

residue from the diethylcyanoacetyl chloride was orange-red in color and quite viscous. On two days' standing it deposited a mass of crystals which were then collected on a large frit filter and washed with a little petroleum ether, then with methyl alcohol which removed the sticky mother liquor. The alcohol washings were collected separately and discarded. White rhombic crystals remained which melted at 127° and showed no change in melting point after recrystallization from ethyl alcohol.

Anal. Calcd. for $C_8H_{10}N_2Cl_4$: Cl, 51.45; N, 10.14. Found: Cl, 51.14; N, 10.19.

The yield in the first crop was 14.2 g. and a second crop of 9.3 g. was obtained by allowing the filtrate, diluted with petroleum ether, to stand for two days. The mother liquor was further diluted with petroleum ether (10 vols.) and treated with dry ammonia, avoiding an excess. After removal of the ammonium chloride by filtration, small amounts of both diethylcyanoacetamide and the tetrachloropyrimidine were obtained by evaporation of the solvent.

Diethylmalononitrile (Formula VIII).—Steam distillation of the final mother liquor gave an oily product which presently solidified and had a strong camphoraceous odor. This came over (about 1 g.) in the first few cc. of distillate and was collected separately. It melted at 44° and was quite volatile.

Anal. Calcd. for $C_7H_{10}N_2$: N, 22.95. Found: N, 23.0.

It is obviously a product formed in the steam distillation, since in no case was it otherwise obtained or its odor detected. Further distillation with steam yielded about 1 g. of the tetrachloropyrimidine, m. p. 127°, which solidified completely in the condenser.

The residue in the distilling flask consisted of a slightly turbid aqueous solution and a brown gummy mass. When clarified with charcoal and evaporated, the aqueous solution yielded about 1 g. of barbital crystals, identified by melting point and taste.

5,5-Diethylmalonylguanidine (Formula X).—The precipitate of ammonium chloride from the ammonia treatment of the second mother liquor from the tetrachloropyrimidine was gummy and evidently contained other reaction products. Extraction of the ammonium chloride with water left a brown gummy mass which dried overnight to a porous brittle mass. Treatment of this with ether dissolved all but a white crystalline powder, insoluble in water and in ether, very slightly soluble in alcohol. By crystallizing from a large volume (1.5 liters) of hot alcohol it was obtained in colorless needles which did not melt when heated to 270°. The substance was readily soluble, however, in dilute acids and alkalies and was reprecipitated by neutralizing the solution.

Anal. Calcd. for $C_8H_{13}O_2N_3$: C, 52.46; H, 7.10; N, 22.95. Found: C, 52.6, 52.7; H, 6.7, 7.1; N, 23.0, 23.3.

The yield was 2.3 g. This substance has been prepared by Fischer and Dilthey[11] from ethyl diethylmalonate and guanidine.

Evaporation of the ether used in the above extraction gave a further separation of barbital. In fact, small quantities of barbital were frequently encountered at various stages of the process of working up the reaction products, especially in mother liquors that had been given a final treatment with water or in residues from steam distillation. It is possible that its presence indicates a regeneration of barbital by hydrolysis of the tetrachloropyrimidine or partially chlorinated intermediate products. On the other hand, it is equally probable that the chlorination is not strictly quantitative and that some of the original substance remains unaltered despite the excess of phosphorus pentachloride used.

A yellowish-brown amorphous residue finally remained from which we were unable to obtain any definitely crystalline substance. On the basis of the total amount of tetrachloro derivative actually isolated (24.5 g.), and the crude diethylcyanoacetyl

[11] Fischer and Dilthey, *Ann.*, **334**, 352 (1904).

chloride (20.6 g.) from which the corresponding amide and acid were prepared, these substances evidently constitute the main reaction products. They are formed in nearly equal quantities under the conditions of our experiments and together account for approximately 46% of the barbital used. In neither case, however, was the recovery quantitative, as was shown by the further isolation of their derivatives from mother liquors.

The formation of a nitrile acid chloride (diethylcyanoacetyl chloride) by the action of phosphorus pentachloride on a cyclic urea such as barbital was at first rather puzzling because no such reaction had been recorded as occurring in the chlorination of numerous purine and pyrimidine derivatives. An interesting parallel, however, was found in the work of Bredt and Iwanoff,[12] who obtained a nitrile acid chloride from phosphorus pentachloride and camphoric imide. The same pyridone ring is present in both glutaric and camphoric imide, but only the latter undergoes this reaction. Now barbital and camphoric imide not only have an imide grouping in common, but both contain also a paired alkyl grouping and in that respect differ from their parent substances which yield only a stable chlorinated ring. The mechanism of the reaction in the case of barbital is not as simple as that proposed by Bredt and Iwanoff for the camphoric imide reaction, since the ring has to break at two places. In the barbital reaction their hypothesis could be applied to the formation of the nitrile grouping, but the formation of acid chloride requires a cleavage by hydrogen chloride. The products would then be diethylcyanoacetyl chloride and carbamyl chloride. The latter boils at 61–62° and would pass off with the hydrogen chloride and phosphorus oxychloride in the first distillate. It may be assumed that the nitrile acid chloride is formed from an intermediate chlorination product, *e. g.*, Formula II, where one of the malonyl carbonyls is still present.

4,6-Dichloro-5,5-diethyldihydropyrimidine (Formula XI).[13]—The tetrachloro derivative, melting at 127°, is readily hydrolyzed by simply refluxing with water. For example, after boiling 0.0694 g. of the substance for two and one-half hours with 25 cc. of water the solution was titrated with *N* sodium hydroxide and methyl red. The titer was 9.94 cc., corresponding to 0.0363 g. of hydrogen chloride, or 98.9% of the value 0.0367 g. calculated for the liberation of 4 hydrogen chloride. During the refluxing a volatile substance solidified in the condenser tube. This had a strong camphoraceous odor and melted at 44°. It is diethylmalononitrile, the substance described above as a product of the steam distillation of the crude chlorination products. The formation of this nitrile, containing the paired ethyl groupings of the original barbital, establishes the fact that the tetrachloro derivative from which it was obtained also has this structure and that no alkyl migration occurred during the chlorination.

Refluxing with zinc dust and water, however, removed two chlorines and gave a product which was readily isolated by steam distillation. It had a camphoraceous odor, but melted at 117°. This substance is considerably more stable than the tetrachloro derivative. No hydrogen chloride was liberated from it by two and one-half hours' refluxing with water. Like the nitrile, it tends to sublime in the condenser tube. The same product was obtained by reduction of the tetrachloro derivative with zinc dust and alcohol and with zinc dust and acetic acid.

Anal. Calcd. for $C_8H_{12}N_2Cl_2$: N, 13.52; Cl, 34.30. Found: N, 13.40; Cl, 33.78.

When the residue from the distillation was made alkaline with sodium hydroxide and distilled further, the distillate was practically neutral and left no residue on evaporation. No evidence was therefore obtained of a further reduction product.

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[12] Bredt and Iwanoff, *Ber.*, **58**, 56 (1925).

[13] The isomeric formula with both chlorines in the 2-position is less in conformity with the properties of the substance.

The hydrolysis of the tetrachloro derivative into diethylmalononitrile is rather a curious reaction. As already stated, hydrogen chloride is liberated quantitatively. It may be supposed that this hydrolysis results first in the formation of an unstable intermediate product, a 5,5-diethyl-2-keto-4,6-dihydroxydihydropyrimidine (Formula VII), which then breaks up into one molecule each of diethylmalononitrile, water and carbon dioxide. This hypothetical intermediate is simply an enolic tautomer of barbital. No oxygen ethers or other derivatives of it are known. It is possible, however, that the ring breaks open after the first stage of hydrolysis involving only the more reactive chlorines in the 2-position. There would then be formed, by hydrolysis and loss of carbon dioxide, a diimine $Et_2C(CCl{=}NH)_2$ which would promptly lose two molecules of hydrogen chloride and form the dinitrile. The former reaction, where all four chlorines are removed by hydrolysis and an enolic barbital is formed, appeals more strongly to the writer in view of the fact that barbital itself appears to yield small quantities of the nitrile under conditions of simple hydrolysis. In a parallel experiment the same quantity of barbital in the same concentration was refluxed for the same length of time with four equivalents of hydrogen chloride. A very minute quantity of needle-shaped crystals sublimed in the condenser and these had a distinct camphor odor, but the yield was altogether too small for a melting point determination. Here we have the suggestion of an enol–keto equilibrium in the case of barbital.

2,4,6-Triimino-5,5-diethylhexahydropyrimidine (Formula IX).[14]—As was to be expected, the tetrachloro derivative in an inert solvent reacts with dry ammonia. A solution of 1 g. in 50 cc. of absolute alcohol was saturated with dry ammonia, tightly stoppered and allowed to stand at room temperature for several days. In about twenty-four hours a separation of transparent granular crystals began. These continued to grow during the next two days, accompanied by the formation of fern-like crystals of ammonium chloride, until they had attained a diameter of about 5 mm. After filtering and washing with cold water to remove the ammonium chloride the yield was 0.585 g. Evaporation of the mother liquor gave a further yield. The substance is soluble in water and gives a copious precipitate with silver nitrate, hence is the hydrochloric acid salt of a base. It contains alcohol of crystallization, and the transparent crystals effloresce in the oven at 100°. This triimino derivative is rather a strong base since it separates as a mono-hydrochloride salt in the presence of a large excess of ammonia.

Anal. Calcd. for $C_8H_{15}N_5{\cdot}HCl$: Cl, 16.32; N, 32.18. Found: Cl, 16.8, 16.2; N, 30.4.

The base has been described[15] as a condensation product of diethylmalononitrile and guanidine. Although the hydrochloric acid salt is moderately stable to dilute acids, the free base is rather easily hydrolyzed. A sample of the hydrochloride salt was treated with the exact equivalent of 0.1 *N* sodium hydroxide and evaporated on the steam-bath. The odor of ammonia was soon recognized and an insoluble residue was finally obtained which had the properties of diethylmalonylguanidine (Formula X). The 2-imino group is evidently more firmly bound than the 4- and 6-imino groups. Further hydrolysis by dilute sulfuric acid yielded barbital.

Summary

Barbital reacts with phosphorus pentachloride at 115–120° with formation chiefly of diethylcyanoacetyl chloride and 2,2,4,6-tetrachloro-5,5-diethyldihydropyrimidine. The former is a cleavage product of an intermediate partially chlorinated pyrimidine, the reaction being somewhat

[14] Possibly the tautomeric 4,6-diamino derivative.

[15] German Patent 165,692 (1905).

analogous to the formation of a nitrile acid chloride from camphoric imide, observed by Bredt and Iwanoff. It was identified by conversion into the amide and the free acid.

The tetrachlorodiethyldihydropyrimidine readily undergoes hydrolysis to diethylmalononitrile. It is suggested that this reaction occurs by way of an enolic tautomer of barbital.

Reduction of the tetrachloro derivative with zinc dust yields a stable dichlorodiethyldihydropyrimidine which does not easily undergo further reduction.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

STUDIES IN THE DIPHENYL ETHER SERIES. III. DERIVATIVES OF THE LOCAL ANESTHETIC TYPE[1]

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The purpose of this work was to study some derivatives of diphenyl ether which differ from the commonly used esters of *p*-aminobenzoic acid mainly in that the amino and ester groups are not attached to the same benzene ring. By a comparison of the local anesthetic action of these compounds with isomers containing both groups in the same ring it is hoped some conclusions may be drawn concerning the mutual effect of these two atomic complexes. The derivatives here reported upon are esters of 4-(4-aminophenoxy)-benzoic acid.

There are several methods which might be used in synthesizing the 4-(4-nitrophenoxy)-benzoic acid necessary for preparing the desired esters. It has been previously[2] obtained in small amounts by the action of the dipotassium salt of *p*-hydroxybenzoic acid upon *p*-chloronitrobenzene. Since the potassium salt of *p*-hydroxybenzaldehyde undergoes this type of reaction very readily, giving an aldehyde which may be oxidized to the desired 4-(4-nitrophenoxy)-benzoic acid, this latter method was used instead of the original one. When this work was practically completed, another feasible method was found in the acetylation of 4-nitrodiphenyl ether and the subsequent oxidation of the 4-(4-nitrophenoxy)-acetophenone.

The 4-(4-nitrophenoxy)-benzoic acid was converted into the acid chloride by the use of thionyl chloride. This was reacted with ethyl, *n*-butyl and β-diethylaminoethyl alcohols to give the nitro esters, which were catalytically reduced[3] to the desired compounds.

[1] Presented before the Organic Division of the American Chemical Society at the Cincinnati Meeting, September, 1930.

[2] Haeussermann and Bauer, *Ber.*, **29**, 2083 (1896).

[3] Adams, Cohen and Rees, THIS JOURNAL, **49**, 1093 (1927).